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GENE THERAPY VERSUS PHARMACOGENOMICS: AN ECONOMIC EVALUATION ON CANCER DISEASES

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Abstract: *By using the model of Danzon et al (2002) we try to analyze in terms of policy implications pharmacogenetics and gene therapy for cancer disease. We conclude that if private-sector increases the investments in gene therapy will obtain a socially sub-optimal solution due to high-cost and small sample of patients treated. On the contrary, pharmacogenetics can be socially optimal, particularly if the proportion of non responders is high and the cost of test is not expensive. However, our results underline that also in the case of pharmacogenetics the investments in R&D may be scarce and lead to a sub-optimal solution.*

JEL classification numbers*:I1, I18*

Key Words*: gene therapy; pharmacogenetics; cancer disease; policy implications*

1. INTRODUCTION

Nowadays many researches are focused on studies about genomics to improve the effectiveness of therapies and diagnostic test. In the medical field the most important uses of genomics are represented by gene therapy, pharmacogenetics and/or pharmacogenomics. Although seems to be a similarity between the gene therapy and pharmacogenetics they are completely different biotechnologies that have only in common the word "gene". Pharmacogenetics is a diagnostic test principally concerned with drug efficacy and safety and it's in increase in conventional drug discovery as knowledge of the human genome increases understanding of disease. The aim of pharmacogenetics is to identify a patient's genotype before treatment, to evaluate those who will not benefit or who may be damaged for therapeutic toxicity. Pharmacogenomics is the study of genomic technologies to new drug discovery and the further characterization of older drugs. However, the terms of pharmacogenetics and pharmacogenomics tend to be used interchangeably. The genomics is used to identify genetic traits that may lead to non-response or to adverse reactions to specific

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medicines for any indication. The growing understanding of the genetic basis for drug response and use of this knowledge to predict the response of an individual patient offers new opportunities to meet the changing needs of health care systems. For the individual patient, overall quality of life should be higher if doctors are able to select the most effective and safest treatments for them. However, the cost of patient evaluation needs to be weighed against the additional therapeutic benefits and savings made by avoidance of unnecessary and inadequate drug use and adverse drug responses. Getting the right medicine at the right dose to the patient first time may reduce costs of medical visits and increase the satisfaction of the treatments. Application of pharmacogenetics to drug development has the potential to streamline the drug development process. Disease and therapy differentiation may lead to stratification of patient groups, and it is possible that the fragmented indications do not always represent commercially attractive markets to the pharmaceutical industry. However, the ability to target patients more accurately may represent considerable commercial value within a given market sector. Changes in health care policy and structures are necessary to overcome short-term budget constraints. In order to realize pharmacogenetics is necessary to consider need, clinical validity and value of resources directed to care chronic diseases in order to prescribe the right drug at the right dose from the outset. Respect to pharmacogenetics that is focused on the effectiveness of testing, gene therapy consists in the insertion of genes into an individual's cells and tissues to produce or regulate the expression of proteins that are related to the patient's disease. In general it is relevant to not curable monogenic diseases and it's expected that may provide long-term therapeutic benefits. The most common form of gene therapy uses DNA that encodes a functional, therapeutic gene to replace a mutated gene (somatic cell gene therapy (SCGT)). The other type of gene therapy is the germline gene therapy (GGT), in which germ cells are modified by the introduction of functional genes into their genomes. However, given the scarce knowledge about possible risks on human beings CGT is prohibited in various countries such as Australia, Canada, Germany, Israel, Switzerland and the Netherlands. The gene therapy is applied to a wide range of disorders. The majority are cancer trials, in phase I oncology trials, inherited disease, infectious disease, peripheral, coronary artery disease, cystic fibrosis, haemophilia, muscular dystrophy, thalassemia and sickle cell anemia (Churchill et al., 1998; Friedmann, 1996; King, 1999). Despite the progress achieved with gene therapy there are still many unsolved problems that may conduct to sub-invest in this innovative therapy for high risks, long-lasting treatments, high costs and too small patients treated arising from: a) The therapeutic DNA integration into the genome and the rapidly dividing nature of many cells prevent it from achieving long-term benefits so that the patients require multiple treatments; b) The rejection of the immune system that may reduces gene therapy effectiveness; c) Multi-gene disorders such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are affected by variations in multiple genes, which complicate gene therapy. In the present research, we focus on the effectiveness of gene therapy treatment and pharmacogenetics by analyzing cancer disease. At an international level there are few studies that specifically

investigate the costs-benefits for society of gene treatments and pharmacogenetics to care cancer disease in terms of policy implications, reimbursement and regulatory regimes. The high costs and uncertainties associated with gene therapy for small patients' sample and long-lived therapeutic effects may lead to sub-optimal levels of commercial researches. In the case of pharmacogenetics, "testing" is in general socially useful even if pharmacogenetics could lead to the stratification of populations based on genetic variants, with the risk that some population groups are too small to be of interest to the pharmaceutical industry. Since this is in part due to the low numbers of patients treated and to the costs of testing, a reduction of R&D costs or a unit price increases may solve the problem and increases expected health gains. The remainder of this paper is organized as follows. In section 2, we examine the model of Danzon et al. (2002) in terms of cost-evaluation by comparing gene therapy and pharmacogenetics. In section 3 we analyze the regulatory issue by comparing Euro Area and United States. In section 3 we analyze cancer disease by applying this model. In section 4 there are conclusions and suggestions for futures investigations.

2. GENE THERAPY AND PHARMACOGENETICS: REGULATORY ISSUES IN EURO AREA AND IN UNITED STATES

The European Medicines Agency (EMEA) and the Clinical Trial Directive (CTD) have the responsibility to supervise clinical trials procedures and drug's activities in the Euro Area. Gene Therapy needs of procedures more rigorous than for other drugs to avoid adverse effects on human health which might arise from the deliberate release of placing on the market genetically modified organisms (GMOs). The process of trials' authorization is long and it is subjected to a peer review process. After the authorization by the European Commission, the Member States will control the authorized products to guarantee safety (Gonin, *et al.*, 2005). In the Unites States, instead, the regulatory process is less fragmented. The Department of Health and Human Services (DHHS) supervises drug development and safety even if the responsibilities are divided between various offices in the same structure (Kuzma *et al.*, 2009; Wolf, *et al.*, 2009). A company before selling a gene therapy product has to inform the Food and Drug Administration (FDA) that regulates human gene therapies and to test it in a laboratory and research animals. Only after a special permission exemption that assesses safety, purity and potency it is possible to study gene therapy in humans. Finally, the last monitoring before selling is made by the National Institutes of Health (NIH) through the Recombinant DNA Advisory Committee (RAC). In the case of pharmacogenetics drugs and diagnostics are in general jointly regulated. Since the licensing of therapeutics test is undertaken jointly by the FDA Office for Combination Products this makes the regulation in the United States more stringent than Euro Area where separate application for diagnostic products must be made to the national agencies and requires a European Conformity Mark.

All in all, pharmacogenetics and gene therapy are considered both useful to society and "morally acceptable". However, although regulation in providing certainty results

advantageous both for the industries and for the patients there are still some directives such as CTD in the Euro Area that may limit industry's innovation and increase industry costs (Bates, 2010; Lesko, *et al.*, 2003; Salerno, *et al.*, 2004). So, in a context in which there are still stringent regulators constraints, the public support results critical for the development and the diffusion of these new technologies.

3. THE MODEL

Starting from the model of Danzon *et al.* (2002) we assume that a new therapy (newt) is considered cost-effective by payers for their patients respect to an existing treatment (oldt) if and only if:

$$\Delta C_{newt,oldt} / \Delta E_{newt,oldt} < K_p \tag{1}$$

And

$$P_{newt}^{\max} = k_p \Delta E_{newt,oldt} + (P_{oldt} + \Delta C_{newt.oldt}^{D} + \Delta C_{newt,oldt}^{I}) = \beta \tag{2}$$

Where the variables of the equations are defined as:

P_{newt}, P_{oldt} = Price of gene therapy and Price of existing treatment;

$\Delta C_{newt,oldt}^{D}$ = Change in direct treatment costs;

$\Delta C_{newt,oldt}^{I}$ = Change in indirect treatment costs;

$\Delta E_{newt,oldt}$ = Change in quality adjusted life years ($QALY_S$);

k_p = Threshold cost per *QALY* of cost-effective treatment of group p.

In this case the equation 2 represents a condition of "socially optimal reimbursement" and β is the social benefits of the new treatment compared with the existing treatment. Replacing the price of payer's cost-effectiveness (Eq. 2) into the producer's break-even profit constraint we obtain the economic cost implications of gene therapy and pharmacogenetics respect to other traditional treatments (Eq. 3).

$$\pi^T = \Sigma^T ((\alpha\beta - M)\, Q^T N^T (1 + r)^{-T}) - F(r, L, p)$$

$$\pi^T = \Sigma^T ((\alpha\beta\text{-M}) Q^T N^T (1 + r)^{-T})\text{-F(r,L,p)} \tag{3}$$

Where the variables of the equation are defined as:

π^T = Profit discounted over T years;

M = Cost per treatment to the producer assumed fixed;

N = Number of patients per year;

Q = Number of treatments for patients per year;

NQ = treatments sold per year;

F = R&D Discounted present value of firm;

L = Expected years from discovery to launch;

p = Probability of success of a clinical trial.

According to equation 3 the total net revenue depends on: 1) The social value of treatment (β) and the share of producer's gain (α) that may be both high if treatment is effective; 2) The number of patients treated per years (N) that may be low because gene therapy in general involve single gene and small sample of patients; 3) The number of treatments for patients per year (Q) that may be small because of the long-term benefits of gene therapies imply that each patient may require treatment to be administered only once or twice a year rather than once or twice a day; 4) The cost of the treatment (M) that could be significantly higher for gene therapies than for other drugs for the impossibility to realize economies scale. If $P = \alpha P^{max}$ the cost of the new therapies is equal to full social benefits. In this case for the payers will be irrelevant if the number of long-lasting treatments for patients per year is low and if the price of therapy increases because the investments in R&D are efficient respect to the duration. However this ideal condition is in general not realizable. The principal problem is the risk of adverse selection that conducts patients involved in long-lasting therapies to switch to other insures. So, the insures that pay the initial treatment do not capture the all savings of the patients and they will avoid to offer long-lived therapies such as gene therapy that will have high cost. This seems not a problem in countries such as Canada and the United Kingdom where patients have a limited choice of health plans. However, in these systems managers and doctors have annual budget constraints that limit their investments in these type of treatments. Another problem consists in the high private costs of R&D for gene therapy compared with conventional therapy in which the probability of success is very low and the expected duration of the R&D process is very long. The high risk of adverse selection and the high costs of R&D could bias the reimbursement systems against other therapies and could conduct to under-investment compared to the social optimum value. The clinical trials of gene therapy relative to cancer or directed to care AIDS and HIV infection confirm the aforementioned problems. Many trials are focused on variants of treatment that would require repeat administration or partial public funding. This underlines strong limits to the application of the gene therapy without changes in incentives or significant public investment. Thus, the characteristics of gene therapy such as long and uncertain R&D, small patient sample, and fragmented treatments may lead to sub-optimal commercial investments in these therapies. Reimbursement systems introduce a bias against gene therapy if payers respond to budgetary or commercial pressures by focusing on short-term drug-budget costs without due weight to long-term health benefits and societal savings. Although society has signaled a willingness to pay additional subsidies to encourage treatments for chronic diseases, however legislation is still low oriented to sporadically treatments such as gene therapy. Starting from equation 3 by introducing responders, non responders and testing costs we examine

the impact of the drug with testing (Eq. 4), without testing (Eq. 5) and the social value of the test (Eq. 6). Payers adopt pharmacogenetics testing before treatment if and only if the savings from treating small patients are higher than the costs of testing. The effects of an investment in pharmacogenetics for a drug company, ceteris paribus, consists in lower revenues per drug that may increase if payers subtract the costs of the gene screening from the price that they are willing to pay or reimburse for the drug.

$$P_{newt1}^{\max} = b_1 - P_t N / N_1 \tag{4}$$

$$P_{newt2}^{\max} = (b_1 N_1 - a_2 N_2) / N \tag{5}$$

$$\Delta P^{\max} = P_{newt1}^{\max} - P_{newt2}^{\max} = (b_1 + a_2)(N_2 / N) - P_t N / N_1 \tag{6}$$

Where the variables of the equation are defined as:

b_1 = Health gains plus savings per patient for current treatment. It's only for N_1 patients who benefit of the drug;

a_2 = Adverse health effect ($QALY_S$<0) plus the cost of adverse reaction for each patient in group N_2;

N = Total number of patients per year;

N_1 = Number of patients who benefit from drug;

N_2 = Number of patients who do not benefit from drug and can't be identified without testing.

According to equation 6 the social value of testing depends on: 1) The health gains plus savings per patient for current treatment (b_1) conditioned by the proportion of non-responders (N_2/N); 2) The adverse health effect (a_2) multiplied by the proportion of non-responders (N_2/N); 3) The cost of testing the whole patient population $P_t N/N_1$. The effects of testing will be positive for the society if the health gains and the adverse health effects will be higher than the costs of testing. From the company perspective the increase of the drug's price for the company that is testing is expressed by the equation 7:

$$\alpha \Delta P_{newt}^{\max} = \alpha(b + a)\left(\frac{N_2}{N}\right) - \alpha P_t N / N_1 \tag{7}$$

The premium price of the company and its propensity to invest more in "targeted products" respect to indiscriminate products depends on: 1) The cost of the test (P_t); 2) The proportion of non-responders to responders $\left(\frac{N_2}{N_1}\right)$; 3) The adverse reactions and the value of share (α). Assume that the firm could make two choices: develop a

traditional drug for all patients of which a proportion receives no benefits and may be damaged or develop a genetic test by identifying the N_1 patients who receives benefits and produces a drug targeted to them. The producer's profit with no testing and with testing are expressed respectively by the equation 8 and 9.

$$\pi_1^T = \Sigma^T((P_{newt1} - M)N^T(1+r)^{-T}) - F_1 \tag{8}$$

$$\pi_2^T = \Sigma^T((P_{newt1} + \Delta P - M)N_1^T(1+r)^{-T}) - F_2 + N^T(P_t - C_t)(1+r)^{-T} \tag{9}$$

Where the variables of the equation are defined as:

P_t =Price of testing;

C_t = Marginal cost that is assumed fixed.

The firm will invest in R&D if and only if its profit with test is greater than the profit without test. However, the firm could have other additional costs to validate the link between the gene and the response or the reliability of the test that make testing unprofitable. In the same way, if the sample of damaged patients is expected large, an untargeted drug may be poor cost-effectiveness. If instead, firm obtains savings in R&D costs ($F_1 - F_2$) also if the final drug price is unchanged (ΔP_{newt}), it will continue to invest in novel testing. These type of savings may be possible if, for example, genetic testing permits phase II-III trials. Finally, we analyze the benefits of testing for payers through equation 10.

$$N_2(a_2 + P_{newt1}) > N_1\Delta P_{newt} + NP_t \tag{10}$$

If there are no adverse effects ($a_2 = 0$) and if the payers does not give to the company a price increases for the introduction of testing (ΔP_{newt}) = 0, testing is cost-effectiveness for payers if and only if the ratio of non-responders respect to the total population will be higher than the ratio of the price of the test respect to the price of the drug (indiscriminate treatment of all the patients (no testing)). In general the value of P_{newt} represents for companies the crucial threshold to decide if invest in new products using pharmacogenetics. However, if companies develop products for non-responders such that results a positive incremental cost-effectiveness below the cost-effectiveness threshold, may happen a rationing issues because payer expenditures will rise. In this case since payer budgets are constrained we will have a sub-investment respect to the optimal value.

3.2 Gene Therapy and Cancer: An economic evaluation starting from a study of Allogeneic Stem Cell Transplantation to care cancer in Children

Currently the cases of cancer in children are in increasing and they represent for the expensive therapies a growing economic pressure on the public healthcare system (Meropol *et al.* 2007; 2009). In this context, government agencies and insurance companies are both interested to maximize the resources and minimize costs in a

perspective of cost-effectiveness treatments. The allogeneic stem cell transplantation (SCT) is used to care patients with high-risk or relapsed leukemia, primary immune-deficiencies, and severe a-plastic anemia. This curative approach is expensive and involves various departments such as transplantation ward, intensive care unit, outpatient clinic, radiation clinic, cell collection unit, cell processing unit and different laboratories. The costs concern donor type, graft source, conditioning regimen, various unpredictable post-transplantation complications, need for medical care. We start from a study of Martin *et al.* (2012) on SCT data of patients followed in SCT outpatient clinic for at least 1 year after transplantation and if necessary readmit to the SCT ward collected from St. Anna Children's Hospital of Vienna in the period between 2004-2009. We perform the analysis by considering two type of costs: a) Overhead costs per diem in the transplantation unit (ICU) or outpatient clinic such as costs for human resources, housekeeping, maintenance, sterile nursing devices and disposable devices, parenteral nutrition, saline infusions, and supportive medications that are less than 5€ per patient per day, routine laboratory diagnostic tests (including viral and bacterial surveillance, fluorescence-activated cell sorting analysis) and chimerism testing; b) Individual patient costs during the first year after SCT such as information on chemotherapy, irradiation, antibody therapy, individual medications, surgical intervention, radiodiagnostics, and blood. According to Martin et. al (2012) the mean cost of pediatric SCT is equal to 163.174€. The major proportion of the cost is related to hospital days (43%), followed by costs for diagnostic procedures, including routine laboratory tests (19%); individual medications, including the conditioning regimen (13%); HLA typing plus graft acquisition (12%); and blood products (10%). The reimbursement of public hospitals by the provincial health funds is based on a modified system of diagnosis-related groups, with a specific number of credit points allocated to each defined medical intervention. The hospital received 186.747 credit points per SCT, with a monetary value of 0.83 per credit point. This is translated into a reimbursement nominal cost of 155.000€ per SCT and a mean real cost of one SCT of 163.174€ with an average deficit of 8.174€.

If we restrict the analysis to the sample analyzed by Martin et al. (2012) we have 141 children treated with age greater than 10 years and a cost of pediatric SCT equal to 136.97€.The analysis involves children with transplantation characteristics known before SCT to evaluate the predictability of the cost of an individual SCT. In this sample twenty-five of the 32 patients early relapse are long-term survivors, with a median cost of 2.922€ per life-year gained ($QALY_S$). If the patients are treated with chemotherapy and palliative therapy the subsequent costs are equal to 111.420€ per patient with 43.639€ per life-year gained ($QALY_S$) and only 2 of the 50 children survived for longer than 10 years.

By applying the model of Danzon *et al.* (2002) the allogeneic stem cell transplantation therapy is cost-effective respect to chemotherapy and palliative therapy for the payer if and only if the general condition of the model is satisfied. In this case given B_1 as potential payer benefit for chemotherapy and palliative therapy and as

potential payer benefit for the allogeneic stem cell transplantation therapy the payer general benefit condition is satisfied if $B_2 > B_1$ or:

$$N_2(a_2 + P_{STEMCELL}) > N_1\Delta P + NP_t$$

To simplify we assume $\Delta P = 0$ then the benefit payer condition is:

$$P_t < (N_2 / N)*(a_2 + P_{STEMCELL})$$

For the payer the maximum benefit price for the allogeneic stem cell transplantation therapy is:

$$P_t < (N_2 / N)* (a_2 + P_{STEMCELL})$$

By restricting the analysis to the only patients with malignant disease and- by considering TRM risk score as the sum of 3 risk factors: age>10 years, advanced disease, and donor other than matched sibling, resulting in 4 risk groups- we have:

1) TRM_1: Present patients = 46% with $N_2/N = 0.24$
2) Present patients = 31% with $N_2/N = 0.35$
3) Present patients = 11% with $N_2 / N = 0.8$

We exclude the case of TRM_0 from our analysis because there are not cases treated in the study of Martin *et al.* (2002).

The threshold risk score (cost per surviving) for each TRM is:

k_{p1} = Threshold risk score (cost per surviving) for =151.22€ which corresponds $QALY_S$ = 2.54€;

k_{p2} = Threshold risk score (cost per surviving) for TRM_2 = 270.51€ which corresponds 3.85€;

k_{p3} = Threshold risk score (cost per surviving) for TRM_3 = 1216.34€ which corresponds $QALY_S$ = 24.03€.

By assuming that there are no adverse reactions ($a_{1,2,3}$ =0) in the patient group that does not respond. If we assume that there are not extra-treatment costs, given $P_{STEMCELL}$ = 136.97€ and given the $P_{CHEMOTH}$ = 111.42€ then the maximum value of the therapy is:

$$P_{tTRM1} < 0.24*136.97€ \text{ or } P_{tTRM1} < 32.87€$$
$$P_{tTRM2} < 0.35*136.97€ \text{ or } P_{tTRM2} < 47.93€$$
$$P_{tTRM3} < 0.8*136.97€ \text{ or } P_{tTRM3} < 109.57€$$

In this case the price of the allogeneic stem cell transplantation therapy equal to 136.97€ is not cost-effective for all TRM risk score. The SCT therapy according to the study of Martin *et al.* (2012) clearly underlines the potential health gains to children that are affected of leukemia. However, in our study the Allogeneic Stem Cell Transplantation in Children is not cost-effectiveness to payers and manufacturers. In

our analysis SCT therapy is not worthwhile because the cost of the therapy is still too expensive for a too small fraction of patients in particular when they are treated patients with advanced cancer disease such as in the case of TRM risk score of 3 that needs of expensive care for a longer period. The causes of low benefits for payers of this therapy could depend on SCT pediatric costs per transplantation unit per year that may increase significantly due to low patient numbers and a heterogeneous patient cohort. Other causes are related to uncertainties that include the "hidden costs" for pediatric SCT, including out-of-pocket expenses and foregone income for the parents if the therapy is not effectiveness (Cohn *et al.*, 2003; Barr *et al.*, 2003). On a microeconomic level, the calculation of expected costs per SCT might be important for the negotiation of realistic reimbursement rates with governmental agencies or insurance companies, the allocation of resources, and cost control. It can also allow evaluation of the cost-effectiveness of defined changes in transplantation modalities or supportive care. Policy suggestion is that when therapy becoming feasible and, in all probability, supplied competitively by third parties, company will face smaller target populations. In some cases the resulting target population may be too small for the therapy to be commercially viable unless payers increase prices to reflect the increase in expected benefits per patient treated. In the absence of such price adjustments, patients who would have benefited may forgo treatment unless R&D costs for targeted therapy can be significantly reduced. Even with such adjustments, the patient population may be too small to enable R&D costs to be recovered.

3.2. Pharmacogenomic and Cancer Disease: An economic evaluation starting from a study on non-small cell lung cancer

Lung cancer is the leading cause of cancer-related deaths in the U.S. with over 150.000 deaths each year and direct medical expenditure for lung cancer equal to $12 billion in 2010 (National Cancer Institute, 2011). For both these reasons, more effective and cost-effective treatment strategies in lung cancer should be necessary. Targeted therapy by using pharmacogenenomic testing is a powerful strategy for cancer treatment and overcome drug resistance however the clinical and economic implications not always are clear (Gerber, 2008). The accumulation of knowledge about the differences between normal and cancer cells and differences among cancer cells has allowed for the development of new anticancer agents which target key molecules involved in cancer initiation, proliferation, differentiation, angiogenesis, survival, and invasion (Gerber, 2008; Hanahan and Weinberg, 2011; Luo *et al.*, 2009). The implementation of second-line therapy for advanced or metastatic non-small cell lung cancer (NSCLC) is a particularly important and challenging clinical and economic situation for two reasons: first, 80% of all lung cancer in the US is non–small-cell lung cancer (NSCLC) and second, these patients, by definition, are showing progression of disease despite ongoing, best available, first-line treatment. In addition to traditional chemotherapy, therapies targeting the epidermal growth factor receptor (EGFR) pathway are available for second-line therapy in advanced or metastatic NSCLC. It is shown that EGFR inhibitors,

which include gefitinib and erlotinib, increase survival in unselected patients in clinical trials respect to placebo (Shepherd *et al.* 2005; Mok *et al.* 2009). We start from a study of Carlson *et al.* (2009) on U.S data of patients affected of advanced (stage IIIB/IV) NSCLC who failed at least one platinum-based chemotherapy regimen and were eligible for treatment with Erlotinib in the second-line setting. We investigate about the benefits of epidermal growth factor receptor (EGFR) inhibitor testing before initiating second-line therapy for advanced refractory non–small-cell lung cancer (NSCLC) versus standard care (no testing). The price of Erlotinib for 150mg is equal to 2.98$, the cost of EGFR gene copy test is equal to 320$, number of patients that benefits of therapy is equal to 32.

We assume as hypothesis that there are no adverse reactions in the patient group that does not respond. Testing is benefit for the payer if and only if the following condition is verified:

$$N_2 / N > P_t / P_{ERLOTINIB} \; or \; P_{ERLOTINIB} > P_t / (N_2 / N)$$

This means that $P_{ERLOTINIB} > 320/0.68$ or $P_{ERLOTINIB}$ 470$

In this case, testing is clearly not effectiveness in economic sense compared to not testing and EGFR pharmacogenomic testing has not the potential to improve quality-adjusted life expectancy in the treatment of refractory NSCLC. Our analysis does not confirm Danzon *et al.* (2002) results. Given the high degree of uncertainty as to the relative effectiveness of these treatments, particularly in the genomic subgroups, our analysis needs of future comparative clinical trials data to confirm or not the optimal treatment in second-line NSCLC and the potential of pharmacogenomic testing.

CONCLUSIONS

Many people in early phase clinical trials have high expectations about the benefits from the research intervention (Ackerman, 1995). This happen in general when there is a diagnosis of terminal illnesses for which standard treatments are not effective, or when they are promoted new therapies (Churchill *et al.*, 1998). In this study we analyze two novel use of genomics such as gene therapy and pharmacogenetics in terms of cost-effectiveness and policy implications in the case of cancer disease. Gene therapy is in general related to early phase or phase I of experimental interventions that assess safety and side effects on small sample of patients. The empirical evidence demonstrates that these early phase studies hold far less potential for improved clinical outcomes for participants than phase II-III studies, which are designed to test the experimental intervention against standard treatment or placebo on a sample large enough to demonstrate whether the intervention is effective (Horstmann *et al.*, 2005). For this reason as it theoretically results from the model of Danzon *et al.* (2002) and afterwards with our analysis the private sector tends to sub-invest in gene therapy respect to optimal-value. The reasons consist in: a) Budget constraints that limit investments in long-lived therapies with high costs and small number of patients; b) Legislation that

is not neutral between once-a-day and long-lived therapies; c) The high uncertainty, high risk and the low probability of treatment's success that may reduce the private investments. The findings of the model are confirmed by our analysis on cancer disease. Public investments are in increasing in the development of gene therapies but still there are reimbursement constraints and drug laws limitations that reduce these interventions. It is therefore important to obtain the full social benefit not only to increase public funding but also raise the payer cost-effectiveness thresholds for monogenic diseases than other diseases. Unlike from gene therapy pharmacogenetics involves larger studies (phase II-III) designed to begin an evaluation of effectiveness at a dose level found to be safe, as well as to continue to test for safety and side effects. Effectiveness in phase II-III trials is often measured by changes in laboratory values that may be surrogates for clinically meaningful measures of how a patient feels, functions or survives (Temple, 1995).

The Pharmacogenetics is used to optimize drug therapy, with respect to the patients genotype, to ensure maximum efficacy with minimal toxicities and adverse drug reactions (ADRs). Through the utilization of pharmacogenetics it is possible to maximize the efficacy of a drug by deleting the costs of the patients who have lack of therapeutic response to a treatment (non-responders) or they are damaged (adverse responders). In this case the doctors taking into consideration the patient's genes, the functionality of these genes and how this may affect the efficacy of the patient's current and/or future treatments may reduce the trial error of prescription. The "personalized medicine" are optimized for each individual's unique genetic makeup. Pharmacogenetics may be applied to several areas of medicine such as Pain Management, Cardiology, Oncology, and Psychiatry. By analyzing pharmacogenetics in the case of cancer disease testing is in general not socially optimal and does not confirm the theoretical results of the model. This could depend on the small proportion of non-responders. We can have also two problems: a) Payers don't accept prices upward adjustments for targeted treatments also if they reflect the increase in expected benefits per patient treated; b) The number of potential treatments may be reduced despite the genetic testing reduces populations eligible for treatment but if prices are not adjusted it does not significantly reduce the costs of R&D. To sum up, it is clear that the two novel use of genomics can lead to innovative views to care chronic disease as cancer, multiple sclerosis, muscular dystrophy, heart failure after an ischemic episode and so on. However, since the sample of patients treated is too small and the costs of treatments are very high the cost-effectiveness effects in terms of positive policy implication remain still low. Pharmacogenetics and gene therapy both represent an high burden imposed on society. Many countries are currently discussing and debating how to create an adequate infrastructures to provide not expensive long-term treatment to people that suffer of neurodegenerative diseases. Policy-makers should may consider about how to manage these newly use of genomics into on-going national systems. This involves distributing responsibility among the public, private and third sectors as well as the family. Therefore, while there has been a move towards public support

to care chronic diseases still remain strong legal limitations that reduce companies investments in this field.

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