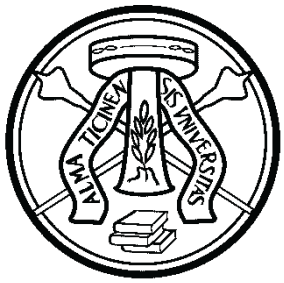

UNIVERSITA' DEGLI STUDI DI PAVIA & UNIVERSITA' DEGLI STUDI DI MILANO

(Joint Programme)

DEPARTMENT OF ECONOMICS AND MANAGEMENT

Philosophiae Doctor (PhD)

in Economics

Essays in Health Economics and Policy

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Thesis of Daniele Corso

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PhD thesis introduction:

Health represents one of the most important resource for society. In particular, good health translates into benefits for the whole society and for the overall economics system. Health and well-being are essential for economic and social development and represent a vital concern for every individual, their families and communities. On the other side, bad health depletes resources in all sectors. Allowing individuals to keep the state of their health and its determinants under control is a founding element of communities and a tool for improving their living conditions.

The good health and well-being of the population can be achieved more effectively if the entire government works to address all the social and individual determinants of health. Good health can support economic recovery and development. It works as a virtuous circle: good health leads to prosperous societies which implies better health and social conditions for individuals.

The direct and indirect effects of the health sector on the economy are significant: not only because it affects people's health and their productivity, but also because today it represents one of the largest economic sectors in all middle and high-income countries. In addition, the sector has always been an important research and innovation engine and a stimulus for competition between professionals, ideas and products. Its importance will continue to grow and, with it, the relevance of its contribution to the achievement of broader social objectives.

Unfortunately, not all counties moved in the same direction and at the same rate. Many groups and different areas have been left behind, and in many cases health inequalities within and between countries continue to grow. Ethnic minorities, some migrant communities and poor individuals represent the most vulnerable groups. Changes in disease, population dynamics and migratory flows can influence progress in health and well-being and require improvements in the management of its governance. The rapid growth of chronic diseases and mental

disorders, lack of social cohesion, environmental threats and financial uncertainties make improving health even more difficult and threaten the sustainability of health and social systems. Responses characterized by determination and innovation are needed. Policies differences has led to discrimination among people and, consequently, among countries.

The aim of my Ph.D. thesis is to deal with health care access through the analysis of two health systems completely different one based on private insurance, USA, and one based on National Universal Coverage, Italy.

The investigation of the USA system was based on the effects of the Affordable Care Act Reform of 2014 – also known as 'Obamacare' – whose aim was to improve access to health care, containing costs and reallocating expenditure. The analysis was carried out on two different levels: first to understand if, how, and how much more protected people tend to abuse from a public service rather than to enhance the benefit of the Reform. In the second part the objective was to understand if the reform resulted in a disparities reduction in health care access.

The second work was focused on Italian public universal health care coverage system. In the Italian scenario each Region may adopt different procedures to introduce a new drug in the market. Obviously, this implies disparities in new therapies access for patients and possible effects in terms of timeliness and expenditures. A preliminary investigation for the understanding of the system was necessary and, after the construction of a pool dataset, a two-step Generalized Linear Model was adopted: first, to investigate timeliness for Italian Regions and its determinants and, second, the influence of timeliness on the pharmaceutical expenditures and their control. Further developments of this research would aim to understand the effect of Regional structure on the total hospital expenditures, since increasing the steps for a new drug approval in the Italian market reduces the pharmaceutical expenditures but older therapies may have resulted into an increment of hospitalization costs.

A previous version of the first chapter of this thesis has been published in 2020 in the journal below.

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Drawbacks and aftermath of the Affordable Care Act: ex-ante moral hazard and inequalities in health care access.

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Abstract

Background: Following the introduction of the Affordable Care Act, various studies have tried to identify the effects of the Reform, without reaching a clear consensus. The aim of this study was to investigate whether expansion of the Medicaid program has led to less inequality in access to health care and to a higher level of ex-ante moral hazard.

Design and Methods: The analysis was conducted on two-year longitudinal data (2014-2015) regarding a cohort of 15,898 individuals from a Medical Expenditure Panel Survey (MEPS). After a data cleaning procedure, a sample of 9,255 individuals was selected for the inequality part of the study and 2,307 for the ex-ante moral hazard analysis. Propensity score matching with nearest-neighbour and kernel matching algorithms, difference-in-difference models and concentration index, corrected according to Erreygers methodology, were adopted.

Results: The analysis showed that disparities were reduced between social classes although the ex-ante moral hazard is a real problem with the Affordable Care Act since individuals covered by public insurance tended to abuse the public service. Among those who benefited from the Act, a reduction in preventive behaviours was observed: there was an increase in smoking and a decrease in level of physical activity. As far as access to health care is concerned, there was a decrease in inequality in emergency visits, but also inability to get care and getting care when needed among beneficiaries of the Reform.

Conclusions: This study demonstrates that the extension of Medicaid has had a dual effect: it reduced disparities in access to health care but, at the same time, it seems to have induced people to take less care of themselves.

(*The present version of this article has been improved and updated with respect to the published one)*

I – Introduction:

In the last years, the debate about the Affordable Care Act has been vigorous. For the first time, the US health system experienced a strong and revolutionary change with the extension of a public programme into a previously totally private system. The debate about the consequences of this policy is open since the effects are still unclear. The analysis reported here is an attempt to add another piece to the puzzle, highlighting some critical aspects from a different point of view in a field that is still controversial.

The concepts of ex-ante and ex-post activities are pillars of the health insurance market, being associated with the main risks for insurance coverage. According to health insurance models, having insurance coverage could undermine an individual's attempt to conduct a healthy lifestyle and preventive activities. This phenomenon is called ex-ante moral hazard [1]. The ex-post moral hazard takes place after the loss of health has occurred with an increment in health care use and/or sick leave [2].

While ex-post moral hazard in the health insurance market has been widely investigated, the evidence about ex-ante moral hazard and analyses of inequalities resulting from the expansion of Medicaid are scant. Medicaid was introduced during President Lyndon Johnson's mandate (1965), but its reform started in March 2010, when the Affordable Care Act (ACA) – also known as 'Obamacare' – was approved, with the final aims of improving access to health care, containing costs and reallocating expenditure.

The aim of this paper is to investigate the effects of the Affordable Care Act (ACA) expansion on the households' personal behaviours and social inequalities resulted.

The double-robust approach, in this study, is ensured by the combination between regression and propensity score. The hypothesis postulated is that the Medicaid expansion will lead to higher level of ex-ante moral hazard, with a

negative behavior, for that US households which benefit to the reform, basing on the principle that health insurance removes the financial consequences of illness. Moreover, a further investigation is conducted on the inequality distribution of health care access level. In detail, if the "Obamacare" enlarged or reduced the disparities among households in terms of health care access.

The rest of the study is organized as follow: Section II the US insurance market with the theoretical definition of the ACA reform, Section III a literature review, data adopted and methodology are presented in Section IV, the estimation of results in Section V and the results discussion and conclusions in Section VI and VII.

II – The US insurance market and Affordable Care Act (ACA):

The most important example of private health insurance market concerns US. The US system is characterized—as with health systems in most countries—by the ratio of private and public insurers funding the system. The uniqueness of US system relies on the dominance of the private element over the public one: coverage is provided mainly through private health insurance that is the largest component of the health care. It was estimated that only 23% of the US population are covered by a public health plan. These programs include Medicare, Medicaid, the Children's Health Insurance Program (CHIP), state-sponsored or other government-sponsored health plans, and military plans system [3, 4].

Medicaid and Medicare were ushered partially during the President Lyndon Johnson mandate (1965). The Johnson reform was focused on the expansion of free health care plants for low level income subjects. Nevertheless, the mismatch of health care expenditures and quality of services increment, was still present. In March 2010 the Affordable Care Act (ACA – also known as "Obamacare") was

approved, with the final aim to improve either the health care access, quality and contain costs.

The US health spending in 2014 and 2015 was accounted to be the highest share of GDP among the OECD countries (16.4% and 16.7% respectively). US public expenditures are almost the same as Italy, where a coverage free of charge for all the subjects from birth to death is ensured. According to the OECD studies the expenditures should increase, reaching 20% of GDP forecast in 2030 (OECD health statistics: http://www.oecd.org/health/).

Medicaid is founded at the federal and state levels, it is designed for all individuals and families with a low income and limited family resources and it has its own discipline and eligibility for patients according to the state.

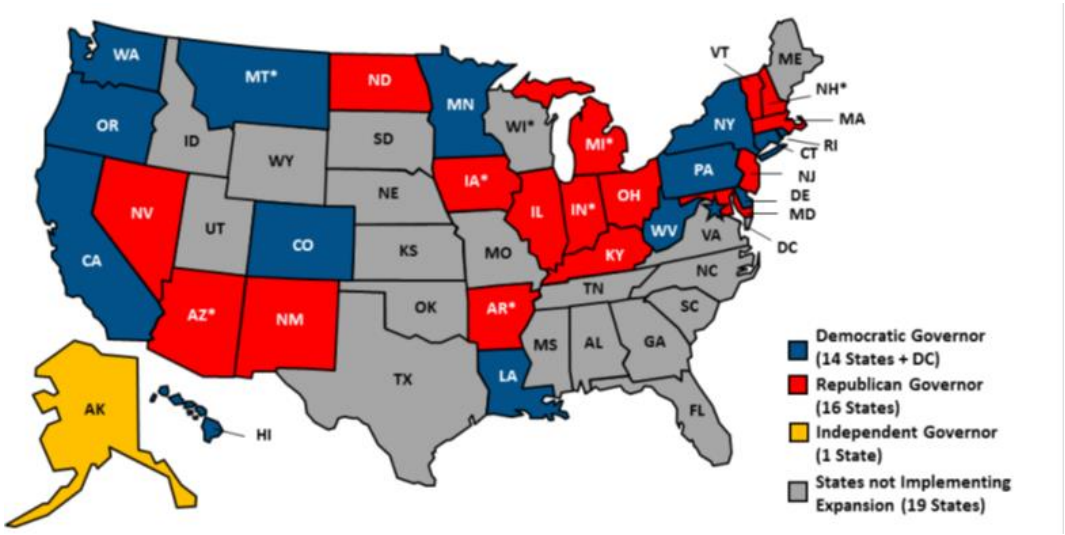
There are two possible ways for applying for Medicaid: through the Health Insurance Marketplace (HIM) or through the state Medicaid Agency.

As a result of the implementation of the ACA in 2014, Medicaid was expanded to a larger proportion of the population. First, the poverty threshold was raised from 100% to 133% and a tax credit premium was introduced for all people whose salary laid between 133% and 400% of the poverty threshold. As a consequence, the threshold to be considered poor passed from $11,489 per-subject per-year to $15,282$ after 2014. Secondly, employers with more than 50 employees were forced to supply insurance coverage; Thirdly, 'cherry picking' was forbidden and companies could not insure people based on their pre-existing conditions. According to the data for the sample of subjects that I studied, the increase in the poverty threshold more than quadrupled the number of people considered poor (from 529 in 2014 to 2,307 in 2015). Although the ACA came into force in January 2014, its implementation was not mandatory and nineteen states decided not to adhere[1] [5].

[1] In January 2020, 36 states and the District of Columbia out of 51 have adopted Medicaid expansion (https://www.kff.org).

Figure 1 presents the situation in 2014, highlighting all the states who implemented and adopted the Obama-extension and who did not, with a specific focus also on the Governor of that time.

Figure 1: US countries who implemented and adopted the Obama-extension and the ones who did not in 2014. Source: The Henry J. Kaiser Family Foundation



According to the ACA reform, the family/personal income and resources need to respect the limits. In the amount of resources are included: cash, bank accounts, retirement accounts, stocks and bonds, cash value of life insurance policies, other investments.

Table 2 highlights the ACA thresholds for being considered as "poor" before and after the ACA expansion (i.e. 100% and 133% of poverty line). In table below are reported also the earnings needed to deserve a tax credit premium for health plants available on the platform "healthcare.gov" (i.e. between 133% and 400% of poverty line).

Table 1: ACA upper limits for being eligible for Medicaid and for participating to the insurance online market.

House-hold Size	Premium Assistance Eligible under 5 year bar	Eligible for Medi-Cal (MAGI)			Eligible for Premium Assistance				
					Enhanced Silver Plan				
					Medi-Cal Kids Eligible (No PA)		Access for Infants and Mothers (AIM)*		
	<100%	100%	133%	138%	150%	200%	250%	300%	400%
1	$0-11,489	$11,490	$15,282	$15,900	$17,235	$22,980	$28,725	$34,470	$45,960
2	$0-15,509	$15,510	$20,628	$21,500	$23,265	$31,020	$38,775	$46,530	$62,040
3	$0-19,529	$19,530	$25,975	$27,000	$29,295	$39,060	$48,825	$58,590	$78,120
4	$0-23,549	$23,550	$31,322	$32,499	$35,325	$47,100	$58,875	$70,650	$94,200
5	$0-27,569	$27,570	$36,668	$38,047	$41,355	$55,140	$68,925	$82,710	$110,280
6	$0-31,589	$31,590	$42,015	$43,594	$47,385	$63,180	$78,975	$94,770	$126,360
7	$0-35,609	$35,610	$47,361	$49,498	$53,415	$71,220	$89,025	$106,830	$142,440
8	$0-39,629	$39,630	$52,708	$55,087	$59,445	$79,260	$99,075	$118,890	$158,520
For Each additional person, add		$4,020	$5,347	$5,588	$6,030	$8,040	$10,050	$12,060	$16,080

Source: https://www.healthcare.gov/medicaid-chip/getting-medicaid-chip/ and https://files.nc.gov/ncdma/documents/files/Basic-Medicaid-Eligibility-Chart-2019-.pdf

In Table 2. the first column indicates the number of people within a hypothetical family, i.e. the family size. A subject is considered as poor if s/he has a personal income lower than 11,489$ per year. After the Obamacare, the upper limit increased to 15,282$. The last six column represent the thresholds for all that subjects which are neither eligible for a public insurance nor able to afford a private one, but this is not the focus of this study.

III – Literature Review:

Incentive problems in insurance markets are well-established in economic theory. One of these incentive problems is related to reduced prevention efforts following insurance coverage. According to the health insurance model, insurance coverage could discourage individual lifestyle improvement and prevention activities. This phenomenon is called ex-ante moral hazard. The ex-ante moral hazard is the result of not having to pay for health care assistance, so people stop to take care about their healthy behaviours [1].

Some authors have postulated that public insurance plans could lead to less inequality in health care access [6,7,8,9] but to a higher level of ex-ante moral hazard, because of negative behaviours in those US households that benefit from the Reform [9,11,12,13]. The roots of this hypothesis lie in the principle that health insurance removes the financial consequences of illness, since expenditure for insured individuals who need healthcare assistance is no longer sustained privately by the person requiring the assistance.

In detail, at the beginning of 2000, Kenkel and Zweifel & Manning [14,15] started to introduce the concept of ex-ante moral hazard. Their perspective was that its burden and relevance was almost zero since the health insurance companies offer incomplete coverage packages.

In 2006 some authors started to dispel the myth about the role of personal behaviours (Dave & Kaestner [16]). These last two focused their attention on Medicare, in particular on the behaviour of all that subjects which switched from a private insurance to a public one. Their results give rise to a new wave of thoughts: the ex-ante moral hazard plays a key role.

Stanciole in 2008 [1] used the U.S. Panel Study of Income Dynamics with a representative longitudinal study of U.S. families. He took into account two waves: 2001 and 2003 with a balanced sample of 5,126 individuals. He estimated a structural model relative to few health personal behaviours such as smoking,

obesity and drinking alcohol. The results show that the presence of a private health insurance has a strong effect on the individual lifestyle choices. In particular, individuals with a private insurance adopt a better lifestyle and behavioural decisions.

Spenkuch in 2012 [7] dealt with the ex-ante moral hazard in a health insurance perspective. He suggested that the presence of insurances lead people to crowd out some precautionary activities, which instead in case of not-coverage they adopt. The study is focused on Mexican states and the overall conclusion is that, despite the economic theory, the ex.-ante moral hazard is not strong and significant. The main explanations could be that the sample, although composed by around 32 thousand observations, is not heterogeneous and is not able to capture the effect since only 19 out of 32 states adhere to the study. A second reason may be related to the short period observed, just few months. Finally, also the fact that the author consider only changes from the demand side, keeping fixed all the characteristic and constraints of the supply side.

In 2014, Qiun and Lu [17] investigated ex-ante moral hazard in China rural areas. In particular, they investigated if having a New Rural Cooperative Medical Scheme (NRCMS) encourages individuals to adopt some negative behaviours. The NRCMS is a universal healthcare coverage plan which, after its introduction in 2003, covers about 98% of rural residents in China. Their study is bases on a 9 years horizon (2000-2009) and it was based on China Health and Nutrition Survey (CHNS). Their conclusion was that, being covered by a rural insurance increases the probability of incurring in risky behaviours: smoking, drinking alcohol, eating fat food and being overweight. This study is one of the forefathers of the ex-ante moral hazard, unfortunately its relines is strongly related on the China market and they found few evidences between negative behaviours and participation on the NRCMS.

Barbaresco et al. (2015) [13] focused their study on young adults (i.e. 23-25 years old) demonstrating that the percentage coverage increased from 5.5% to 6.7%. As in this study, they focused on preventive care utilization, risky behaviours

and self-assessed health. The limits of this study are related to the selected cohort since it is based on a sample of young adult from a telephone survey. Though the adoption of difference-in-difference models in young adult cohorts they postulated from one side, that the coverage provision increases the probability of risky drinking in young adults and, on the other, that increasing the percentage of coverage does not have any correlation with positive preventive behaviours.

Sommers et al in 2016 [18] tried to start the first concrete steps of investigations regarding the healthcare access and prevention. Their analysis was based on three states (two of them implemented i.e. Kentucky and Arkansans and one did not, Texas). Their analysis has represented a turning point moving the attention from insured/uninsured to a wider view based on the concrete consequences of ACA reform. Indeed, the study was focused only on three states as representative of the whole US. Furthermore, the timeline was, as in this work, two years horizon, but very close to the reform. In this way the direct effect may not be immediately observable, sine also only 21% of eligible subjects took part to the study. The analysis was based on specific diseases, such as chronic diseases, depression and self-reported access to health and quality of care. Their conclusions are in line with the expectations: after the Obamacare reform more people passed from uninsured to insured (about 22% of individuals) and all these subjects reported higher level of health quality and access to care. The difference with the current study is at the sample level: here the whole USA, so all respondents, coming from different regions, are considered. So that, the sample is not based on regional characteristics, it is heterogeneous. Moreover, the health care access is based on, from one side on the emergency care and, on the other, on the prevention for all the diseases, not only for specific ones (i.e. the probability of subjects which go to the physician for any kind of prevention).

Furthermore, Cotti et al (2019) [11] investigated the effect of Medicaid expansion on the behaviour of the subjects in areas such as: smoking behaviour, alcohol drinking behaviour, snack-food and beverage drinking. They found very few evidence that the Medicaid expansion, in contrast with the previous literature, had a strong impact and, moreover, an impact in terms of ex-ante moral hazard. In

detail, they concluded that the number of smokers and cigarettes consumption has decreased after the reform.

Courtemanche et al. (2017)[2] [12] and Simon et al. (2017) [19] focused their attention on different outcomes, with specific focus on the self-reported health, the mass index and smoking behaviour. Courtemanche et al. (2017) discovered that the impact of ACA expansion had a positive effect in terms of insurance coverage and the access to care, but without a statistically significant proves for the consequent unhealthy behaviours. They estimated that the reduction of uninsured individuals has been reduced about 5.9%. The coverage advantages has been stronger for individuals with low level of education, unmarried and without children in house, Anyway, they do not find any evidence that the ACA reform crowed out the private insurance. Similarly, Simon et al. (2017) found that the self-assessed health has been improved by the Medicaid expansion. Maclean, Pesko, and Hill (2017) [20], in contrast with Courtemanche et al. (2017), found that, after the introduction of Medicaid, the number of prescriptions for smoking cessation drugs has increased.

Glied et al. (2020) [10] reviewed the evidence on the consequences of ACA extension in terms of law's effectiveness of reaching the goals postulated from the Reform. In detail, they proved that the Obamacare had the positive and substantial effects in terms of reducing the population risk of illness; moreover, the rate of uninsured individuals was reduced; it improved the access to care and it reduced also the private spending, as consequence of more public insured individuals [47].

According to the randomized control experiment some controversial results emerged. In detail, Baicker et al (2013) [21] run an experiment with 6387 adults who were randomly selected to be able to apply for Medicaid coverage and 5842 adults who were not selected. They applied different proxy measures for prevention as: blood-pressure, cholesterol, self-reported diagnoses, health status and health care utilization. They assumed random assignment to calculate the Medicaid effect. This

[2] The hypotesys were confirmed in the study extension Courtemanche, C., Marton, J., Ukert, B., Yelowitz, A., & Zapata, D. (2020). The impact of the Affordable Care Act on health care access and self-assessed health in the Trump Era (2017-2018). Health services research, 55, 841-850.

study demonstrated that the effect of passing from not being covered to having a public insurance, did not generate improvements in physical health outcomes. On the other side, an increase of health care services was demonstrated.

Taubman et. al. (2014) [22] and Finkelstein (2016) [23] investigated the effects on emergency use as Medicaid consequence. The formers studied the emergency department in Portland. Using a database of 25,000 participants in 18 months of observation, they demonstrated that Medicaid coverage has the effect of increasing the emergency use by 1 visit per person on average. Moreover, the increment in emergency visit use is typical for those conditions which may be treated in normal primary care. The latter run a similar random experiment in the Oregon scenario and they concluded that Medicaid increased emergency department visits by 40% in the first 15 months.

To the best of my knowledge, only two studies have focused on the impact of the ACA on socioeconomic inequalities in access to health care, showing a positive effect on access to health care, with greater equality in use of preventive services, quality of care and access to a doctor [6,7]. On the other hand, the Oregon Health Insurance Experiment suggested that the expansion of Medicaid did not have strong positive effects on reducing inequalities [24,21].

In the end, there is not a unique conclusion about the effects of the ACA Medicaid expansion. Indeed, as shown in this section, the results are still controversial. This lack of a common consensus, pushes the necessity to deepen this field, since the understanding of the Medicaid effects are relevant for improving the situation of low socio-economic status and poor people.

On the background of the lack of a common consensus in this field, the aim of this study was to shed light on the effects (drawbacks and aftermath) of the ACA on personal behaviours and possible inequalities in access to health care. Unlike previous studies, the analysis was performed on a heterogeneous dataset representative of the whole USA.

In my knowledge this is one of the first studies with this application, which have some benefits: first, the varied implementation of the ACA's Medicaid expansion across US households, allows to investigate how relatively low-income households' increased access to health insurance impacted certain risky health behaviours within the same household over time. Furthermore, relying on these data, this study will not suffer from the classical problems in self-reporting health, which is considered as misleading measures related to education (Choi & Cawley, 2018) [25], from one side, and problems such as incentives to give false answers, implicit value clues, wrong understanding of the scenario, on the other (Kanninen, B. J. 1995) [26].

IV – Design and Methods:

This project started in October 2019. Two-year longitudinal data, derived from responses to the Medical Expenditure Panel Survey (MEPS)[3] were analysed. Each MEPS panel is a subsample of the National Health Interview Survey (NHIS), with enrichment of information from low-income households. The MEPS provides information about expenditures, payments, different insurance plans and healthcare use, demographics, socioeconomic status, self-reported health and health care access. The period under investigation was between 2014 and 2015. The two-year period was selected because the MEPS provides information on a two-yearly basis and no comparison between panels is possible because of anonymization of data. The initial dataset contained records for 15,898 individuals; 92.1% of the respondents' information was available for both years and in the remaining 7.9% of cases only for one year due to death, birth or the person left the country.

After the data cleaning procedure, including elimination of individuals for whom complete, two-year information was not available, and through an interaction

[3]MEPS data started to be collected in 1996 and they are provided by the Agency for Healthcare Research and Quality (AHRQ).

between the poverty threshold and total personal income, a balanced dataset[4], was derived. All household members aged below 18 and above 65 years were excluded, since the former are eligible for other government health insurance programs (CHIP) and the Medicare program covers the latter. Finally, data from a sample of 9,255 individuals were selected for the inequality part of the study and data from 2,307 individuals were used for the behavioural analysis. The two datasets are connected, since the dataset containing 2,307 individuals represents a subsample of the 9,255 individuals. In detail, in the largest dataset either rich and poor individuals were included, by contrast in the smaller one only poor ones. The main analysis has been conducted on the second dataset, the smaller one, since the investigation was based on the effect of ACA on poor individuals. On the contrary, the inequality section concerns either rich and poor individuals, in order to investigate the effects of the reform in terms of gap between the two groups. Since privacy restrictions, no information about the state of provenience was available. In this way, data did not provide information if the household belonged or not to a state in which ACA reform was implemented. Individuals who did not have Medicaid insurance in 2014, but who were receiving this public healthcare coverage in 2015 after the rise in the upper limit to define poverty, were assumed to come from those states adhering to the new "Obamacare" policy (https://www.healthcare.gov/.). This procedure, obtained with the interaction between the poverty line threshold and the personal total income, allows to identify the individuals which benefited from the reform, since individuals whose income was between $11,489 and $15,282, before the reform they were not covered since the threshold was the former. After the reform, households which switched their condition from not having Medicaid coverage to having it, must belong to those states which, increasing the threshold, took part to the Obama policy. In this way, is possible to understand if the individual belongs or not to a state which adhere to the policy.

The variables considered in our analysis are reported in Table 2: *Race* represents a dummy variable which distinguished between white individuals and different minorities, grouped together; *Married* identifies whether the individual

[4]Characterized by the absence of missing values and the satisfaction of unbalanced conditions.

under observation was married or not in 2014 and/or 2015; *Years of education*[5][27] was assigned the value of zero if the individual had no education or, anyway, less then primary school level, then the score increased progressively; *Unemployment* identifies individuals without a job or the possibility of returning to work within the year of investigation; *Blood control, Breast exam, Check-up, Obesity, Junk and fat food eating, Low level of physical exercise, Smoking, Stroke, Heart attack,* and *High cholesterol level* are binary variables indicating specific behaviours, preventive and not, which an individual may adopt; *Self-assessed health*[6] is a categorical variable with a score ranging from 1 to 5; *Total personal income and Total family income* captures the individual's and family's income, respectively, in 2014 and 2015; *Medicaid insurance, Private insurance* and *Uninsured* are variables that document the type of insurance that the subject had or whether the individual did not have insurance coverage.

The study can be divided into two sections: a behavioural analysis and an inequality one (see Appendix 1 for further details). In detail, the former was performed in three different steps. Concerning the behavioural section, first, probit models were run to understand whether or not individual behaviours (i.e. *preventive behaviours, check-up, obesity*[7]*, smoking, health condition*[8] and *low level of exercise*) were influenced by demographic and social variables. The probit non-linear regression model was necessary as a first step to investigate the probability with which an individual may or may not develop a specific behaviour (i.e., the dichotomous dependent variable). Probit models were conceived for the analysis of individual choices since individuals often make choices between two distinct alternatives. The interpretation of probit coefficients was essential to understand

[5]The discrimination between high and low level of education was provided by Armstrong *et al.* (2014): below high school education, individuals are considered to have a low level of education. Thus, two dummy variables were generated for high and low level of education.

[6]Where 1=excellent health, 2=very good health, 3=good health, 4=fair health, 5=poor health. This means that the unitary marginal increment of Self-Assessed Health moves from a better condition to a worse one.

[7]This is calculated according to the Body-Mass Index (BMI) whose threshold for discriminating obese individuals is based on the international Body-Mass Index thresholds published by the NHS: for values above 30, the subject is considered obese.

[8]This variable expresses a series of negative health conditions: heart problems, high blood pressure, high cholesterol, stroke, diabetes, asthma, arthritis and cancer.

how the probability of adopting a specific behaviour varies. In probit models, the marginal effects, reported in Table 3, vary with the characteristics of the individuals. Based on the signs and significance of the estimated coefficients of the explanatory variables, it is possible to establish the effect on personal behaviours.

However, probit models cannot provide any information on the magnitude of policy effects. For this reason, the probit models' results have been propaedeutic for identifying those behaviours on which it was possible to observe an impact of the ACA[9]. Thus, second and third steps of the behavioural analysis, with the selected behaviours, was conducted. It aimed to define how and how much the expansion of Medicaid resulted in individual negative behaviours and the change in ex-ante moral hazard (i.e. *preventive behaviours, smoking* and *low level of physical activity)*. For this purpose, Propensity Score Matching (PSM) and Difference-in-Difference (DID) models were run (see page 23-28).

PSM reduces distortion, solving the problem of bias generated by confounding variables, and avoids problems of endogeneity[10], through the adoption of a double-robust approach by combining the regression analysis and propensity score[28]. PSM is intended to obtain pairing of cases and controls under randomization. The propensity score can be defined as the conditional probability of having experienced the Medicaid expansion, given all the observed demographic and social characteristics, which may determine the selection, in a region of common support[11][29,30]. Once the propensity score is computed, the process of matching, adopting nearest-neighbour and kernel matching algorithms, is provided by the so-called 'statistical twins' procedure, which is able to solve the problem of self-selection [31,32]. In detail, the algorithm provides 'statistical twins' that differ

[9] ACA is a dummy variable, calculated for each household, which is defined as the interaction between the poverty line threshold and the pre and post condition (between 2014 and 2015) of being covered or not by Medicaid insurance.

[10]Patients may adopt some specific behaviours because of lower income or their own individual characteristics.

[11]Matching procedures try to select, from the non-treated individuals, a group of controls in which the distribution of observed variables is as similar as possible to the distribution in the treated group. In other words, for any confounding variable value, both in treatment and control groups, a unit *i* can be observed

only for having or not having Medicaid coverage. Subsequently, the Average Treatment Effect of Treated (ATET) is computed for the two groups in order to understand the average impact of the ACA on personal behaviours [33].

After determining the average effect of the policy, the DID approach was used, as third step, to identify the true effect of the changing condition (treated vs. control) of Medicaid coverage, based on household income, before and after the expansion resulting from the ACA[12][34,35] (see page 29). The control group consisted of individuals not covered by the expansion of Medicaid, whereas the treatment group was formed by individuals who became beneficiaries of the ACA Reform. Of note, necessary and sufficient conditions[13] for the implementation of DID were respected [36]. In detail, it is reasonable to suppose that if in 2014 there had not been the Medicaid Reform, people would have not changed their personal behaviours. Thus, the DID (or 'double difference') estimator could be defined as the difference in average outcome in the treatment group before and after treatment minus the difference in average outcome in the control group before and after treatment [34].

Concerning last section of the analysis, the inequality investigation, carried out using the concentration index methodology [37,38], was focused on the effects of the ACA in terms of healthcare access. The aim of this analysis was to establish whether the ACA had a positive or negative effect in terms of degree of inequalities among US citizens, including very poor and rich people (9,255 individuals). Attention was focused on the gaps generated by the Reforms on health care access and the possibility of prevention (i.e. *prevention, outpatients' visits, getting care when needed, inability to get care* and *emergency visits)*. Inequalities related to socioeconomic status are rank-based measures. Since indicators for healthcare access are dummy variables, Erreygers (2009) suggested a correction of the base index version [39], which is able to compute inequality in healthcare access [40]. Healthcare access and services can be represented as a function of a person's need

[12]2014 is the pre-treatment period and 2015 indicates the post-treatment one.

[13] Similar dimension of groups, parallel trend assumptions and absence of systematic composition changes within each group.

for healthcare, the predisposition to use healthcare services and factors that enable or prevent the usage.

V – Results:

Table 1 shows the descriptive statistics for the low-income group (i.e. 2,307 individuals) and the whole sample. Individuals eligible for Medicaid were more frequently younger and female (67%) and their mean years of education after primary school was less than four. According to the methodology of Armstrong *et al.* (2014), these individuals are categorized as having a low level of education. In our sample, such individuals accounted for nearly one-third (n=645 subjects, 28%) of the whole cohort. It is supposed that individuals with a lower level of educations are likely to have lower salaries, and therefore, are less likely to buy out-of-pocket insurance.

About 9% of the subjects eligible for Medicaid insurance were married. With regard to ethnicity (White, 62%; Black 26%; Asian 7%; multiple ethnic groups 5%), Medicaid was extended to 185 new White subjects and 115 individuals from different ethnic groups.

In line with MEPS data, between 2014 and 2015, the number of unemployed decreased (from 1,695 to 1,597) and the percentage of insured increased in both the private and public sectors. According to the data, the number of individuals considered very poor and covered by Medicaid increased from 736 (31.9% of all individuals) in 2014 to 899 (39%) in 2015. Among the 2,307 individuals, 736 were insured before and after the Reform, 1,271 were uninsured before and after the Reform (i.e. the control group); and 300 subjects (13%), with the increase in the poverty threshold, gained Medicaid insurance (i.e. the treated group). It is worth noting that 18 individuals in the treated group (i.e. about 6% of this group) became smokers after the ACA came into force, 42 (14%) stopped physical activity, and 26

(9%) stopped taking care of themselves through the adoption of preventive behaviours.

When comparing the inequality sample (9,255 subjects) with the group of individuals with a low income, the average age, the percentage of married individuals (10% increase) and the average years of education (about 5 years after the end of primary school) were higher in the former group.

As expected, low-income individuals were more frequently covered by Medicaid or uninsured and less frequently owned private insurance. Furthermore, the average personal income in the low-income group was ten times less than that of the whole sample and the average family income was almost half.

As reported in Table 3, probit models showed a positive relationship between age and personal behaviours. In detail, between the two years of the Medicaid expansion, older people used more prevention, had more check-ups, had worse health conditions, were more frequently obese, performed less physical exercise and smoked less. Males did less prevention and had fewer periodic check-ups, with changes between the two years from about 4% to 9% and from about 11% to 14%, respectively. Males had higher levels of physical activity, they were less frequently obese and smokers. This might justify their better health conditions. Ethnicity played a key role (p-value < 0.001) for all the behaviours (i.e. obesity, smoking, check-up, health conditions and low level of physical activity) taken into account except for preventive behaviours. Having a low level of education had a negative impact in terms of obesity, smoking, low level of physical activity and health conditions. In other words, with a higher level of education the prevalence of smokers decreased, individuals were less obese, exercised more and suffered less from negative health conditions. Unemployment showed significant positive correlations with prevention and check-ups, negative correlations with smoking, physical activity and health conditions, and only a negative trend for obesity. In all cases self-assessed health was significant (p-value < 0.001), with a positive effect at the margin with preventive behaviours, check-ups, low level of physical activity, the incidence of obesity, smoking prevalence and negative health conditions for worse reported health.

The Obama Reform (ACA) had a significant impact at the margin in terms of preventive behaviours, smoking and low level of physical activity. According to the results of this study it can be inferred that having Medicaid coverage generates a reduction of prevention, increasing the negative behaviours of smoking and a sedentary life.

Figure 2 provides a graphical representation of the PSM procedure, showing data before and after the matching procedure. Despite the limited time horizon, PSM (Table 4) demonstrated that the ACA had strong effects on personal negative behaviours in the sample of low-level individuals. The Reform resulted in an approximately 8% increase in smokers, 12.5% reduction in physical activity and 4.3% decrease in individuals who used prevention between the two years under investigation.

These results were also highlighted with the DID approach (Table 5), although the impact with this model was weaker. As shown in the table, the expansion of Medicaid led to an increment in negative behaviours: 1,5% and 4,9% increases for smoking and low level of physical activity and a 1% reduction in the proactive behaviour of taking care of oneself ($p < 0.10$).

Table 6 reports the results of the inequality analysis. Medicaid increased disparities in preventive activities in favour of rich people (from 6.7% to 8%), in other words the gap between rich and poor individuals got larger between the two years. Outpatient visits, although not significant, remained stable over the two years (0.1%). Following the ACA Reform, disparities in Emergency visits increased, in favour of poor people, with an increment of 1.2%, which means that poor individuals are more protected in the case of emergencies, rather than in the case of prevention or regular check-ups. The disparity in inability to get care when needed, which was greater among poor people in 2014, decreased slightly between 2014 and 2015 (0.3%). Finally, the ability of individuals to get care when needed had a pro-rich distribution, in line with the expectations, since it is the reverse of the previous variable. Anyway, in this case the improvement among the poor was greater (2.8%).

VI – Discussion:

The aim of the study was to investigate the possible drawbacks and aftermath of the Medicaid Reform in terms of higher levels of ex-ante moral hazard and possible reduction of inequalities, given that the economic literature focusing on this field is limited and controversial.

Descriptive statistics of the low-income sample (i.e. 2,307 subjects), proved that individuals covered by Medicaid are more frequently younger and female, probably due to socioeconomic drivers. As already reported by Blau and Kahan (2006) and Angelov et al. (2016) these individuals have lower incomes because they are at the beginning of their career or because of the gender gap and, consequently, it is more likely for them to end up below the poverty threshold [41,42]. By contrast, there were few married individuals in this group, probably because the increase of income in a family reduces the possibility of obtaining public insurance coverage [43,44]. In line with MEPS data, between 2014 and 2015, the number of unemployed decreased (from 1,695 to 1,597) and the percentage of insured increased in both the private and public sectors (from 31.9% to 39%). As expected in the inequality sample (9,255 subjects), on average, individuals were older, more frequently married and had a higher level of education than low-income individuals. Among the 2,307 subjects in the low-income group, 736 individuals were insured before and after the Reform, 1,271 were uninsured before and after the Reform (i.e. the control group); and 300 subjects (13%) gained Medicaid insurance after the increase of the poverty threshold (i.e. treated group).

Through probit models, the ex-ante moral hazard was confirmed for *prevention, smoking* and *low level of physical activity*. Thus, from a general perspective older people, suffering from more physical problems, use more prevention and young individuals tend to smoke more for social acceptance [45] and because of a more stressful life [46]. In line with literature, race and gender had an impact in terms of prevention and personal behaviours. Ethnicity played a key role (p-value < 0.001) in all cases but prevention. The main explanation can be provided by the intrinsic characteristics of individuals. According to Cossrow and Falkner

(2004), in recent years there has been an increase in obesity among African-Americans and Hispanic/Mexican-Americans rather than Caucasian [47]; moreover, Giga et al. (2008) noted that all non-Caucasian individuals face fewer employment opportunities with the direct consequences of some negative personal behaviours [48]. Furthermore, individual lifestyles may generate some racial disparities (e.g. physical exercise ensures the possibility of obtaining social and educational results and incentives). In detail, Egli et al. (2011) studied these differences in college students and concluded that race differences provided significant differences in eight of 14 exercise motivations [49].

Higher levels of education had a positive impact on prevention and personal behaviours. This result confirms the analyses of Feinstein et al. (2006) and Fonseca et al. (2019), who concluded that more years of education lead to a higher level of health, with more years of schooling being associated with a reduction in reported poor health [50,51]. Unemployment reduced negative health conditions and increased the level of physical activity. The former effect could be explained by the characteristics of the sample: younger individuals have a higher probability both of being unemployed and of being in good health. The latter effect could be explained by the availability of more free time. Self-assessed health was in line with expectations: a lower level of reported health and higher level of prevention are observed more frequently in people with more negative health conditions and behaviours. In fact, individuals who feel worse tend to adopt more proactive behaviours to change their negative condition and, at the same time, they represent that part of the population in a disadvantaged health state. Finally, having Medicaid coverage generated a reduction of prevention and increased negative behaviours such as smoking and a sedentary lifestyle. This is in line with literature: individuals covered by public insurance, relieved of personal expenditure on health, tend to abuse the public service, acquiring some negative behaviours (i.e. ex-ante moral hazard) [6,8].

Probit models cannot provide any information regarding the magnitude of an individual's negative behaviours and changes in ex-ante moral hazard after implementation of a new policy. Thus, adopting PSM and DID methodologies, a

second analysis was conducted on those behaviours for which the ACA had been seen to have an impact (i.e. *preventive behaviours, smoking* and *low level of physical activity)*. Despite the limited time horizon, in the sample of low-income individuals, PSM demonstrated that the Medicaid expansion had strong negative effects on personal behaviours, with an increase of smokers, and reductions in physical activity and prevention. Importantly, smoking and physical exercise are two behaviours that people can change immediately. Therefore, the PSM procedure was able to capture ($p < 0.05$) the proactive negative behaviour and the reduction in prevention. These results were confirmed by the application of DID.

Finally, the concentration index was used to evaluate any inequalities generated by the Reforms on access to healthcare and the possibility of prevention (i.e. *prevention, outpatient visits, getting care when needed, inability to get care* and *emergency visits)*. Differently from Kino and Kawachi (2018), in this study, Medicaid coverage increased disparities in *preventive behaviours* in favour of rich people, due to the fact that implementation of the ACA increased both the demand and supply sides [7]. Garthwaite (2012) proved that as public programmes increased the number of individuals with health insurance, the number of hours of assistance spent with a single patient decreased [52]. Consequently, rich people, taking advantages of their private plans, may benefit from the healthcare system more than poor individuals. The tendency to use emergency care would expect to be reduced after he Medicaid extension substituting with ordinary care. By contrast, when dealing with *emergency visits,* the ACA favoured poor people, protecting them better in the case of emergencies. Reductions in disparities were also observed when the *inability to get care when needed* and *getting care when needed,* were considered. In line with Finkelstein et al. (2016) emergency care usage increased after the reform. Reasons may be multiple: a. new Medicaid patients had not yet established a contact with their physicians; b. new insured individuals increase their care in different settings; c. increasing the number of insured, Medicaid may encourage emergency care usage [23]. Although Medicaid should reduce disparities, improving the healthcare status of poor individuals, the concentration index demonstrated an increase of benefits in daily and normal care even for rich people, because of spill over and indirect effects.

VII – Conclusions

The final aim of the ACA – also known as 'Obamacare' – was to improve access to health care and to increase the number of individuals covered by public insurance.

Through the analysis of two-year longitudinal data (2014 - 2015) provided by the MEPS and the implementation of econometric strategies (probit models, PSM, DID models and the concentration index), I observed that the ACA had a dual effect: on the one hand, personal negative behaviours increased, specifically less prevention, more smoking and lower levels of physical activity; on the other hand, disparities were reduced in the case of emergency care with indirect benefits in daily and normal care also for rich individuals.

In conclusion, the ACA produced a paradox: the pursuit of better healthcare leads individuals to take less care of themselves

Appendix – Models' empirical specifications

I – Propensity Score Matching (PSM)

The PSM is a statistical technique which has the aim of measuring the effect of a policy, called treatment. It is based on the evaluation of covariates which predict treatment being received. This methodology can solve the problem of bias generated by the confounding variables (i.e. variables which are correlated either with the dependent and independent variables, generating spurious associations) [33, 52].

In principle, a simple regression for estimating the impact is sufficient:

$$(1) \qquad prevention_i = \beta_0 + \beta_1 ACA_i + \beta_2 X_i + \varepsilon_i$$

where ACA which assumes value 1 if the individuals is covered by Medicaid and 0 otherwise, and Xi are all the variables that which may affect the preventive or negative individual behaviour (income, age, gender, etc), ε_i is the error term.

However, including these controls in a regression specification, and at the same time including ACA dummy variables may lead to endogeneity problems (i.e. predictor variables are correlated with the error term).

Indeed, patients may adopt some specific behaviours because of lower income or for their own individual characteristics. So, the double-robust approach is ensured by the combination between regression and propensity score [28].

According to the data, control variables can be grouped as: demographic variables (age, sex and region) and social variables (years of education, marital status, personal income, unemployment status).

Thus, a probit regression is performed. The form is presented below (2):

$$(2) \quad treatment_i = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + ...(+\gamma_1 X_{1i}^2 + \gamma_2 X_{2i}^2 + ...) + \varepsilon_i$$

On the left hand side, the probability of receiving the treatment and on the other side all the covariates which determine the selection.

In the current case the binary treatment indicator is represented by having or not experienced the ACA expansion (=ACA). On the other side all the covariates which can be observed are expressed within the vector Xi. In detail, Xi contains: age, sex, race, region, marital status, personal income, education, unemployment and self-assessed-health. So the propensity score can be defined as the conditional probability of the treatment, given all the observed characteristics [29].

$$(3) \quad E(x) = \Pr(ACA = 1 \mid X = x)$$

The matching methodology assumes that all the differences between the two groups can be captured by the observable control variables. Matchings tries to select from the non-treated individuals, a group of control in which the distribution of observed variables is as similar as possible to the distribution of the treated group. This implies that matching must be performed on a region of common support [30].

The propensity score is the predicted value of the treatment. An important requirement is that the model for treatment, above specified, has not to deal with variables which may affect the participation in the treatment (i.e. or time invariant or variables which are not affected by anticipation of participation) [33]. In other words, the propensity score is the probability of a household to be assigned a specific treatment given all the covariates which may determine the selection.

Finally, the outcome is fixed as: smoking behaviours, low level of physical exercise and preventive behaviours. Once the propensity score is computed, the process of matching is provided by the so-called "statistical twins" procedure. In detail, the algorithm provides statistical twins which are different only in sense that one of the twins is covered by Medicaid and the other is not. This procedure can solve the problem of self-selection. Nearest-Neighbour and Kernel (with caliper 0.5) matching were chosen as matching algorithms. In detail, differently from the first approach (i.e. Nearest-Neighbour methodology) the second uses the maximum amount of data and the imposition of a tolerance threshold avoids the risk of bad matches [31,32].

The Average Treatment effect of Treated is calculated (ATET) and computed for the two groups [33]. Moreover, the common support restriction is adopted. This option implies that the test of the balancing property is performed only on the observations whose propensity score belongs to the intersection of the supports of the propensity score of treated and controls. Thanks to the common support property the quality of the propensity score increases for the estimation of the ATET.

II – Difference-in-Difference (DID)

The third part of the analysis is based on models called Difference-in-Difference models [34,35], where the identification comes from changes in Medicaid availability due to state-level Medicaid expansions which took place in January 2014 for many states of US (although 19 states did not adopt the new policy), among households likely eligible for Medicaid versus households likely ineligible for Medicaid, based on household income.

According to data, two groups are generated:

- Control Group (C): individuals who have not received the treatment, so individuals who are not covered by the Medicaid extension (i.e. all individuals who belong to those states which did not increased the coverage to 133% of poverty line). T = 0
- Treatment Group (T): individuals who, instead, experienced the treatment, so subjects who took part in the ACA reform. T = 1

Furthermore, individuals are observed in two periods, t = 0,1 (in detail 2014 and 2015). 2014, and so time 0, indicates the time before the policy introduction, i.e. pre-treatment; by reverse, 2015, so time 1, indicates the time in which the policy has been introduced i.e. post-treatment.

The outcome Yi (with i=1..N) can be obtained with the following equation:

(4) $$Y_i = \alpha + \beta T_i + \gamma t_i + \delta(T_i \cdot t_i) + \varepsilon_i$$

Where the coefficients α, β, γ, δ are the unknown parameters and εi represents an unobserved, random error term which contains all the determinants of Yi which are omitted from the mode [36].

In detail,

- α: represents the constant
- β: represents the treatment group effect (it is able to capture the average permanent difference between treatment and control).
- γ: is a common factor, according to the parallel trend assumption, either in the control and treatment group and represents the time trend
- δ: represents the true treatment effect

In detail, Y_i represents the ex-ante moral hazard of the individual *i* at time *t*. The purpose is to determine the true effect, δ.

The assumptions for having an unbiased estimator are respected in the current study (i.e. similar dimension, parallel trend assumptions, absence of systematic composition changes within each group). The parallel assumption violation takes place when something, other than the treatment, changes in one of the two groups but not in the other. In detail, according to the literature and common knowledge, it makes no sense to suppose that in 2014 if there had not been the Medicaid reform, people would have changed their behaviours both with respect to ex-ante moral hazard and with preventive behaviours. In this way the Achilles' heel of DID is not violated. However, DID analysis presents the limit of time horizon, since only two years were analysed.

In this way, equation 4 can be used to determine expected values of the average outcomes:

$$
\begin{aligned}
E\left[Y_0^T\right] &= \alpha + \beta \\
E\left[Y_1^T\right] &= \alpha + \beta + \gamma + \delta \\
E\left[Y_0^C\right] &= \alpha \\
E\left[Y_1^C\right] &= \alpha + \gamma
\end{aligned}
\tag{5}
$$

The difference in difference (or "double difference") estimator can be defined as the difference in average outcome in the treatment group before and after

treatment minus the difference in average outcome in the control group before and after treatment: literally a "difference of differences" [34].

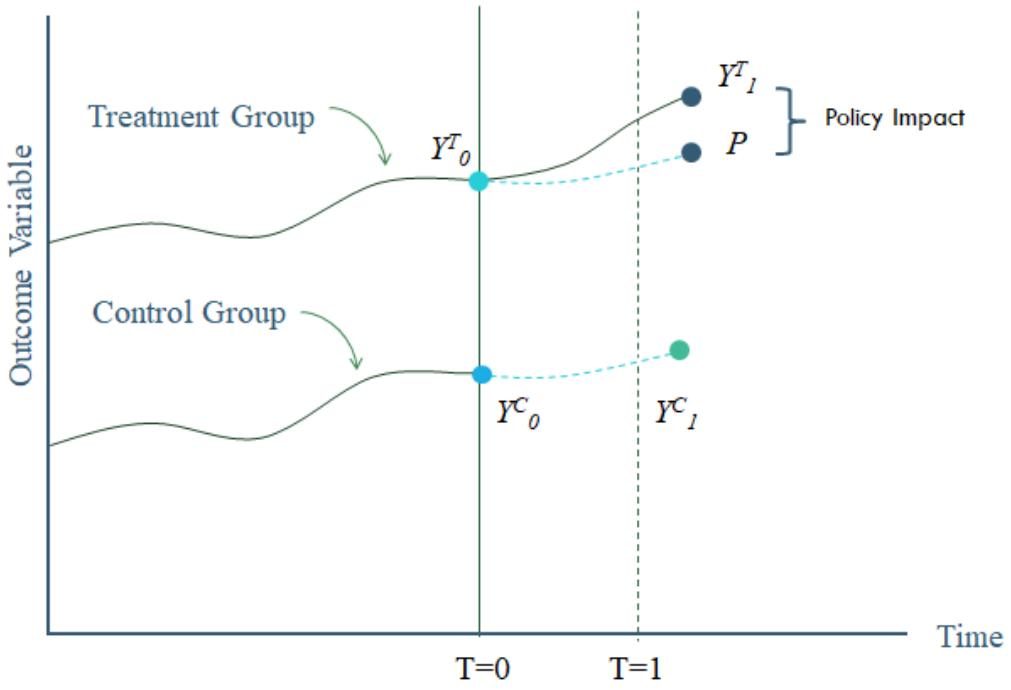
$$\hat{\delta}_{DD} = \bar{Y}_1^T - \bar{Y}_0^T - \left(\bar{Y}_1^C - \bar{Y}_0^C\right) \tag{6}$$

Taking expectations:

$$\begin{aligned} \delta_{DD} &= E\left[\bar{Y}_1^T\right] - E\left[\bar{Y}_0^T\right] - \left(E\left[\bar{Y}_1^C\right] - E\left[\bar{Y}_0^C\right]\right) \\ &= \alpha + \beta + \gamma + \delta - (\alpha + \beta) - (\alpha + \gamma - \gamma) \\ &= (\gamma + \delta) - \gamma \\ &= \delta \end{aligned} \tag{7}$$

Figure 3 below provides a graphical representation of the DID effect:

Figure 3: Difference-in-Difference graphical representation



In the above graphical representation, the outcome, and so the effect of the policy on the ex-ante moral hazard, is represented by the line “Treatment Group”. By reverse, the outcome of the control group (i.e. the effect of not having experienced the Obamacare expansion on the individual behaviours), is represented

by the line “Control Group”. The dependent variable is firstly measured before the introduction of the policy, this means at time 0 (T=0), indicated by Y_0^T and Y_0^C. After the healthcare reform, at time 1 (T=1), both groups are again measured, identifying points Y_1^T and Y_1^C. The idea behind is that not all the difference between the two new equilibrium points can be explained by the policy introduction. This is based on the principle that the two groups (treatment and control) did not start out at the same point in the first period of observation, i.e. T=0. The Difference-in-Difference algorithm calculates the trajectory if no policy had been introduced, in figure point P. It is important note that Y_0^T P and Y_0^C Y_1^C have the same slope. The real treatment effect is represented by the difference between the actual (i.e. observed outcome) and the normal trend outcome, i.e. Y_1^T - P.

III– Concentration Index (CI) and Erreygers Correction

Finally, the last part is focused on the investigation, legitimation and quantification of inequality across individuals before and after the Medicaid expansion. In this section not only very poor are included in the analysis but also rich people. According to the data cleaning performed at the beginning, 6,948 observations are included, starting from the 2,307 of previous sections. The total number of individuals analysed in this section is 9,225.

In order to measure the health care access disparities across individuals, direct measures, in detail disposable income, is necessary for the measurement of living standards. The analytical tools for measuring the socioeconomic-related inequalities are rank-based measures.

Before the real application of the Index, a global view can be provided by concentration curves. Inequalities continue to be consistent between different socioeconomics groups, in particular poor people have less possibility of accessing health care than rich people. The concentration curves yield an inequality distribution graphical representation. The Lorenz curve is a graphical instrument which is able to provide a graphical representation of the actual distribution of income and, consequently, of health. From a theoretical point of view, the main diagonal represents the perfect equality between the two groups (i.e. at any point the cumulative income is exactly equal to the cumulative population). However, the mere fact that the concentration curve lies above or under the perfect distribution line does not logically mean that the dominance is consistent or not. In particular the Gini coefficien (ranged between zero and one) represents the area between the perfect line of equality and the actual distribution, the higher the index, the higher the inequality [53]. So, there is one-to-one correspondence between the Lorenz curve and Gini coefficient:

- With perfect equality in distribution the Gini coefficient is exactly equal to zero and the Lorenz curve coincides with the main diagonal.
- With perfect inequality the Gini coefficient is equal to one.

Although useful for a general representation of the inequality, concentration curves are not able to yield a measure of the inequality [54]. This leads to the necessity of using a more accurate tool: the concentration index. In general, the concentration index is capable of capturing the degree of the inequality [37,38].

Inequalities (and inequities) in health care access are calculated by means of the concentration index (CI) [38]. According to the O'Donnell O. at al. (2008) [55] definition, the concentration index represents "twice the area between the concentration curve and the line of equality (the 45-degree line)". Hence, we face concentration index equal to zero in a situation in which there is no socioeconomic-related inequality. Conventionally, when the concentration index assumes a negative value, this implies that the concentration curve lies above the perfect distribution curve. In this condition we face a disproportionate concentration in favour of poor people. Reversely, a positive value means a disproportionate concentration in favour of rich people [37].

Formally:

$$CI = \frac{2}{n\mu}\sum_{i=1}^{n} Y_i r_i - 1 = \frac{2}{\mu}\mathrm{cov}(Y_i, r) \tag{8}$$

According to O'Donnell O. et al. (2008) and the general definition of concentration index, equation (8) can be explained as follows: μ represents the healthcare access mean sample, n represents the size of the sample, Y is an indicator of health care services by individual i and R_i describes the i^{th} rank of the individual within the distribution of the wealth index. The index value can be defined as two times the covariance between, on one hand, the health care access indicator (Y_i) and, on the other, the living standard rank of each individual (R_i), which is divided by the access average (μ). Finally, everything is multiplied by 2, ensuing to the concentration index to vary in an interval between -1 and +1 [53,54]. In the three extreme situations:

- if the concentration index assumes the value +1 means that the health care access is concentrated mainly among rich individuals.
- by contrast, if it assumes the value -1 this means that is pro-poor.
- finally, if it assumes 0 as value, this implies a perfect distribution.

Since the indicators for health care access are distributed between 0 and 1 (dummy variables: i.e. healthcare services utilization yes or no), Erreygers (2009) suggests a correction of the base index version which is able to compute inequality in health care access [40].

This index is defined as:

$$E(Y) = \frac{4\mu}{(b_n - a_n)} C(Y) \quad (9)$$

Where b_n and a_n represent the maximum and the minimum of the health care access variable (Y) (in our case 0 and 1), μ is the health care variables mean in the population, and *C(Y)* represents the concentration index specified before [39,40,55].

In order to compute the inequality index, the estimation of the determinants of health care access for both 2014 and 2015 and a study of the trend a probit model is required, where the independent variable is represented by the total disposable income. On the other hand, the dependent variable is a dummy (i.e. binary) variable, which assumes value one if there is health care access and zero otherwise.

In this view, to consider both the personal possibilities and also the public assistance, as dependent variables: outpatients visits, inability to get care, emergency visits, got care when needed and the possibility to benefit of preventive periodic controls.

The idea behind this study is to compute the inequality index in healthcare access, looking at the individual, before and after the reform described above.

Thus, healthcare access and services can be represented as a function of a person's need for healthcare, the predisposition to use health care services and factors that enable or impede the usage. Hence, three dimensions can be defined to categorize the independent variables engaged in the demand for health care services prediction as suggested by Di Novi, Piacenza, Robone and Turati in 2015:

1) need factors: this factors are strictly related to the individual characteristics and health status (age, sex, health conditions, self-assessed health). The health condition variable is composed by: had or not a stroke or heart attack in the current year, suffering of diabetes, having a cancer, high level of cholesterol and high blood pressure;

2) social characteristics also known as "predisposing factors" (education and marital status). In the marital status variable, a dummy variable is generated and, in particular, married category is used as reference category, all the other categories are: divorced, single and widowed. For the education category, three levels are taken into account:
    a. low education;
    b. medium education, reference category;
    c. high education;

3) enabling factors (private health insurance, employment status, and wealth).

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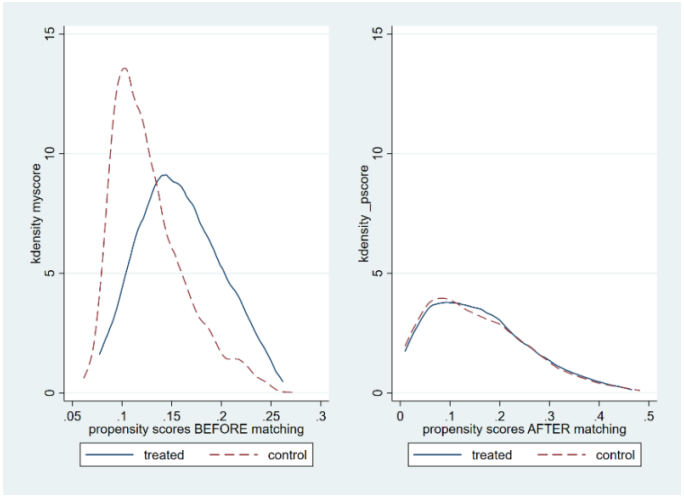
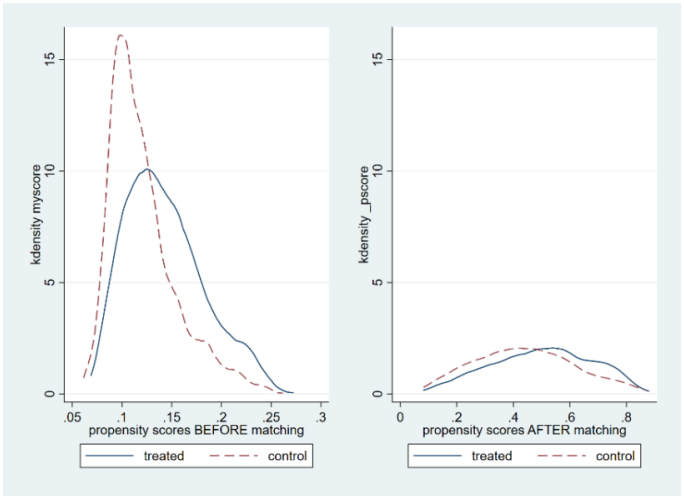
Figure 2: Distribution of individuals (treated vs not-treated) before and after the propensity score matching procedure.

A. Smoking



B. Low Level of Physical Activity



C. Preventive Behaviours

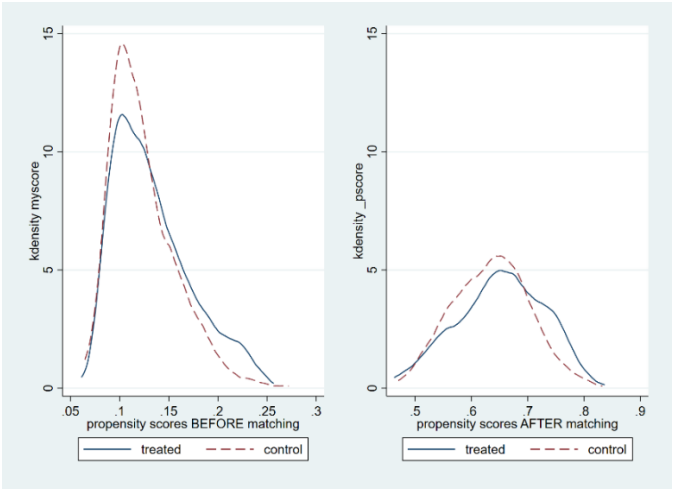


Table 2: Variables, Mean and Standard Deviation of low-income individuals and whole US sample – 2014 and 2015

	Low-income individuals				*Whole US sample*			
	2014		*2015*		*2014*		*2015*	
Variable	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**
Age	35.5722	14.4258	36.5722	14.4258	40.1844	13.2567	41.1844	13.2567
Sex	0.3303	0.4704	0.3303	0.4704	0.4708	0.4992	0.4708	0.4992
Race	0.6242	0.4844	0.6242	0.4844	0.6674	0.4712	0.6674	0.4712
Married	0.3424	0.4746	0.35215	0.4776	0.4629	0.4986	0.4736	0.4993
Years of Education	3.7642	2.0121	3.7642	2.0121	4.8567	2.3947	4.8567	2.3947
Unemployment	0.7350	0.4414	0.6922	0.4617	0.2922	0.4548	0.2886	0.4531
Blood Control	0.7282	0.4450	0. 7152	0.4514	0.7431	0.4370	0.7051	0.4385
Breast Exam	0.3026	0.4595	0.3108	0.4629	0.2790	0.4485	0.2824	0.4502
Check Up	0.6030	0.4894	0.5961	0.4908	0.6001	0.4899	0.6159	0.4864
Obesity	0.3237	0.4680	0.3213	0.4670	0.3231	0.4667	0.3316	0.4708
Junk and Fat food Eating	0.2744	0.4463	0.3130	0.4638	0.3059	0.4608	0.3335	0.4715
Low level Physical Exercise	0.3658	0.4818	0.4109	0.4921	0.3922	0.4827	0.4217	0.4939
Smoking	0.0997	0.2997	0.0863	0.2808	0.0735	0.2609	0.0727	0.2597
Stroke	0.0269	0.1618	0.0325	0.1774	0.0213	0.1447	0.0216	0.1560
Heart Attack	0.0212	0.1442	0.0256	0.1579	0.0184	0.1343	0.0216	0.1454
High Cholesterol Level	0.1964	0.3973	0.2172	0.4124	0.2228	0.4161	0.2460	0.4307
Self-Assessed Health	2.5067	1.1781	2.5267	1.1317	2.3407	1.0555	2.3412	1.0407
Total Personal Income	3168.248	3786.913	4679.147	4958.745	31268.03	35171.14	32806.87	35652.18

Total Family Income	39225.84	46826.14	40677.20	46558.95	63040.5	57794.99	65105.43	58784.02
Medicaid Insurance	0.3191	0.4662	0.3897	0.4878	0.1498	0.3569	0.1921	0.3940
Private Insurance	0.2679	0.4430	0.3016	0.4591	0.5213	0.4996	0.5679	0.4954
Uninsured	0.2618	0.4397	0.2280	0.4196	0.1957	0.3967	0.1655	0.3717
Individuals	*2,307*		*2,307*		*9,255*		*9,255*	

Table 3: Probit models marginal effect results

	2014			2015		
A. Preventive Behaviours	Coeff.	Std.Err.		Coeff.	Std.Err.	
Age	0.0021	0.0007	***	0.0042	0.0006	***
Sex	- 0.0364	0.0204	*	- 0.0873	0.0195	***
Race	0.0096	0.0200		0.0165	0.0193	
High Education	0.0197	0.0202		0.0326	0.0196	*
Unemployment	0.0405	0.0216	*	0.0044	0.0201	
Self-Assessed-Health	0.0370	0.0089	***	0.0443	0.0089	***
ACA	- 0.0565	0.0291	**	- 0.0301	0.0290	*
B. Check-Up	Coeff.	Std.Err		Coeff.	Std.Err	
Age	0.0028	0.0007	***	0.0040	0.0007	***
Sex	- 0.1083	0.0198	***	- 0.1438	0.0193	***
Race	- 0.4954	0.0199	**	- 0.0444	0.0196	**
High Education	0.0137	0.0201		0.0443	0.0196	**
Unemployment	0.0720	0.0213	**	0.0363	0.0208	*
Self-Assessed-Health	0.0589	0.0086	***	0.0689	0.0089	***
ACA	0.0243	0.0297		- 0.0026	0.0286	
C. Obesity	Coeff.	Std.Err		Coeff.	Std.Err	
Age	0.0011	0.0007		0.0007	0.0007	
Sex	- 0.1213	0.0200	***	- 0.1296	0.0198	***
Race	- 0.0582	0.0190	**	- 0.0273	0.0192	
High Education	- 0.0760	0.0196	***	- 0.0491	0.0196	**
Unemployment	- 0.0090	0.0207		- 0.0276	0.0206	
Self-Assessed-Health	0.0438	0.0090	***	0.0477	0.0090	***
ACA	0.0211	0.0281		- 0.0035	0.0284	
D. Smoking	Coeff.	Std.Err		Coeff.	Std.Err	
Age	- 0.0003	0.0005		- 0.0011	0.0004	**

Sex	- 0.0599	0.0139	***	- 0.0474	0.0131	***
Race	- 0.0272	0.0122	**	- 0.0473	0.0117	***
High Education	- 0.0453	0.0122	**	- 0.0584	0.0129	***
Unemployment	- 0.0405	0.0132	**	- 0.0212	0.0122	*
Self-Assessed-Health	0.0217	0.0059	***	0.0232	0.0059	***
ACA	0.0410	0.0179	**	0.0505	0.0168	**

E. Health Conditions	Coeff.	Std.Err		Coeff.	Std.Err	
Age	0.0092	0.0006	***	0.0093	0.0006	***
Sex	- 0.0976	0.0179	***	- 0.0911	0.0181	***
Race	- 0.1066	0.0167	***	- 0.1060	0.0172	***
High Education	- 0.1396	0.0171	***	- 0.1315	0.0176	***
Unemployment	- 0.1146	0.0182	***	- 0.0781	0.0192	***
Self-Assessed-Health	0.0520	0.0079	***	0.0480	0.0086	***
ACA	- 0.1147	0.0182		- 0.0247	0.0266	

F. Low level of Physical Activity	Coeff.	Std.Err		Coeff.	Std.Err	
Age	0.0026	0.0007	***	0.0023	0.0007	**
Sex	- 0.1812	0.0195	***	- 0.2031	0.0193	***
Race	- 0.0562	0.0193	**	- 0.0228	0.0193	
High Education	- 0.0513	0.0193	**	- 0.0329	0.0201	*
Unemployment	- 0.0642	0.0208	**	- 0.0272	0.0214	
Self-Assessed-Health	0.0586	0.0086	***	0.0618	0.0092	***
ACA	0.0716	0.0290	**	0.0741	0.0291	**

Number of individuals: 2,307

*Note: *** indicates p <0.001, ** indicates p <0.05 and * indicates p <0.1*

Table 4: Propensity score matching for preventive behaviours, smoking and low level of physical activity

	Nearest-Neighbour			Kernel		
	Preventive Behaviour	*Smoking*	*Low level of Physical Activity*	*Preventive Behaviour*	*Smoking*	*Low level of Physical Activity*
Average Treatment Effect on the Treated (ATET)	- 0.061 (0.040) *	0.077 (0.037) ***	0.109 (0.060) ***	- 0.043 (0.033) **	0.080 (0.012) ***	0. 125 (0.029) ***
Number of individuals: 2,307						

*Note: *** indicates p <0.001, ** indicates p <0.05 and * indicates p <0.1 – Robust Standard Errors between parentheses*

Table 5: Mean in Control and Treatment groups and difference between Treatment and Control in preventive behaviours, smoking and low level of physical activity

		Preventive Behaviours	*Smoking*	*Low level of Physical Activity*
Before				
	Control (C)	0.394	- 0.055	- 0.094
	Treated (T)	0.543	0.002	- 0.067
	Diff (T-C)	0.149	0.057	0.027
		(0.021)	(0.015)	(0.021)
		***	***	
After				
	Control (C)	0.400	- 0.083	- 0.077
	Treated (T)	0.538	0.010	0.002
	Diff (T-C)	0.138	0.072	0.076
		(0.020)	(0.013)	(0.020)
		***	***	***
Difference-in-Difference (DID)		- 0.010	0.015	0.049
		(0.028)	(0.019)	(0.028)
		*	**	*
Number of individuals: 2,307				

*Note: *** indicates p <0.001, ** indicates p <0.05 and * indicates p <0.1 – Robust Standard Errors between parentheses*

Table 6: Concentration indexes with Erreygers correction relative to 2014 and 2015 in healthcare access

	Preventive Behaviours	*Outpatient Visits*	*Emergency Visits*	*Inability to Get Care*	*Got Care When Needed*
2014	0.067	0.010	- 0.071	- 0.023	0.139
	(0.042)	(0.013)	(0.020)	(0.001)	(0.008)
	*		*	***	***
2015	0.080	0.011	- 0.083	- 0.020	0.111
	(0.029)	(0.014)	(0.018)	(0.006)	(0.150)
	*		**	*	***
Number of individuals: 9,255					

*Note: *** indicates p<0.001, ** indicates p <0.05 and * indicates p<0.1 – Robust Standard Errors between parentheses*

Pharmaceutical Expenditures and the Timing of Access to New Drugs: Regional Disparities across Italy

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Abstract

Italian Regions can determine whether and how adopting new drug at regional level. The aims of this study are: to understand the process of drug approval, changes implemented and the actual procedure for the introduction of new drugs in Regional Therapeutic Handbooks (RTH) and to identify if different regional structures lead to a delay in new therapies availability. The first aim was investigated through a survey and the second through an econometric evaluation.

The analysis, conducted between 2015 and 2018, is based on the 19 Italian Regions and 2 autonomous ones (Bolzano and Trento). After direct interviews and preliminary descriptive statistics, different combinations of Generalised Linear Model (GLM) procedure were adopted for the investigation of timeliness and its influence on the pharmaceutical expenditures. Descriptive statistic showed that different Regional structures lead to clear differences in access to new drugs. GLM models demonstrated that more complex is the Regional system, the longer is the time of drug availability in the market. The second GLM step observed a negative relationship between timing of new drug market introduction and pharmaceutical expenditures. In conclusion, the increase of the complexity of the system lead to cost saving but, at the same time, this entail disparity in access to new therapies.

Key words: GLM, NHS, drugs, access, Regions –
JEL codes: H50 (National Government Expenditures and Related Policies), I10 (Health General), I14 (Health and Inequality), I18 (Government Policy • Regulation • Public Health), R12 (Size and Spatial Distributions of Regional Economic Activity)

I.I – Introduction

The Italian health care system has changed in the last decades with strong reforms intended to implement fiscal federalism. The strongest turning point took place with the modification of Title V of the Constitutional Charter. Unfortunately, a series of inconsistencies, in contrast with the principle of universality and uniformity of health care provision, have emerged. One inconsistency refers to the mechanisms related to access to health care treatments.

Before the "Riforma Sanitaria" of 1978, Mutual Funds (MF) system was in place[1]. MF reimbursed health benefits in an uneven manner. According to the 1978 Reform, health became a fundamental pillar of the Italian State since all individuals (Italian and non-Italian), were deemed equal concerning the access for health care from birth to death.

Over time, the evolution of the reform was defining constraints, resources and expenditure responsibility by Regions, Local Health Authorities[2] (LHA) and hospitals. This procedure resulted in lack of homogeneity in access to care and, consequently access to therapies and drugs.

The last step of fiscal federalism in Italy took place in October 2001 when a Constitutional reform was approved, altering the balance of power between central and local governments, transferring to the latter a large number of previously centrally held governmental functions. The Italian system was strongly modified, shifting a centralised system into a decentralised one (Bordignon and Turati, 2002).

Since the effects of the decentralization process are ambiguous, this work aims to first map the legislative and political Italian scenario for the market access

[1] Before 1978, the Italian health system was based on a form of insurance-social security protection in which the right to health protection was closely linked to the working condition. This health care was financed by the contributions paid by the workers themselves and their employers. Consequent strong inequalities among the beneficiaries were present, since levels of assistance varied according to contributions paid to the insurance.

[2] LHAs are public bodies belonging to the Italian National Health Service and they are divided into basic health districts. LHA are companies endowed with organizational, managerial, technical, administrative, patrimonial and accounting autonomy with public legal personality (Olivetti & Rossi; 2012).

new drug introduction and then to identify if different regional structures and procedures may lead to a delay in new therapies availability for patients with relative consequences for timeliness, expressed in terms of days of access, and for equity.

The mapping procedure, updated at 2021, is the result of a direct survey conducted with literature revision and, especially, from direct interviews to specialists selected from three big-pharmas firms. The second part of the study concerns an analysis between 2015 and 2018, based on the 19 Italian Regions and 2 autonomous ones (Bolzano and Trento). Data result from a collection of information gained from different sources: AIFA, Ministry of Health, ISTAT and Aspect of Daily Life, Pharmaceutical Industries and active Regional legislation. The econometric section envisages preliminary descriptive statistics and different combinations of Generalised Linear Model (GLM) procedure, for the investigation of timeliness and its influence on the pharmaceutical expenditures.

According to the surveys conducted, a map of the Italian scenario has been generated (Table 1). This was the starting point to understand the possible influence of regional structure on timeliness and equity.

Descriptive statistic showed that different Regional structures lead to strong differences in access to new drugs: on average Regions with a leaner administrative structure perform better with shorter time of introduction into the markets of new drugs. Expenditures are constant over time, at the aggregate level (i.e. threshold of 14,85%), with a reduction of expenses for A class drug and an increment of H class drug in correspondence to Budget Law of 2017. All Regions exceeded the threshold of 14,85% in all the years, a part from Veneto, Trento, Bolzano and Valle d'Aosta. Lombardy, Piedmont and Emilia Romagna on average face a balanced budget.

According to the GLM procedure, more complex is the Regional system, the longer is the time of drug availability in the market. Moreover, there are also other determinants for the delay in access, such as: being in Repayment Plan, Rate of people in bad health, Receivership conditions, Active Mobility and Frequency of meetings for updating the therapeutic handbooks. The second GLM step

observed a negative relationship between timing of new drug market introduction and pharmaceutical expenditures.

I.II – Literature Review

According to theory, the decentralization process was aimed to ensure more delegation to local authorities in order to improve services through a combination of better knowledge of local needs, preferences and providers' characteristics, enhancing competition among jurisdictions.

Although the theoretical literature moves in this direction, according to empirical studies is impossible to produce a unique conclusion, since scant and contradictory literature. The still open question is: do local authorities operate better than the central government? (e.g., Shankar and Shah, 2003; Gil et al., 2004; Rodrıguez-Pose and Ezcurra, 2010).

Decentralization implementation is based on a trade-off between costs and advantages (Joumard et al., 2010). Oates (1999) was the first one who suggested this vision: advantages lie in the principle that through the decentralization process, local authorities can understand local needs (i.e. more direct information and discourage of public good discrimination by central authority). On the other side, costs are related to the spillover[3] effect among regions. One can also notice that advantages themselves are ambiguous: Bardhan and Mookherjee (2000) show that there is no theoretical reason to suppose that local governments are more prone to understand better people needs than central ones. Levaggi and Smith (2003) claim that sub-central governments are better informed about the constraints of local supply and about variations in demand, strongly related to local needs.

[3] For instance, better health prevention in one region benefits its neighbours. In case of decentralization, it is possible that each region decides to invest sub-optimally reducing the quality of services. Moreover, some problems may arise at the vertical level: is regional government are responsible for some specific programs which are already offered by the central authority (since the public characteristic of health), may happen that the local authorities have small incentives to provide the service optimal level, since everything is ensured by the state itself.

Some experts (Tanzi, 1996; Prud'homme, 1995; Bird et al., 1995) suggests that moral hazard phenomena, also known as "soft budget constraint" effects [4], may be the reason of federalism failure. In detail, gains from decentralisation process are strongly related to the timeliness and responsibility of local authorities. If local governments do not operate in the right manner, some perverse effects may arise. According to Bird et al. (1995), it is possible that local governments externalise costs of local services to other regions or to higher level of jurisdiction.

Boetti, Piacenza and Turati in 2012 showed that more fiscally autonomous municipalities exhibit less inefficient behaviour, thus supporting the waves of reforms towards the devolution of taxing power to lower government tiers.

Regarding the inequality studies, according to Rodríguez-Pose and Ezcurra (2010), decentralization and health expenditure favours economic convergence toward the equilibrium, but investment in social protection — contrary to expectations — is also associated with an increase in regional inequality. By reverse Gil et al. in 2004 proved that decentralization has a negative relationship with the reduction of inequalities.

Di Novi et al (2019) investigated the effects of decentralization between- and within-regions with the conclusion that fiscal decentralization does not impact on between-regional inequalities.

Shankar and Shah in 2013 concluded that regional development policies have failed in almost all countries, both in federal states and more centralized ones.

Therefore, the decentralization effects remain ambiguous without a strict conclusion on the efficacy of federalism.

The literature on the time of access of new drugs on the market is scant. Some studies investigated the field of Regional differences. By reverse, the literature on national differences about time of access has been enriched over time

[4] the problem of moral hazard is strongly related to the soft budget constraint. Budget constraints imply that if the regions are in deficit, the state intervenes to cover the excess in spending. This translates into less tax and expenditures discipline.

with different contributions. EFPIA (European Federation of the Pharmaceutical Industries and Associations) was the first that highlighted the Regional differences, demonstrating how higher level of local responsibilities lead to differences among Regions within the same country. Pickaert (2018), with a work based on 2012 data, showed how Italy, after Portugal and Spain, faced longer access times at national level. Russo et al. (2010) provided another specific contribution with a focus only on innovative and oncological drugs either at national and Regional level. They highlighted the following issues:

(i) Net of the times of European approval, the average time of access to Regional markets for products surveyed between 2006 and 2008 was on average equal to 561 days

(ii) The presence of binding handbooks generated longer timescales.

A more recent contribution made by Prada et al. (2017), always referring to cancer drugs, estimated that the average time of pricing and refund procedure concerning drugs approval[5] in the 2013-2016 period was 247.6 days.

From a national perspective, according to the EFPIA Patient W.A.I.T. Indicator Study (2018), the average number of days' Italian citizens must wait for a medicine to be available is 402 days, with an increment of 19 days compared to the previous analysis. This study considers 121 new drugs introduced between 2015 and 2017 in 29 different countries where Italy ranks 14th. On the podium, with Germany (119 days), there are Denmark (146) and Switzerland (171). At the bottom of the ranking Portugal (634), Lithuania (726) and Serbia (925).

To the best of our knowledge, the most recent study, conducted by Lidonnici et al. in 2018, was aimed to investigate the average length of time for AIFA to formulate pricing and reimbursement decisions for 85 oncological drugs and innovative drugs. The authors, through the scrutiny of Italian and European Journals and meeting reports of STC, proved that the average time-to-market was 258 days,

[5] From the initial (Scientific Technical Committee) STC meeting to the inclusion of the new drug in the Regional handbook

mainly dedicated to administrative procedures. Again, the analysis has been conducted at the national level, without any kind of discrimination among Regions.

However, our country instead is characterized by differences among Regions leading to consequent differences in time of access to new drugs. This lack of analysis in the literature highlights the need to consider this issue. Regional differences play a key role either from the point of view of patients, who face different opportunities in treatment and care, and from physicians' side, as the latter are limited in their chances to adopt specific therapies. This may suggest that in Italy the average time to market a new drug may be very long. Furthermore, some drugs may be available in some hospitals and not in others. This represents one of the strongest problem of discrimination in access to health care, with an impact on the differentiation of the pharmaceutical essential level of care (LEA) on the national territory.

This system may induce the Regions not to transpose innovative drugs (often at high cost), or to transpose them late, through the filter of Therapeutic Handbooks. Despite of the negative effects of the decentralizations process in terms of timeliness and equity, a positive effect on the moral hazard behaviour may arise when pharma expenditures are controlled locally.

I.II – Pharmaceutical expenditure

Every year, as a share of national health fund devoted to each Region, AIFA allocates annual expenditure for pharmaceutical assistance. In detail, AIFA defines, for companies holding a marketing authorization (MA), the threshold the 14.85% of the NHF to be devoted to pharmaceutical expenditures.

When the budget is exceeded, the overrun system of payback [6] is triggered. The payback procedure is borne by the company itself and it is proportional to the prices of medicines.

This exogenous constraint determines a diversified pharmaceutical policy among the Italian Regions, which responsible for the budget overruns.

The pharmaceutical expense (14,85% of NHF) borne by the National Health System (NHS) can be divided into two components, with relative thresholds: the expenditure on affiliated pharmaceutical expenditure (territorial pharmaceutical) and to pharmaceutical expenditure for direct purchases (hospital pharmaceutical). Moreover, according to the 2017 Budget Law, from January 1, two further Funds were established reimbursing Regions for:

- 500 million euros per year for innovative non-cancer medicines;
- 500 million euros per year for purchase of innovative cancer medicines (through resources use of the comma 393)

[6] The mechanism provides that, in the event of the pharmaceutical spending ceiling at national level being exceeded, the companies must cover the excess through payments to the Regions of the amounts attributed by AIFA to each individual company. With the new 2019 Budget Law, however, the contribution of each company is no longer calculated on the basis of company budgets, but by a system based on the market share which has led to a simplification of the entire process.

I.II.I – Agreed pharmaceutical expenditure (Territorial expenditure)

With regard to the components, the territorial pharmaceutical expenditure indicates the total of the expenditure referable to reimbursable class A[7] drugs (essential drugs and those for chronic diseases), gross of the share of the cost to be paid by the patients, distributed through the public and private affiliated pharmacies.

The Legislative Decree 95/2012, reduced the initial ceiling for territorial pharmaceutical expenditure from 13.1% in 2012 to 11.35% 2013. In 2017, according to the Budget Law (Article 1, paragraph 398), the territorial expenditures threshold was re-determined down again, bringing it up to 7.96% of NHF, and it was renamed as "Agreed pharmaceutical expenditure".

The Legislative Decree 159/2007 introduced, in article 5, a system for regulating the expense of drugs paid by the NHS, according to which AIFA attributes to each company holding drugs MA an annual budget, calculated separately for generic and patented medicines. The sum of these two budgets corresponds to the burden of the NHS for territorial pharmaceutical assistance, which can be increased by the Fund for innovative drugs. In the event of exceeding the ceiling for territorial pharmaceuticals, the private sector (pharmaceutical company, wholesaler and pharmacist) is required to cover any overruns. Pursuant to article 5, paragraph 3, letter c), of Legislative Decree 150/2007, the pay-back system applies to pharmaceutical companies. They pay the amounts due directly to the Regions where the overruns occurred. The re-payment is proportional to the exceeded regional spending ceiling of 14.85%.

[7] Further details on drug classification in section “Agenzia Italiana del Farmaco”.

I.II.II – Pharmaceutical expenditure on direct purchases (Hospital pharmaceutical expenditure)

Hospital pharmaceutical expenditure indicates the expenditure referable to H-class[8] medicines purchased or made available for use by healthcare facilities directly managed by the NHS.

The hospital pharmaceutical expenditure was re-shaped by the article 15, paragraphs 4 to 11, of law decree 95/2012. The decree specified the definition of direct purchases and its components. Furthermore, according to the decree, the roof increased, since 2013, (at the national level and in each Region) from 2.4% to 3.5% of the NHF. In 2017, according to the Budget Law (Article 1, paragraph 398), the hospital pharmaceutical expenditures threshold increased from 3.5% to 6.89% including hospital drug expenses, direct distribution (File F) and class A drugs in direct distribution through hospitals and local health services. Consequently, the ceiling of hospital pharmaceutical expenditure was converted into "ceiling of pharmaceutical expenditure for direct purchases [9]".

Currently, AIFA calculates the budgets of hospital pharmaceutical expenditure based on the expenditure and consumption relating to each drugs of H and A class.

The breakthrough of the ceiling of hospital pharmaceutical expenditure at national level and in each individual Region occurs when the spending limit

[8] Further details on drug classification in section "Agenzia Italiana del Farmaco".

[9] They are calculated net of: sums paid by the pay-back mechanism by pharmaceutical companies against the suspension of the 5% reduction in the price of drugs established with AIFA Determination no. 26 of 27 September 2006 on the public price including VAT of all drugs reimbursable by the NHS (band A-H); sums returned to the Regions and autonomous provinces by pharmaceutical companies following the exceeding of the maximum spending limit set for the medicine during the negotiation; sums returned by pharmaceutical companies, also in the form of extra discounts, in application of conditional reimbursement procedures for innovative drugs.

assigned to it by law is not respected, i.e. when the 6.89% of the NHS funding is exceeded [10].

Anyway, Regions that have recorded an overall economic balance are not required to pay anything. On the other hand, the shelf paid by the individual companies holding MA takes place through payments to the Regions and autonomous provinces (pay-back).

From now on, for easiness of reading and alignment with the existing literature, the two components of pharmaceutical expenditures will be renamed as "inpatient expenditures" and "outpatient expenditures" substituting then the "pharmaceutical expenditure on direct purchases" and the "agreed pharmaceutical expenditure", respectively. In the inpatient category are included all that drugs which are provided by hospitals and belong to the H class drugs. By contrast, in the outpatient category are included that drugs which belong to the A class.

[10] In these cases, a deficit is created, which must be made up for 50% by the pharmaceutical companies that have exceeded the budget assigned to them and for the remaining 50% by the Regions where the breakthrough of the roof took place.

I.III – Marketing Authorization (MA) and Italian Authorities

In Italy, is possible to divide the procedure of new drug market introduction into two steps: the first one related to the marketing authorization phase and the second one to local legislation and authorities' intervention.

I.III.I – Marketing Authorization (MA)

The first step of authorization is common also for non-hospital drugs and it concerns the marketing authorization and the determination of the redemption price.

In order to be marketed in Italy, new drugs must have obtained the release of the Marketing Authorization (MA) from AIFA or the EMA (European Commission Agency). The MA is obtained following a scientific assessment of the quality, safety and efficacy requirements of the medicine. To obtain the MA, the applicant is obliged to submit an application consisting of a dossier containing information concerning chemical-pharmaceutical, preclinical and clinical aspects, structured according to a standardized format (CTD - common technical document). The data and studies submitted to support the MA application must comply with European guidelines[11]. No drug can be marketed on the territory of a state without the release of the MA.

[11] Three feasible procedures for requesting the MA are available: A) National procedure: it involves the MA request to the specific supervising national drugs authority. In this case, the validity of the authorization is limited to the national boundaries. B) European procedures: the decentralized procedure (also known as mutual recognition): it is based on the evaluation of a new drug by a group of Member States. This evaluation is than validated by all the others through the approval of the assessment they made; C) the centralized procedure: this procedure is the one more frequently adopted, especially for innovative drugs; through this procedure the MA is directly required to European Medicines Agency (EMA), a decentralized European organization with the final objective to protect either human and animal health, whose release is valid throughout the whole European Union. This last procedure is also typical for the H drug class. Drugs that obtain the MA with the centralized procedure are reported in the Official EU Journal. Staring from the day after the publication, AIFA has the possibility to start the process of completing the MA.

I.III.II – Agenzia Italiana del Farmaco (AIFA)

In Italy, the final access for A and H drugs is subject to different supervising authorities, which discipline medicines control and authorization. First AIFA and then regional intervention.

AIFA was established with the Law Decree n. 269/2003 (art. 48, paragraph 2) and, among other functions, has the main role of ensuring drug access, its safe and appropriate use as a health defence tool, and it manages the pharmaceutical expenditure in a context of economic compatibility and competitiveness of the pharmaceutical companies, ensuring the national unity of the pharmaceutical system, in agreement with the Regions. Further AIFA functions can be summarized as follow: promotion of drug knowledge and culture, R&D promotion of investments in Italy, maintenance of an open dialogue with the communities of patient associations and the medical-scientific world, strengthening the relationships with the EMEA and the drug policy authorities of other countries.

Normally, AIFA is supposed to express its decision[12] on the MA granted in a national procedure context. Moreover, its decision for Italian marketing is also required in centralized procedure and mutual recognition. In these last two cases, AIFA approves the response of the EMEA or the mutual recognition request, through the community sub-commission, and subsequently starts, within the "Committee Prices and Reimbursement", the procedures for defining the admission price for reimbursement.

After the MA release, the authorization holder starts its bargaining with AIFA. The procedure is aimed to determine the reimbursement price, in detail, in which class of drugs the medicine should be included. There are three classes:

[12] The AIFA evaluation of the new drug is bases on Health Technology Assessment (HTA) procedure and approach. HTA is characterized by: a procedure of evaluation which is cost-effective oriented; no barrier to drug transposition; evaluation with a multidisciplinary approach; involvement of different categories of stakeholders (doctors, patients, pharmaceutical companies, economists, statisticians and patient associations).

- “A” class: includes essential drugs and drugs for chronic diseases. The cost of these medicines is borne by the State. The medicines that fall into this range are therefore sold for free even if, depending on the Regional regulations, a ticket can be added as a co-payment by the citizen
- "C" class: all other drugs not belonging to band "A". The expenditure for band C drugs is entirely borne by the citizen. In practice, as a residual criterion, drugs that treat minor pathologies or, in any case, not considered essential or life-saving are included in this range. It is important to underline that it exists also a subgroup of “C”, which is the class "C-bis" in which self-medication drugs, also paid by the citizen, were included.
- Finally, there is an "H" band; it includes drugs which, due to pharmacological characteristics, to the method of administration, to innovation or for other public health reasons, are only dispensable in hospitals (or on behalf of these in pharmacies) or administered in specialist clinics.

AIFA inserts the drug in the National Pharmaceutical Handbook (NPH) according to the corresponding range.

I.III.III – Regions and Regional Therapeutic Handbooks (RTH)

After this first step, a series of additional and necessary authorizations by Regional and Local Commissions, which evaluate the possibility of introducing the new drug in Local and Regional therapeutic handbooks, is necessary.

Therefore, even if the evaluation and approval steps of the EMA through the release of the MA, and the approval of the AIFA ensures that the drug is safe and effective, the local therapeutic boards, which preside and decide the composition of the territorial handbooks, can block the prescription of a hospital drug that in principle may be prescribed on the whole European territory, having the MA and

being included into the European database publicly accessible and managed by the EMA - EudraGMDP[13] (Good Manufacturing Practice).

Actually, the Territorial Therapeutic Handbooks (TTH), were born as a Regional list (with no binding purpose) of all the drugs used in the Regions' hospitals. In 1996, since the high level of discretionarily and freedom, the Regional Decree n.4690 established that decisions by the Hospital Therapeutic Commissions had to respect Regional decisions and TTH became a binding list.

The government introduced territorial Handbooks as a decentralized pharmaceutical assistance tool aimed to contribute to the dissemination of information on characteristics of the drugs, their correct use, supporting training initiatives and update. The ratio of Territorial Handbooks is to respect the appropriateness principle[14] and a rational use of pharmaceutical expenditure.

Through the years, since the timing of committee meeting and the methods of carrying out their work, Regional Therapeutic Handbooks (RTH) mission partially changed. The new aim is a direct control of spending, with a filter upon entry into the Regional hospital pharmaceutical system, through an increase of procedures and decision-making levels which results in a delay of local availability of the new drug (Reverte-Cejudo and Sanchez-Bayle, 1999; Repullo, 2007).

One main consequence, is that new drugs are in the meantime available in one Region, but cannot be prescribed in another one.

The RTHs are updated by a Regional technical-scientific commission (RTC), which meets according to the Regional legislation. The RTC has full discretion in examining the opportunity to allow marketing and the use of a drug in the hospitals of the Regional health system. Normally the RTC is mainly composed

[13] Database which records Good Manufacturing Practice Certificates and Manufacturing Importation Authorisations by NCA Inspectors.

[14] According to the World Health Organization it can be defined in different ways and different dimensions. Anyway, some common factors allow a definition of the appropriateness principle: "care is effective (based on valid evidence); efficient (cost-effectiveness); and consistent with the ethical principles and preferences of the relevant individual, community or society" (World Health Organization; 2000)

by Pharmacists. Obviously, RTH cannot replace the EMA and AIFA role in the MA concession, but it has a very strong power: the legal-regulatory ability to limit the upper decisions at the Regional level. It really works as a real further level of evaluation. From a schematic point of view, the hierarchy can be summarized as follows:

$$\text{EMA} \rightarrow \text{AIFA} \rightarrow \text{RTH}$$

Moreover, once the drug is placed in the RTH, before the DRGs hospital application, it must be included also in the Local (Hospital, LHA or Province) Handbook. Also for these steps there are technical-scientific commissions, which operate as a real fourth level of evaluation and choice. Again, the paradox is present: a formal hierarchy that degrades downwards, with effective decision-making power at the lowest level.

The handbooks supply chain cannot anyway be traced back to the principle of subsidiarity defined by the Treaty of Maastricht[15]. From one side Regional Handbooks question and return on choices already taken at higher levels. First EMA

[15] The principle of autonomy has been recognized by the Italian constitutional system since 1948; art. 5 cost. provides that "The Republic promotes local autonomies and implements the widest administrative decentralization". The present principle of subsidiarity in Italy was implemented with law no. 59 of March 15, 1997, known as the Bassanini law. Subsidiarity is therefore outlined as a relational principle, concerning the relationships between the different levels of government (State, Regions, Provinces, Municipalities). The Bassanini law therefore represented a moment of reorganization of the entire administrative system and not just a law of mere redistribution, attributing administrative functions to Regions and local authorities also in matters of legislative power of the state, and sanctioning the abandonment of the principle of the parallelism of functions. The reform of Title V of the Constitution (approved with Constitutional Law 3/2001), in the first paragraph of the new article 118, the principle of vertical subsidiarity: municipalities are attributed the generality of administrative functions except that, to "ensure the unitary exercise ", are conferred to higher level entities.
The legislator has assigned the role of cornerstone of Italian institutional architecture to the principle of subsidiarity. However, the principle of subsidiarity presupposes the full autonomy of local authorities, which must be able to dispose of the structural and economic resources necessary for the exercise of the assigned functions. An assumption that, at the time of the approval of the reform of Title V, did not find correspondence in the Italian reality, anchored to an indestructible centralism, only from recognizing, in the Regions and local authorities, institutions capable of an efficient and autonomous management of resources (Muraro, G.; 2003).

and then AIFA verify the validity of the new drug on the basis of proven technical-scientific documentation shared by the international community. On the other side, the duplication of passages and the binding condition of higher levels of drug evaluation limit the responsibility and full autonomy of hospital physicians, who have direct contact with the patient and can appreciate the needs. This dichotomy can prevent the choice of the best way to adopt a new therapy.

I.IV.IV – RTH Structures and hallmarks

The main results that emerged from a field survey conducted through articles review and direct interviews with drug policy experts and representative major pharmaceutical companies present in Italy, are presented in Table 1 below.

For the purposes of the following discussion, it is useful to remember that the territorial handbooks are valid only at the regional level. In the current regulatory-framework, territorial handbooks for the expenditure's containment can be divided into four groups:

- Regional Therapeutic Handbooks (RTH)
- Province Therapeutic Handbook (PTH)
- Vast Area Therapeutic Handbook (VATH)
- Local Therapeutic Handbooks (LTH)

Higher-level handbooks (starting with the NPH) always have a hierarchical predominance, in the sense that the drugs that are not included at higher levels, cannot be used in the lower-level handbooks [16].

The hierarchical chain can be summarized ad follow:

$$NPH \rightarrow RTH \rightarrow HTH$$

[16] Only in Abruzzi the RTH is not binding on the HTH. It is the lower level handbooks, however, which, have the power to filter/veto the actual entry of drugs into the DRGs.

Although some exceptions are allowed (see Table 1), according to Regional legislation and pharmaceutical information, in 2019 we could observe the following situation of Regional Handbooks:

- Sixteen Regions with a Regional Therapeutic Handbook (RTH), with Molise whose RTH was not binding
- One Vast Area Region (Vast Area Therapeutic Handbook: VATH) - Tuscany
- Three Regions with no RTH

Figure 1 and Figure 2 represent the Italian situation updated at 2021. In Table 1, below, are reported the results of the interviews: a) for each Region Steps for the introduction in Territorial Handbooks; b) who is responsible for the submission of request of the drug inclusion in Territorial Handbooks; c) how long the commission meets for Territorial Handbook updating and d) notes about some particularities of the Region.

We would like to point out that from the interviews interviews and research, we can conclude that there is no correlation between the regional dimension and the complexity of the system: some small regions present more decision levels than bigger ones. For instance, Liguria structure is more complex than the Lombardy one: the former is a three-tier region and the second is only one-tier region. Moreover, the Italian scenario is characterized by many exceptions: Calabria, for example, which is a two-tier region but with the first level which is a mere container and operates only as duplication of bureaucratic procedures. Thus, we cannot define a general pattern.

Moreover, there are no proofs, neither in the literature nor from the interviews, showing that more decision levels imply a more accurate evaluation of appropriateness of drug usage. Indeed, the evaluation has already been conducted at the European level, though the scientific assessment of the quality, safety and efficacy requirements of the medicine for the MA, and then though the HTA procedure conducted by AIFA at the national level.

Table 1: Therapeutic Handbooks Procedure and hallmarks

Region	*First Level of TH*	*Second Level of TH*	*Third Level of TH*	*Impulse of insertion process*	*RTH Update - Months*	*Note*
Abruzzi	RTH Binding	HTH	None	- TLC - Clinician - MA owner company	12	
Basilicata	RTH Binding	HTH	None	- Clinician	2	If local committee include the molecule in the HTH; it triggers the request to the TRC inclusion in the RTH, which in case of positive response makes the insertion of the molecule into the other HTHs. Preferential routes for cancer drugs.
Calabria	RTH Binding BUT a mere passive container. Hospital drugs in the NPH are automatically transferred to the RTH	HTH	None	- Clinician - TLC	6	The committee has 15 days for the approval. In case of a positive opinion, the clinician can use the drug, but with the request for an opinion from the TRC that must be expressed within the first useful review.
Campania	RTH Binding	HTH	None	- TLC - MA owner company	6	File F implementation for onco-haematologic drugs.
Emilia-Romagna	RTH Binding + GREFO (authority for Economic Valuation)	PTH - Macro Regional	None	- TRC - PDC	12	HTA approach evaluation.
Friuli-Venezia-Giulia	None	HTH Binding	None			
Lazio	RTH Binding	HTH	None	- MA owner company	Automatic	File F implementation; drug approval insertion in RTH before Regional evaluation

Liguria	RTH Binding ONLY for six therapeutic categories	LTH	HTH	- TLC - Clinician	6	RTH sub-commission. Categories: - B (Blood and hematopoietic organs); - C (Cardiovascular system); - J (Antiinfectives); - L (Antineoplastics and immunomodulators); - N (nervous system); - Innovative drugs
Lombardy	None	HTH Binding	None			File F implementation for onco-haematologic drugs.
Marche	RTH Binding	HTH	None	- MA owner company - TLC - SSNI	3	the positive evaluation involves the insertion of the drug in the RTH, but not automatically into the LTH. It happens ONLY with an explicit approval of the latter.
Molise	RTH NOT Binding	HTH	None	- TRC - Clinician	6	
Piedmont	RTH Binding	HTH	None	- TRC	12	HTA approach evaluation only for Molinetti Hospital (Turin).
Puglia	RTH Binding	HTH	None	- TLC - Clinician	3/4	
Sardinia	RTH Binding	HTH	None	- TRC - Clinician	6	
Sicily	RTH Binding	HTH	None	- Clinician - MA owner company	1	Specific discipline for antiblastic drugs in Day Hospital, whose repayment was stopped in 2008 for patients resident in other Regions.
Tuscany	VATH + RTH	HTH	None	- Clinician		Characterized by three vast areas: North, Centre, South. To each area a TH is associated. Drug not yet inserted in the VATH, but present in the NPH, can be prescribed by the clinician and reimbursed by the Region, but with

						reference to limited quantities.
Trento	None	PTH Binding	None	- Primary Physician	2	PTH coincides with HTH
Bolzano	None	PTH Binding	None	- Primary Physician	2/3	PTH coincides with HTH
Umbria	RTL Binding	HTH	None	- Clinician	3	
Valle D'Aosta	RTH Binding	HTH	None	- Clinician	6	RTH coincides with HTH since only one hospital
Veneto	None	HTH Binding	None	- TLC - SSNI - Clinician		Specific regulation for high-cost cancer drugs. HTA approach evaluation.
Note: TH: Therapeutic Handbook – RTH: Regional Therapeutic Handbook – HTH: Hospital Therapeutic Handbook – PTH: Provincial Therapeutic Handbook – TLC: Therapeutic Local Commission (LHA and Hospitals) – TRC: Therapeutic Regional Commission – LTH: Local Therapeutic Handbook – VATH: Vast Area Therapeutic Handbook – PDC: Provincial Drug Commission – SSNI: Scientific societies of National Importance – RTL: Regional Therapeutic List						

Figure 1: Regional Therapeutic Handbooks: one, two, three tier Regions

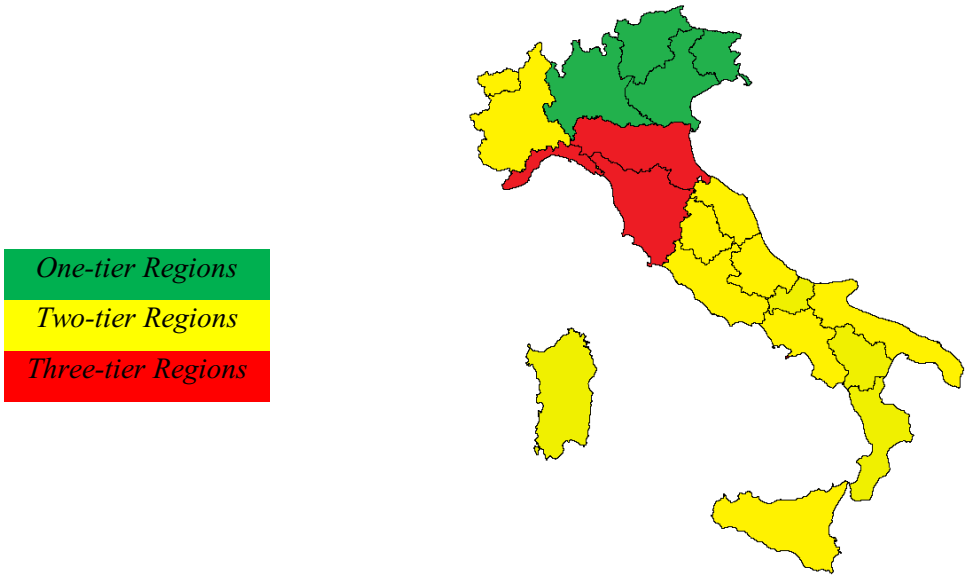
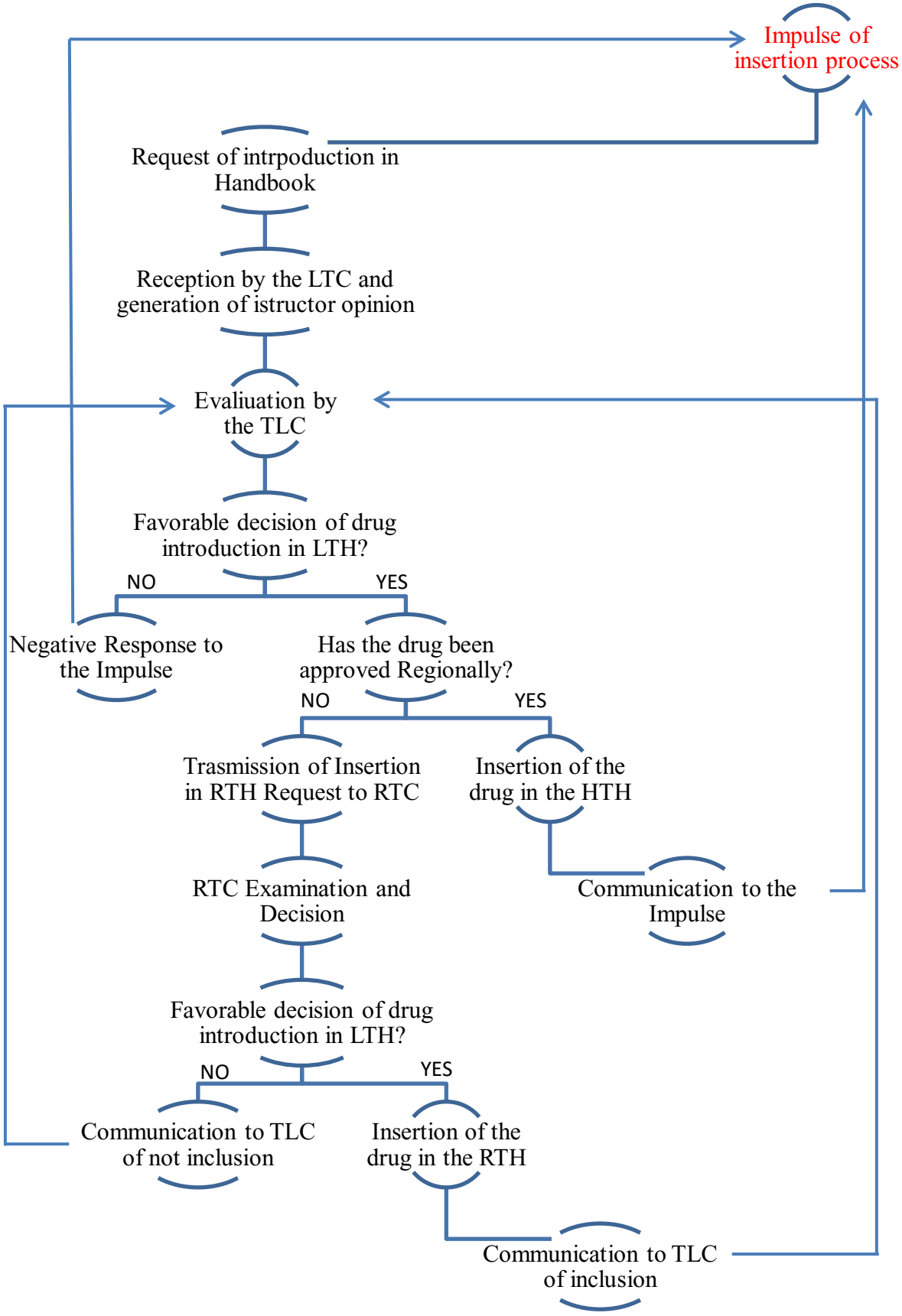


Figure 2: Binding and not binding Regional Therapeutic Handbooks – Source: Tomino, C. et al. (2017); Regional legislation and pharmaceutical information

In Figure 3 below a framework of the general steps for the insertion in regional handbooks process is provided.

Figure 3: Process of Handbooks drug insertion



I.IV – Drawbacks and consequences of regional differences

Based on the autonomy granted to them, Regions determine whether to adopt a new drug. The multiplication of the drug evaluation levels and the decision on its inclusion within hospital DRGs is fraught of negative consequences:

- From the equity perspective: the opportunity of accessing drugs in a homogeneous manner on the national territory is significantly limited. Citizens, which are resident in certain Regions or cities, will have delayed access to the possible benefits of a new drug. In some extreme cases, they will not even benefit from it if not moving to other Regions/cities and in any case without mutual assistance from the NHS. The effect is a differentiation of pharmaceutical LEA both among regions and within the same Region.

- The second effect is market segmentation with effects on competitive interaction. In fact, the characteristics of the Italian market are: product life cycle longer on average, lower turnover of market shares, less propensity for innovative products. Elongation of the decision chain contributes to increase pharmaceutical Italian market features. The distortionary effects of competition have a double effect on the citizen who uses the National Health Service:
    - the delay in time to market of the drug could have negative effects on the company's decision to invest in Research and Development in Italy. This may happen due to the uncertainty created by the decisions timing of local therapeutic commission, finding over time an unclear and fragmented regulatory behaviour.
    - Companies may decide not to compete on the market since lowering the price may lead to losses since the uncertainty of new drug market introduction. Softening of competition, potential and effective, slows down the price convergence towards efficient production costs for off-patent products since the direct bargaining power with regions increases.

II.I – Data

Data adopted result from a collection of information gained from different sources: AIFA, Ministry of Health, ISTAT and Aspect of Daily Life, Pharmaceutical Industries and active Regional legislation. The analysis is based on 19 Italian Regions, 2 autonomous provinces (Bolzano and Trento). All these Regions are observed in a time horizon of four years: from 2015 to 2018. The small time horizon represents a limit for this study but no more recent data were available. The final dataset is pooled and balanced since all the information are available for all the years. Given the low number of observations, the generation of a pool dataset allowed us to observe variations and differences among Regions but not within them. On the contrary, the initial national and Regional mapping is updated at 2021.

1. AIFA

AIFA data have been collected through pharmaceutical expense monitoring reports. In detail, from the monitoring reports about: National Health Fund (NHF), Territorial Expenditure, Direct Purchase Expenditure and Expenditure for innovative oncological and non-oncological drugs. Since the reports provided by AIFA are constantly updated and, those used, represent a final balance at the end of the year, they take into account regional movements, so all the data provided are net of regional transfers. Data used for the processing of the outpatient pharmaceutical expenditure come from the information flow of the pharmaceutical services provided through public and private pharmacies, affiliated with the NHS and by the Summary Accounting Lists (SAL) that AIFA receives monthly from Regions. In the OsMed flow, information is also provided by Federfarma (National Federation of private pharmacies affiliated with the NHS) and by Assofarm (Association of Public Pharmacies) which receive data from their provincial offices and subsequently aggregate them at Regional level. Direct purchases information is provided by New Health Information System, of the flow of "drug traceability", aimed at tracing the movements of medicines with MA on the national territory.

2. Ministry of Health

Information are taken from the official site of the Ministry of Health (http://www.salute.gov.it/portale/home.html). In detail from the Hospital Activity Report (HAR), provided annually by the Ministry of Health's New Health Information System. The HAR has the aim to offer different level of data and analysis about hospital care. The HAR is characterized by tables which are the results of annual Hospital Stay Charts (SDO) review. The HAR is focused on treatments and hospitalization for acute care. In detail, thanks to this platform, information about the number of prescriptions, the consumption trend in terms of Defined Daily Doses (DDD), the escape and attraction indices, the active mobility among Italian hospitals and Regions and average hospital stay (adopted as efficiency indicator) have been collected.

3. ISTAT, Aspects of Daily Life and Health for All

Data are collected both from The Italian National Statistical Office, from the household survey "Aspects of Daily Life", which is part of the "Multiscopo" survey system and from "Health for all" database. Aspects of Daily life[17] are repeated cross-sectional which offer information about school, family, leisure, politics, health, lifestyle etc. of individuals and their families. Heath for all database is characterized by more than 4000 indicators on the health system and health in Italy. It is structured in such a way that it can be queried by the HFA software provided by the World Health Organization adapted to national needs. Data are updated periodically to the last available year, the historical series are expanded by going back in time and information is enhanced at the provincial level. In detail from these data different rates were selected: hospital discharge rate, rate of people in good health, rate of people in bad health and cancer discharge rate.

[17] This survey collects many information fundamentals for our country and, for this reason, it is included in the national statistical program. Aspects of daily life and ISTAT database provided information about per capita GDP, old age index, weighted population and number of individuals who declare that they are in good health.

4. Pharmaceutical Industries

Data and information are finally checked with to three big-pharmas firms which have been identified and contacted for interviews. The pharmaceutical professionals are: specialists of market access, either at national and Regional level, managers and physicians. The selected industries, together with Regional legislation (https://www.gazzettaufficiale.it/), have been useful in understanding the changes in the Italian evolution of Regional differences and disparities. Pharmaceutical industries provided also further information related to real frequency of meetings, which Regions are in return plan and Receivership conditions. Big-pharmas, according to their internal analysis and studies, shared also data about funds for innovative oncological and non-oncological drugs and the average time for H class drugs to be available for patients following AIFA drug approval in a time horizon of 7 years, from 2010 to 2017.

II.I.I – Dependent Variables

Dependent variables are listed below:

- *Time Access:* Indicates the average time for a drug to be available on the market for patients. Data refers to 120 class H drugs with MA/reimbursement in a time span from 2010 to the end of 2017. The innovative drugs are not considered in this calculus since there are many exceptions and innovative drugs follow a specific path of approval. On the other hand, H class drugs are subject to similar procedures and rules in all Regions. It considers only the period between the time of AIFA approval and the effective insertion of the drug into the relative handbook (RTH, PTH, VATH[18] and LTH).

- *Outpatient Expenditures (Territorial Expenditure):* the affiliated pharmaceutical expenditure, is determined in accordance with the ceiling pursuant

[18] Important to be noted, in Tuscany's vast areas, time of access are different: ESTAV north has a mean of 351 days, ESTAV central a mean of 239 days and ESTAV south a mean of 489 days.

to law 232/2016, article 1 paragraph 399. It is defined as the expenditure incurred by the NHS for the delivery of drugs through pharmacies open to the public, and it is calculated gross of Regional tickets and net of discounts paid by pharmacies, the 1.83% pay-back paid to the Regions by the companies and also the various pay-back paid to the Regions (according to law no. 122 of 30 July 2010).

- *Inpatient Expenditures (Direct Purchase Expenditure):* Pharmaceutical expenditure for direct purchases are verified in compliance with the 6.89% ceiling of the NHS basing on data sent by pharmaceutical companies to NHIS pursuant to Ministerial Decree of 15 August 2004 (drug traceability). The data are net of spending on vaccines and of funds for innovative non-oncologic and oncologic drugs.

II.I.II – Independent Variables

Independent variables adopted in the analysis are:

- *Expenditure for Oncological Drugs & Expenditure for Non-Oncological Drugs:* provides monitoring of the two years (2017 and 2018) expenditure for non-cancer and cancer innovative medicines provided pursuant to art.1, paragraphs 402, 403 and 404 of the L. 11 December 2016, n.232, net of pay-back, relating to Regions expenditure repartition.

- *Weighted Population:* The resident population is calculated on 31 December of each year. To obtain the weighted reference population, the resident population has been divided by age groups and the ministerial weights used in the allocation of the national health fund for the year 2017 and 2018 were applied to each class, as required by paragraph 34 of the 'art. 1 of L. n. 662/96. The value is in thousands.

- *Old Age Index:* Indicates how old a Region is considered. In other words, how many old individuals are present on the Regional area. It is calculated

as the ratio between the population aged 65 and over and the youngest population (0 - 14), and it is expressed in percentage values.

- *Per-capita GDP:* The Gross Domestic Product, defined as the total value of goods and services produced in a year in a specific Region, it is defined at market prices per inhabitant.

- *Individuals in good health:* Represents the number of individuals which declare to be in a general good health condition. The unit of measure of the variable is in thousands.

- *Active Mobility:* the general definition is related to the flow of incoming funds for the compensation of services provided in a specific area, i.e. Region, of competence to clients of another origin Region, by virtue of laws or treaties. In this case, this data is converted in number of individuals discharged, coming from other Regions.

- *Average Hospital Stay:* Considered from the government as an efficiency indicator. The Hospitalization stay represents the number of days between the date of hospitalization of a patient and the date of his discharge; the length of stay of patients hospitalized and discharged on the same day is equal to one day.

- *Attraction Index*: This index measures the ability of a Region to attract patients from other Regions. It is given by the ratio between the number of discharges of patients not resident in the Region and the total number of hospitalizations carried out in the Region.

- *Escape Index*: The escape index quantifies the propensity of the population to move away from their Region of residence to take advantage of the services requested in other Regions. It is calculated as the ratio between the number of discharges of patients residing in the Region carried out in the rest of the national

territory and the total of hospitalizations of residents in the Region, carried out on the whole National territory.

The last two indicators can be interpreted as a proxy of quality of healthcare provided in a given Region: a high escape rate may be due to supply shortages concerning welfare services, while a high attraction index may be due to the presence of centres of excellence for particular pathologies, or more generally to a health care considered qualitatively better (for example, in terms of effectiveness, waiting times etc.).

- *National Health Fund (NHF)*: The reference NHF for each year is communicated by the Ministry of Health in March of the following year. It represents the way in which the State finances Regions. The NHF is allocated among Regions according to the "Capita Quota" criterion: it measures the Regional quota by applying a fixed fee for each resident on the Regional territory and providing for an adjustment linked to the compensation of 'healthcare mobility'. This variable indicates the distribution of the NHF among Regions.

- *Fund for Oncological Drugs & Non-Oncological Drugs:* These variables indicate how the two national funds for oncologic and non-oncologic drugs are regionally distributed. The distribution is based on Ministery of Health directions with reference to the resources of the Fund referred to in article 1, paragraph 401, of the law 11 December 2016, n. 232. Moreover, Friuli Venezia Giulia, Valle d'Aosta, Sardinia and the autonomous provinces of Bolzano and Trento do not join the fund for innovative drugs, Sicily only in part (50%). It is important to notice that in the first year, 2017, the fund for Oncological and Non-Oncological Drugs is the same, since 2017 was the first year of fund introduction.

- *Ceiling of 6,89%, Ceiling of 7,96% & Ceiling of 14,85%:* All the ceiling are calculated on the basis of the NHFs, each of them with respect to the reference year.

- *Hospital discharge rate:* The indicator refers to hospital discharges under the ordinary regime, relating only to acute care activities of accredited public and private care institutions, disaggregated by sex and age groups. Calculated as the ratio between number of discharged patients and the total number of hospitalizations.

- *Rate of people in good health:* The indicator is the result of the ratio between the number of individuals who declare to be in a good health status over the total number of inpatients.

- *Rate of people in bad health:* The indicator represents the ratio between the number of individuals who declare to be in a bad health status over the total number of inpatient.

- *Cancer discharge rate:* It represents the ratio between the number of cancer patient discharged under the ordinary regime over the total number of cancer hospitalization patient within the year of investigation.

- *Frequency of meetings*: This value is expressed in days and it indicates the average real time at which the Committee for the insertion of new drug in therapeutic handbooks meets. This variable is constant overtime, since between 2015 and 2018 no changes took place.

- *Repayment Plan:* it is a dummy variable which is equal to 1 is the Region has an active repayment plan and 0 otherwise. The repayment plans were found with the 2005 Finance Law (Law 311/2004). They represent a written agreement between the State and Regions that governs the methods of repayment of health regional debt. The Plans must contain both the measures aimed at guaranteeing the provision of the essential levels of assistance (LEA) in compliance with the national programming and with the DPCM 12/01/2017 for setting the LEAs, and the measures to guarantee the balance of health budget. In case of failure to achieve the objectives, the repayment plans continue according to operational

programs, lasting three years. This variable is constant overtime, since between 2015 and 2018 no changes took place.

- *Receivership conditions:* If the outcome of the monitoring procedure reveals the persistence of the non-compliance of a region in the Return Plan both from an economic-financial point of view and the provision of essential levels of assistance, the Council of Ministers, in implementation of art. 120 of the Constitution, appoints an "ad acta" Commissioner for the entire duration of the Return Plan. On data, this is represented by a binary variable: 1 if Region is under receivership conditions and 0 otherwise.

- *Regional Therapeutic Handbooks (RTH):* Three dummy variables were generated for three regional scenarios for regional complexity structure: more steps for drug approval, more regional complexity. To be noted that this characteristic is constant over the years under observation, since no changes took place between 2015 and 2018. RTH variables are used as proxy for timeliness:
  - *RTH1*: it represents those Regions which face only one step for the introduction of the new drug in territorial handbooks. In detail, Lombardy, Veneto, Friuli V.G, Trento and Bolzano face only one level of commission, which is the HTH. This structure should represent the faster way of making a new drug available on the territories.
  - *RTH2*: it represents all Regions that face 2 steps for the new drug introduction in therapeutic handbooks. This is the most common condition since 13 regions deal with it. The first step is at regional level (RTH) and the second at the local level (HTH or LTH or PTH).
  - *RTH3*: this last scenario is typical of Liguria, Emilia Romagna and Tuscany. In this framework, the new drug needs to be approved by three commissions before being available on the market.

II.II – Methodology

The first step of the analysis is based on descriptive statistics, in order to understand the possible relationship between:

- Average time of access for new drug and different scenarios of RTH structure
- RTH scenarios and NHFs
- Pharmaceutical expenditures, attraction and escape indexes
- Pharmaceutical expenditures and North-South gradient
- Total Pharmaceutical expenditures as a share of NHFs

The potential influence of each variable reported above will be firstly investigated through a basic model: a multivariate Ordinary Least Square (OLS) regression model. The OLS model relies on the central limit theorem, according to which the mean of a sample, when is large enough, is normally distributed, without any affection of its population distribution. This model assumes a linear relationship between costs and its determinants (Pagano 2015).

OLS is easily applied and the estimations are easier to interpret. Thus, OLS model will be used as benchmark in the final model. Without loss of generality, the model is based on the so-called "natural" scale where no prior transformation is required. The effects of covariates (x) are used.

(1) $$y_i = x_i^{'}\beta + \varepsilon_i$$

In detail, the OLS model, with robust standard errors, can be estimated by predictions of the conditional mean of regressors, which are given by (White 1980):

(2) $$\hat{\mu}(x_i) = x_i^{'}\hat{\beta}$$

According to the previous literature (see for instance Jones, 2009; Pagano, 2015) it is well known that, in general, health care variables are not normally

distributed (i.e. asymmetric distribution of errors) and OLS (which assumes a normal distribution of the error terms) may produce estimations that are not robust enough and inaccurate standard errors and confidence intervals (Pagano, 2015).

According to Polgreen and Brooks (2012) the implications of a skewed (i.e. some Regions have much-larger-than-average time access) dependent variable should be taken into account during the estimation. According to Jones (2009), a potential solution to the problem of the skewness in the residuals, could be adopting a log transformation of the dependent variable. Thus, the regression model is no longer specified with the row scale, but on a transformed scale.

In detail, the log transformation ensures the possibility to gain a reasonable normalization effect, in presence of highly skewed data too (Moran et al. 2007; Jones 2009; Pagano 2015). Notwithstanding, one problem related to this model is the use of two-part specifications to deal with the zeros. The main bias of the log transformation is that it provides predicted effects on a log scale, while analysts prefer outcomes which are expressed in terms of actual values. Therefore, a back-transformation into the original scale, for the interpretation of results, is required i.e. exponential transformation - however this process does not ensure predictions on the original scale (Moran et al. 2007). In order to solve the problem, a "smearing factor" needs to be applied. However, problems may arise in case of retransformation. (Jones 2009, Pagano 2015).

The log regression model:

$$\ln(y_i) = x_i'\beta + \varepsilon_i \tag{3}$$

The standard properties of the error term are:

$$E(\varepsilon) = 0 \qquad E(x'\varepsilon) = 0 \tag{4}$$

The prediction of time access on original scale, given $E(\ln(y)) \neq \ln(E(y))$, relies on retransforming:

$$y_i = \exp(x_i'\beta + \varepsilon_i) = \exp(x_i'\beta)\exp(\varepsilon_i) \tag{5}$$

The dominant approach to modelling health care variables in the recent literature has been the use of Generalized Linear Models (GLM). As Polgreen and Brooks (2012) argue, GLM can be considered a valid alternative model since it enables to avoid and overcome all the complications related to the retransformation in the log model. GLM model can be described according to the following equation:

$$(6) \qquad E(y) = g^{-1}(x\beta) \qquad \text{where} \qquad y \approx F$$

The function *g(.)* denotes the (monotonic) link function. The link function connects the mean of the distributor to the linear predictor. *F* represents the exponential distributional family which has the role to relate the variance function to the mean. OLS model is simply a GLM with Gaussian family and an identity link. In detail an identity link means that the link function, *g(.)*, is an identity function i.e. $E(y) = x\beta$. In the Gaussian model the variance is not correlated to the mean, this does not imply that errors are distributed normally, as instead OLS presupposes.

Hence, the GLM model with a Gaussian family and log link ensures the determination of a model similar to the classical Log-transformed OLS model. However, as said previously $E(\ln(y)) \neq \ln(E(y))$ in terms of estimations. The two main advantages of GLM model are, from one side, that it is estimated on the untransformed scale, so the retransformation is not needed and, on the other hand, that predictions allow for heteroskedasticity through the choice of distributional family (Moran et al. 2007; Jones 2009; Polgreen and Brooks 2012).

The GLM model with a log link is mostly used for a better alignment between the variance function and the mean function in the data.

According to Polgreen and Brooks (2012) the Gamma family is another widely used set of GLM models in literature. The main difference with the Gaussian family is that Gamma models involve that the square of the mean function and the variance function increases proportionally.

In both families, the link functions most commonly used in healthcare models are: log -where covariates act multiplicatively on mean and the expected effect of x_i on y is a function of the level of the remaining independent variables in x - and identity -where covariates act additively on mean, so that the interpretation of coefficients is the same as linear regression- link functions (Jones 2009). The most used specification of GLM in healthcare is the log-link with gamma error.

For instance, the expression of a GLM with an identity link is:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \varepsilon \quad (7)$$

The incremental effect, for instance, of x_1 is represented by $\delta y/\delta x_1$, which is equal to β_1. In case of non-identity link, the GLM presents the form:

$$y = g^{-1}(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \varepsilon) \quad (8)$$

The incremental effect rule is:

$$\frac{\delta y}{\delta x_1} = \beta_1 [(\delta y / \delta g) g^{-1}(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \varepsilon) \quad (9)$$

Lastly, all the covariates and coefficients in the model determine the incremental effect.

Furthermore, Stata's link test (see Pregibon (1980) for further details), a specification test that considers whether the 'link' is appropriate, was implemented. In the link test, the dependent variable is regressed on the predicted values and their squares. If the model is specified correctly, the squares of the predicted values would have no power.

All the analysis were run with STATA 15 econometric software.

In this study, two GLM model's combinations were applied. The two steps of the model correspond to as many equations. The first aims to explain the level of timeliness, expressed as time days' access, in terms of health system characteristics

(step 1). The second equation uses it to determine the pharmaceutical expenditures (step 2).

Starting from the equation of step 1, we assumed there are eight factors that can influence the time access of the new drug on the market: first of all, the structure of regional approval (i.e. the number of steps for introducing the new drug on local therapeutic handbooks), since increasing the complexity of the system, time access should increase also; secondly, the amount of NHF devoted to the region: higher funds may lead to lower time of new drug availability; repayment (RP) and receivership (RC) conditions, since these regions should be more attentive to cost-effectiveness evaluations; active mobility: regions which are more attractive (AM) are supposed to be more timely in terms of time of access, since they may have more effective health care availability; rate of people in bad health (BS): Regions with an higher number of individuals in bad conditions, may be pushed to speed up the process of new drug market introduction; frequency of meeting (FM): Regions whose committees meet more frequently, should also have shorter time in updating the handbooks and consequently faster time of new drug adoption.

Thus, the first step equation can be represented as:

$$(10)\ TimeAccess_i = \beta_0 + \beta_1 RTH2_{it} + \beta_2 RTH3_{it} + \beta_3 NHF_{it} + \beta_4 BS_{it} + \beta_5 RP_{it} + \beta_6 RC_{it} + \beta_7 AM_{it} + \beta_8 FM_i + u_i$$

$$i = Region$$
$$t = Time$$
$$u_i = Region - specific\ undetected\ components$$

The error u_i, is a stochastic variable with mean over all Regions (i) always zero and variance σ^2 (to be estimated together with the model parameters). It takes into account structural factors and economic conditions that differentiate the Regions and which remain unchanged throughout the period considered for the estimation. Specification of the random effects model was preferred over specification a fixed effect, as the latter, taking into account only the "within" dimension of the Regions panel, is at risk of excluding sources of interregional heterogeneity from the analysis (Kinal-Lahiri, 1993).

Finally, through the effect on the timeliness, regional structure and economic, social and demographic context variables influence the pharmaceutical expenditures (outpatient, inpatient and total). This link is captured by the equation of step 2 in which the dependent variable of step 1 appears as an explanation:

$$(11) \quad AgreedPharmaExpenditures_{it} = \beta_0 + \beta_1 TimeAccess_i + u_i$$

$$(12) \quad DirectPharmaExpenditures_{it} = \beta_0 + \beta_1 TimeAccess_i + u_i$$

$$(13) \quad TotalPharmaExpenditures_{it} = \beta_0 + \beta_1 TimeAccess_i + u_i$$

$$i = Region$$
$$t = Time$$
$$u_i = Region - specific\ undetected\ components$$

Moreover, according to the 2017 Budget Law, from January 1, the threshold of outpatient and inpatient pharmaceutical changed. A check for discontinuity was run in order to understand the effect of the policy, through the introduction in the second step of a dummy variable which assume value zero before 2017 and 1 after the Reform.

Finally, given the intrinsic characteristic of variables, all the factors may be correlated each other, causing a multicollinearity effect. Since we are aware about the multicollinearity problems, with consequence on underestimation of coefficients, we also run the Variance Inflation Factor (VIF) (Mansfield and Helms, 1982). Although the explanatory power of the model would not be reduced by the multicollinearity, there would be problems related to variances of the coefficients leading to insignificance. In detail there is a threshold, after which the interpretation of the significance will be meaningless (i.e. 10). We run the test with different model combinations and the limit was never overcome (the average was 7.25). For this reason, we shall abstain from detailed treatment.

III.I – Results and Discussion

III.I.I – Descriptive Statistics

Starting with some general descriptive statistics, mainly within regions, it is possible to appreciate some changes in the four years under investigation.

All regions increased or maintained the average time of stay: Piedmont, Friuli V.G., Liguria, Tuscany, Campania, Puglia remained constant; Lombardy, Veneto, Umbria, Lazio, Abruzzi Calabria, Sicily and Sardinia increased the stay of 0.1; Trento, E. Romagna and Basilicata of 0.2; Valle D'Aosta was he only one who increased on average half of a day of stay (0.5). From a general point of view, the length of stay among regions is similar oscillating between a minimum of 6.38 days in Campania and a maximum of 7.64 and 7.63 days for Liguria and Veneto. Regions can be grouped in thresholds:

- < 7 days of stay: Piedmont, Lombardy, Bolzano, Tuscany, E. Romagna, Umbria, Abruzzi, Puglia, Basilicata, Sardinia and Campania;
- > 7 days of stay: Valle D'Aosta, Trento, Friuli V.G., Marche, Lazio, Molise, Sicily and Liguria and Veneto.

On the other side, the number of per-capita prescription changed a bit more. In particular, Liguria, Marche and Friuli V.G reduced about one prescription per individual; on the reverse in Campania, the effect was opposite, on average one per-capita prescription more in 2018. From a general point of view, the number of per-capita prescription is different across Regions, from a minimum registered in Bolzano with 6 prescriptions (5.6 in 2017 and 6in 2018) per-patient to a maximum of about 12 prescriptions in Umbria (12 in 2017 and 11,5 in 2018) and Calabria (11,4 for 2017 and 11,7 for 2018). In 2018, three Regions reported to prescribe:

- between 7 and 8 per-capita prescriptions: Valle D'Aosta (7.2), Lombardy (7,6) and Veneto (7);

- four between 8 and 9: Trento (8.4), Friuli V.G (8,6), Liguria (8.6) and E. Romagna (8.6);
- two between 9 and 10: Piedmont (9) and Tuscany (9.2);
- four between 10 and 11 prescriptions per-patient: Marche (10.5), Lazio (10.8), Molise (10.5) and Sardinia (10.8);
- finally, seven Regions with more than 11 prescriptions per-patient: Umbria (11.5), Abruzzi (11.3), Campania (11.5), Puglia (11.1), Basilicata (11.1), Calabria (11.7) and Sicily (11).

According to literature and data, Bolzano is the youngest Region in Italy, immediately followed by Campania, in terms of average aging. By reverse, the oldest Region is Liguria, followed by Friuli V.G and Molise at equal footing. The aging process is a strong phenomenon which characterizes the whole country, indeed the percentage increment in Italy of older individual is 2,18%. All Regions experienced a percentage increment of old individuals, but some more than others. In detail, only Bolzano faced a positive variation lower than 1%; Liguria, Emilia Romagna and Tuscany experienced a senior citizens increment slightly higher than 1%; the highest number of Regions increased about 2% their percentage of old individuals (i.e. Piedmont, Lombardy, Friuli Venezia Giulia, Umbria, Marche, Lazio, Abruzzi, Molise and Calabria); for Trento, Veneto and Sicily the percentage variation was about 2.5%; Valle D'Aosta, Campania and Basilicata increased their percentage of old individuals of about 3%; in Puglia and Sardinia the increment was the strongest, about 3.5%. In this framework, the alarming situation concerns Sardinia which is the 4th older Italian Region.

In terms of attraction index, some Regions are well balanced as Piedmont (6.1% attraction and 6.9% escape), Bolzano (5.7% vs. 4.4%), Veneto (8.1% vs. 6%), Friuli V.G. (8.3% vs. 6.6%), Umbria (13.7% vs. 11.6%), Marche (11% vs. 13.4%), Lazio (7.7% vs. 8.4%) Molise (29.2% vs. 27.4%). On the other side, in some Regions, normally northern Regions, the attraction effect is much stronger than the escape one: Lombardy (10.8% attraction vs. 3.9% escape), E. Romagna (14% vs. 6.2%) and Tuscany (11.2 vs. 6.2%). Although some exceptions are present (Valle D'Aosta with 11% vs. 15.3%, Trento with 9.7% vs. 15.2% and Liguria 9.7%

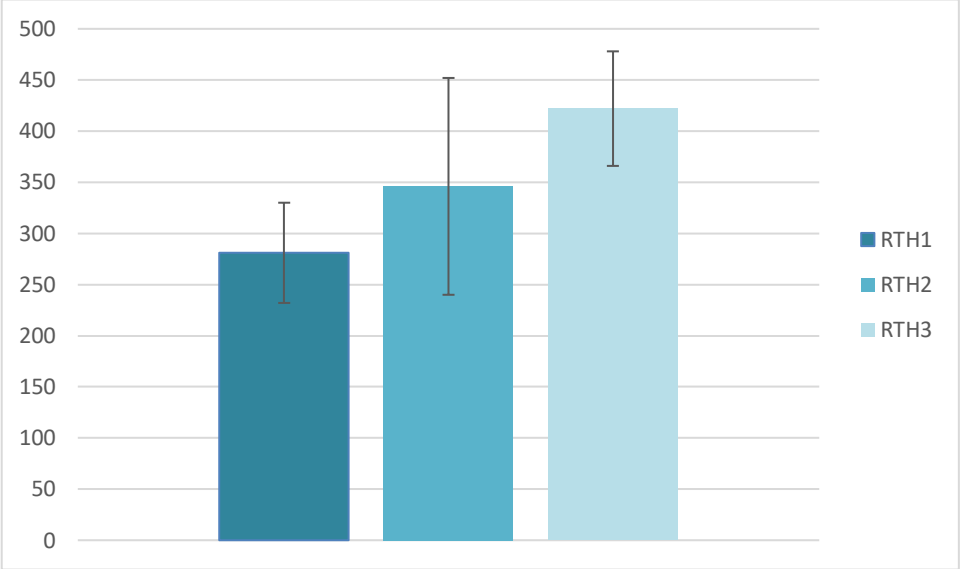
vs. 14.4%), in the southern part of Italy the escape effect is much stronger than the attraction one, especially in Calabria: Abruzzi (10.5% attraction vs. 17.3% escape), Molise (2.4% vs. 10.3%), Campania (4.7% vs. 9.4%), Puglia (17.3% vs. 25.9%), Calabria (2.4% vs. 24.7%) Sicily (1.8% vs. 7.7%) and Sardinia (1.9% vs. 5.3%). In terms of variation between the two years, the effect remained stable. In Valle D'Aosta, Trento, Liguria, Tuscany, Umbria, Abruzzi and Basilicata the attraction index was reduced but in a small percentage (< 0.5%); Lombardy, Friuli V.G, E. Romagna, Marche Lazio and Sardinia it is possible to observe the same but reverse effect (< 0.5%); only in Molise the attraction effect has been estimated to be higher than 1%. By contrast, the escaping process was lower in 2018 than 2017 for Piedmont, Trento, Liguria, Marche, Lazio, Calabria and Sardinia but with an average of 0.2; in all other Regions the escape effect increased between the two years with a stronger percentage variation in Calabria (0.4%), Basilicata (0.4%), Molise (0.7%) and Abruzzi (0.8%). The strongest negative effect was observed in Valle D'Aosta (1,5%) this may also be related to the unavailability of oncological and non-oncological funds.

Table 2 reports a descriptive statistic with mean, standard deviation, minimum and maximum of regions days of access clustered for RTH structure.

Table 2: Descriptive statistics of RTH levels.

RTH	#Regions	Mean	St.Dev.	Min	Max
1	5	281	48,86	217	342
2	13	346	105,83	217	530
3	3	422	56,05	360	491

Figure 4: RTH levels and Standard Deviation.



On average, one-tier Regions are timelier in terms of days of access: 281 days for a new drug to be available on the market. Progressively, increasing the complexity of the system, the timing of access increases too: 346 days for two-tier Regions, 422 days for three-tier Regions. As reported in Table 2 and in Figure above (Figure 4), the standard deviation is similar for one and three-tier Regions but almost double for two-tier ones. This suggests that the two-tier typology is the most variable with some Regions which operate as good as one-tier Regions and some which operate also worse than three-tier ones.

Table 3: Variation in National Health Fund and Fund for Oncological and Non-Oncological Drugs

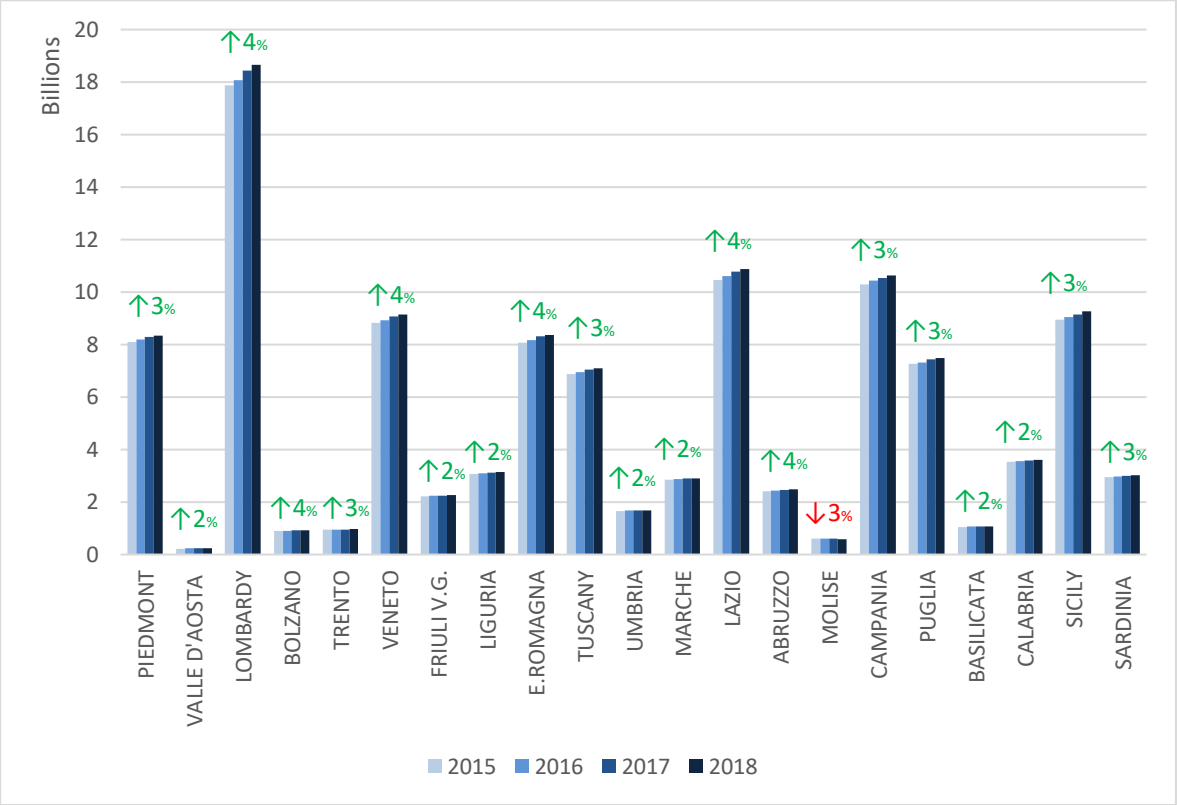
Region	*Δ National Health Fund (2015-2018)*	*Δ Fund for Oncological Drugs (2017-2018)*	*Δ Fund for Non-Oncological Drugs (2017-2018)*
Piedmont	261.339.506	-83.515	2.445.433
Valle D'Aosta	4.007.028	0	0
Lombardy	779.664.598	201.061	23.374.569
Bolzano	37.432.693	0	0
Trento	31.589.032	0	0
Veneto	327.847.935	7.959	-643.100

Friuli V.G.	48.679.911	0	0
Liguria	63.422.995	-61.209	392.065
E. Romagna	300.281.029	9.155	-3.432.382
Tuscany	225.642.910	-9.899	-4.633.868
Umbria	42.126.669	-16.030	473.526
Marche	56.917.755	-44.304	-2.512.599
Lazio	408.297.862	133.956	-14.851.762
Abruzzi	63.356.668	-25.150	-1.366.057
Molise	-17.355.067	-11.820	-1.363.518
Campania	332.733.216	8.720	5.778.706
Puglia	221.447.096	-30.209	-5.602.726
Basilicata	26.039.231	-22.805	1.362.161
Calabria	79.440.221	-18.773	-2.170.449
Sicily	318.585.529	-37.139	2.750.002
Sardinia	83.840.034	0	0
Italy	3.695.336.851	0	0

In Table 3 are reported the funds variations. In detail the NHF variation and the two funds for innovative drugs (oncological and non-oncological). In the distribution of the NHF to the Regions there are three level which are considered for the repartition: the prevention, the district and the hospital levels. The "prevention" level represents 5% of the fund. The "district" level corresponds to 51% of the NHF and is in turn made up of four sub-levels: basic medicine (7%), pharmaceuticals (13.57%), the specialist (13.3%), and territorial medicine (17.13%). The level of "hospital" care represents 44% of the fund. The NHF was increased from 2015 to 2018, passing from about 109 billion to 112.8 billion. According to the repartition Regions Lombardy has the primacy (18.7 billion for 2018), followed by Lazio and Campania with 10.9 and 10.6 billion respectively. Then, 9.3 billion in Sicily, 9.1 billion in Veneto, 8.4 in E. Romagna, Piedmont 8.3, 7.5 in Puglia and 7.1 in Tuscany. Then it is possible to observe a wide gap: Calabria with 3.6 billion, then 3.1 billion in Liguria and 3.0 billion in Sardinia, 2.9 billion in Marche, 2.5 billion in Abruzzi, Friuli V.G 2.3 billion, 1.7 billion in Umbria and 1 billion in Basilicata. Then all the remaining Regions (i.e. Bolzano, Trento, Valle D'Aosta and Molise) have funds for less than 1 billion. In terms of variation between the years under observation is possible to observe a positive variation, reported in Figure 5 below, but for Molise with a negative trend. To be noted that two Regions experienced a decrement in funds only in the last two years: Marche, with a reduction of 8,7 million and Molise with 17,3 million. All other Regions

augmented their possibilities with a maximum of 219.7 million in Lombardy and a minimum of 5.7 and 2.2 million in Umbria and Basilicata.

Figure 5: NHF across the four years of investigation with relative percentages of increment/decrement of funds.

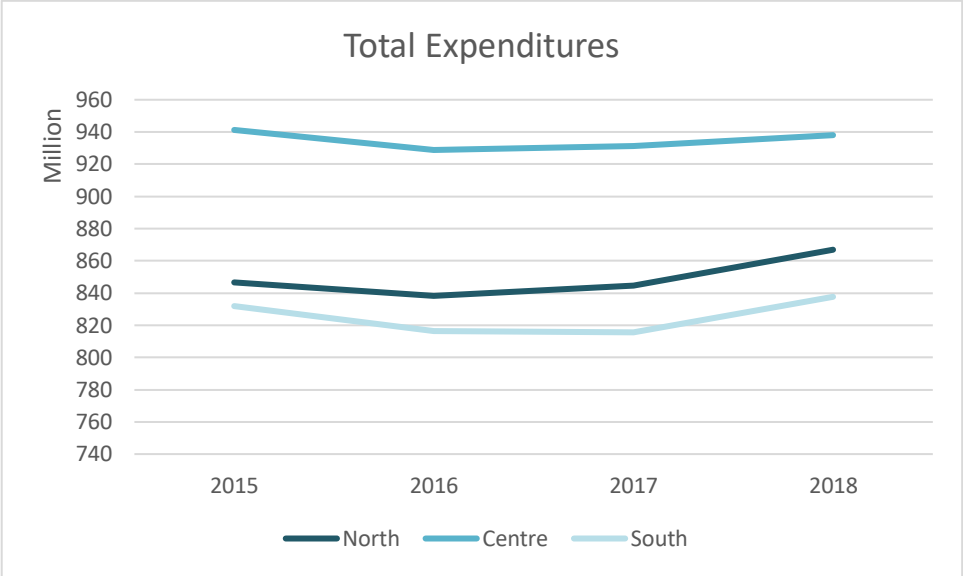


For innovative oncological and non-oncological drugs, it is important to underline that not all Regions can tap into the funds: Friuli Venezia Giulia, Valle d'Aosta, Sardinia and the autonomous provinces of Bolzano and Trento do not join the fund for innovative drugs, Sicily only in part (50%). 2017 was the first year of concession of these funds, for these reasons the oncological and non-oncological one were equal in the same Regions, but obviously different for each Region. In 2017 the repartition of funds follows more or less same trend as the NHF repartition: Lombardy has the higher share of the 500 million available: 92.4 million. Lombardy

is followed by 54 million in Lazio and 52.2 in Campania. Sicily (23.5 million) is bypassed by Veneto (45.5 million), E. Romagna (41.6), Piedmont (41.6), Puglia (37.2), Tuscany (23.5). Then Calabria (18), Liguria (15), Marche (14.5), Abruzzi (12.4), Umbria (8.4), Basilicata (5.3) and Molise (2.9). In 2018, the fund for innovative drugs faced some small variations, but from a general point of view it can be considered stable. By reverse, the fund for non-oncological drugs changed for different Regions, starting from Lombardy which passed to 115.8 million. Regions which increased funds between 1 and 3 million are Piedmont (44), Sicily (26.2) and Basilicata (6.7); between 3 and 6 million is Campania (57.9). By reverse, Regions whose fund was reduced between 1 and 3 million are Veneto (44.7), E. Romagna (38.2), Calabria (15.8), Marche (12), Abruzzi (11) and Molise (1.6); between 3 and 6 million: Puglia (31.6) and Tuscany (30.7). Finally, for Liguria and Umbria funds increased less than 1 million. The outlier in repartition is represented by Lazio (39.2) whose fund was reduced about 15 million.

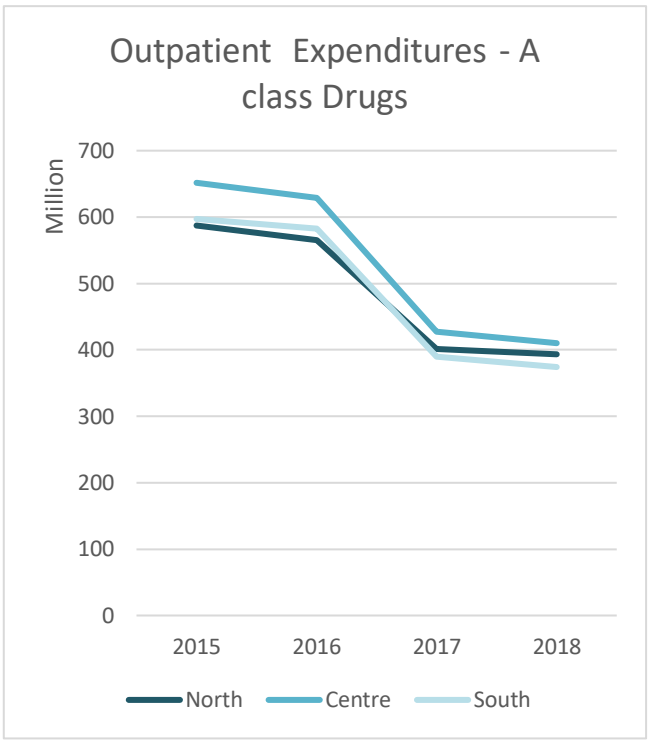
Clustering Regions into North, Centre and Southern, it is possible to graphically observe (Figure 6) that the total expenditures, across the years has been pretty stable. The average expenditure per region is more consistent in Centre Regions with a gap from Northern ones of about 100millions euros per year, and from Southern ones of about 120million.

Figure 6: North, Centre and South clustering of total pharmaceutical expenditures between 2015 and 2018.



The second step was to split the pharmaceutical expenditures between inpatient and outpatient expenditures. According to Figure 7 is possible to observe a switch in trend in the two class drugs expenditures. Outpatient expenditures decreased progressively in the four years. North Regions spending was about 600 million of euros in 2015 decreased to 400 million in 2018. Southern Regions followed more or less the same path of northern ones (from 600millions to 370millions). Finally, Centre regions decreased spending from 650millions to 410 million. The strongest impact was in Sardinia with a reduction of 87% and the smallest effect was observed in Lombardy (-32%). Reverse trend took place for H class drugs, where expenditures increased, compensating the reduction in outpatient expenditures. In detail: Centre regions increased from about 300 million to 530 million, Northern from 250 million to 460 million and Southern with an increment of 230 million (from 230 to 460 million). Trento increased expenditure of 58%, by reverse Tuscany experienced the smallest increment (32%). For further details, see Appendix A and Appendix B.

Figure 7: North, Centre and South clustering of outpatient and inpatient pharmaceutical expenditures between 2015 and 2018.



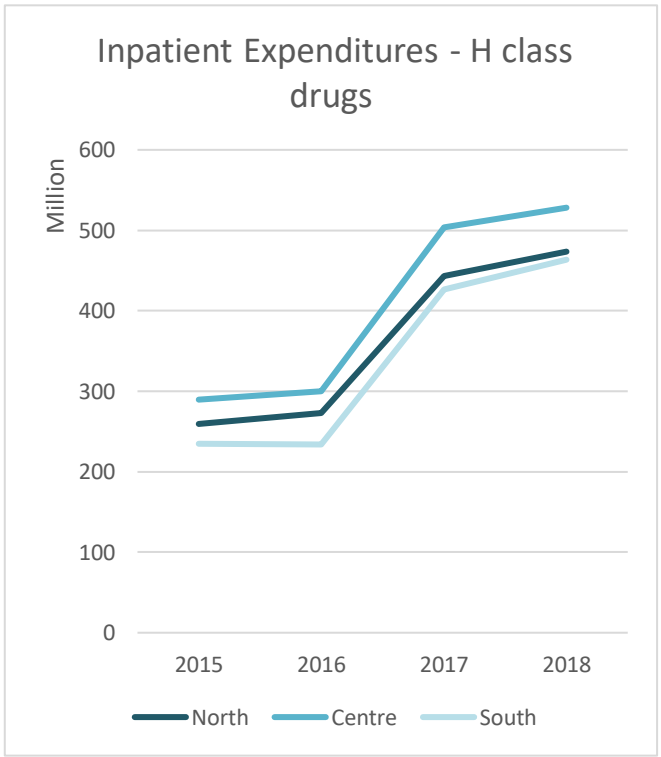
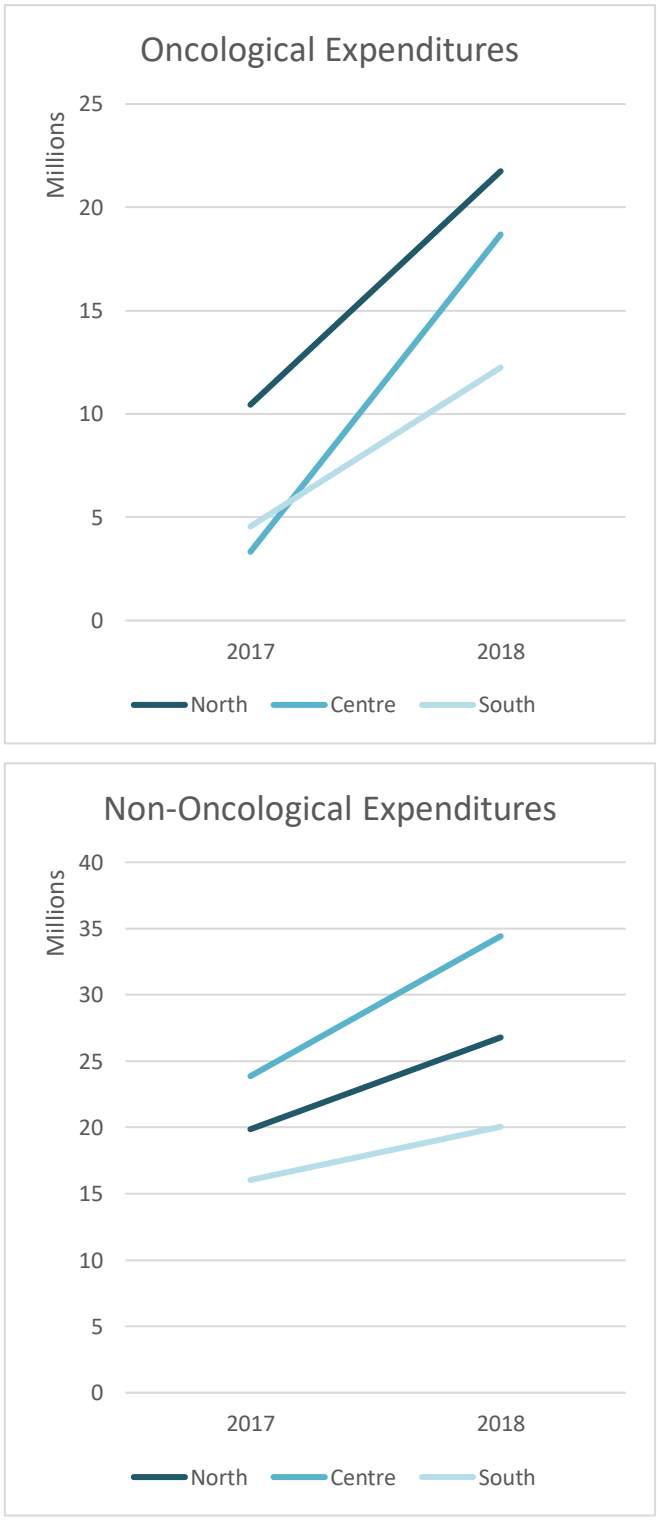


Figure 8: North, Centre and South clustering of oncological and non-oncological pharmaceutical expenditures between 2017 and 2018.



Regarding the oncological and non-oncological pharmaceutical expenditures (Figure 8) for innovative drugs, in both scenarios, expenditures increased. The North of Italy, continued to be the first for investment in Oncological drugs (from 10 million to 22 million invested). Anyway, Centre of Italy, from the third position, jumped trying to catch the north (from 3.3 million to 18.5 million invested). The non-oncological investments follow the same incremental path but in this case Centre of Italy tend to invest more in that: from 24 million in 2017 to 34.5 million in 2018. For further details, see Appendix C.

The overall expenditure is fundamental since a compensation between the two is possible. The only Regions which did not exceeded the threshold in the period 2015-2018: Valle D'Aosta, Trento, Bolzano and Veneto, which has been able to compensate losses generated from direct expenditure, with savings gained from affiliated purchases (For further details see Appendix D).

Figure 9 shows the percentages of total expenses deviation from the relative ceiling in the four years of investigation. Positive values indicate that the Region exceed the ceiling, negative ones that Region spent less than the threshold.

Figure 9: percentages of total pharmaceutical expenditures deviation from the relative ceilings between 2015 and 2018 divided per Region.

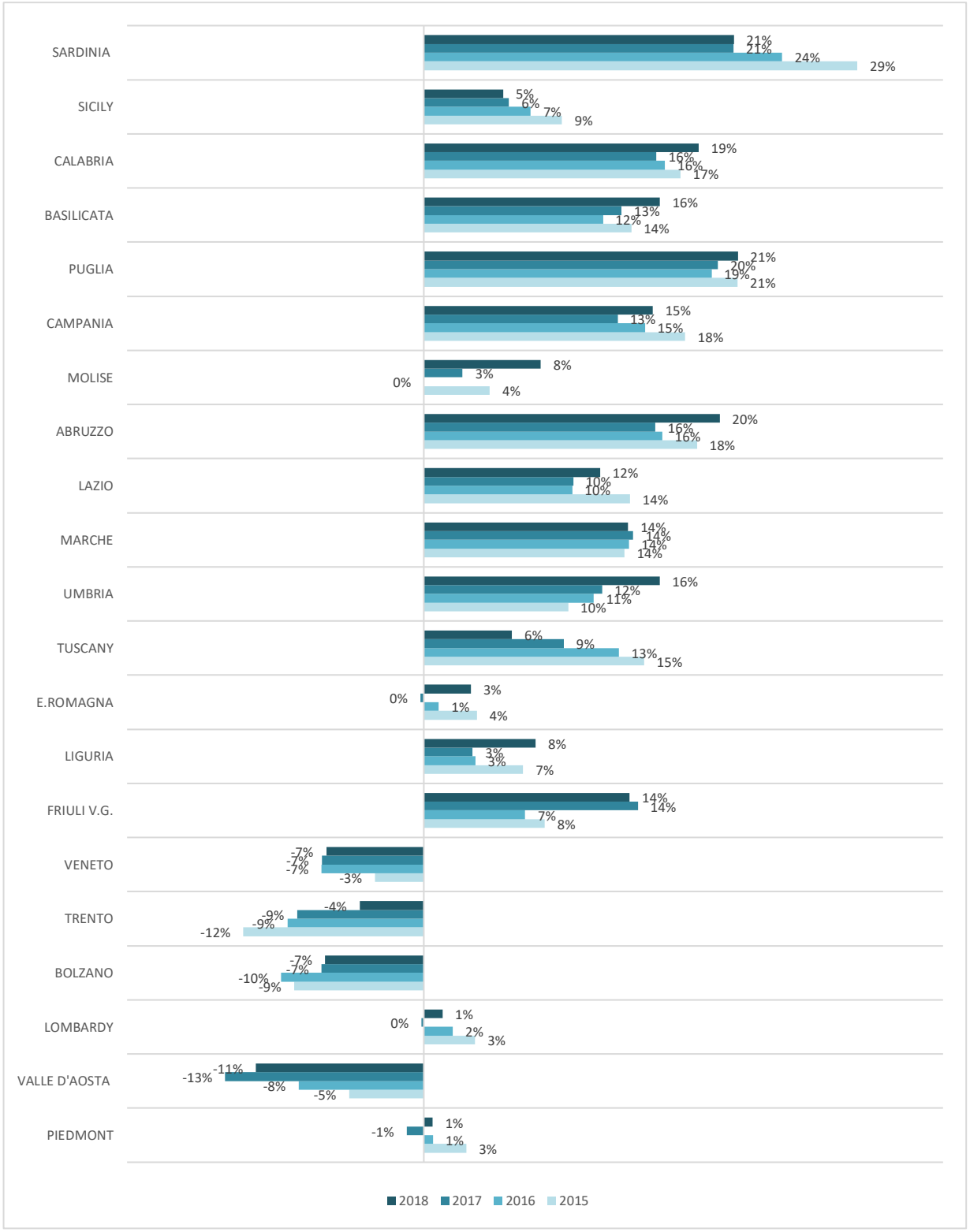


Table 4 reports the average time of access for drugs in H class, which obtained the marketing authorization in a time horizon of 7 years, from 2010 to 2017.

Table 4: average time access for class H drugs with MA/reimbursement in a time span from 2010 to 2017 divided per Region.

Region	Days		Region	Days
Molise	530		Trento	327
Liguria	491		Lazio	289
Piedmont	453		Veneto	275
Campania	435		Calabria	260
Sardinia	427		Friuli V,G,	244
Marche	426		Sicily	237
E, Romagna	416		Abruzzi	219
Valle D'Aosta	403		Umbria	218
Basilicata	387		Puglia	217
Tuscany	360		Lombardy	217
Bolzano	342		Italy	341,6

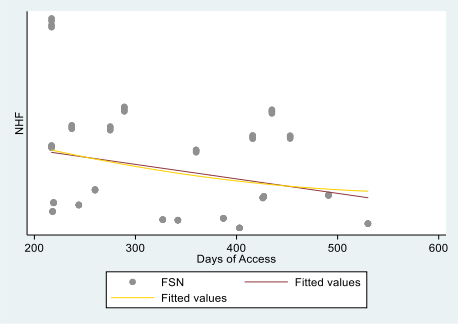
The average time of access for new drugs varies strongly according to the Region:

- On the podium, with Lombardy (217 days), there are Puglia (217), Umbria (218) and Abruzzi (219);
- Sicily, Friuli V,G, Calabria, Veneto and Lazio have access times of less than 300 days (237, 244, 260, 275 and 289 days respectively);
- between 300 and 400 days: Trento (327), Bolzano (342), Tuscany (360) and Basilicata (387)

- between 400 and 500 days: Valle D'Aosta (403), E, Romagna (416), Marche (426), Sardinia (427), Campania (435), Piedmont (453) and Liguria (491);
- finally, as taillight Molise with 530 days,

Figure 10 below, highlights the correlation between days of access and funds devoted to regions.

Figure 10: correlation between time access for class H drugs and NHF.



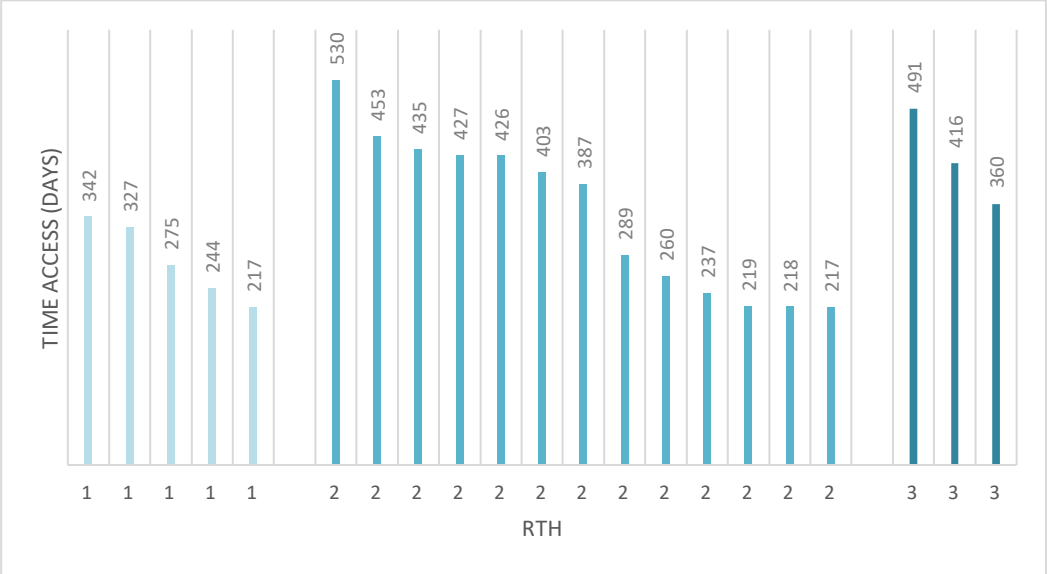
In detail, is possible to see a negative relationship between the two. Increasing funds, also the days of access reduce with a correlation coefficient of -0.1960 (p-value: 0.07) provided by the Spearman test.

These differences in days are a first demonstration of what previously stated: different structure of new drugs introduction generate strong differences in access for patients and physicians to new drugs. This means that if a generic new drug available in Lombardy or Puglia today, will be, on average, available in 27 more days in Veneto, 72 in Lazio, 143 in Tuscany, 236 in Piedmont and 313 more days

in Molise, Obviously, this implies heterogeneity in access, which is in contrast with Italian Constitution principle of equity of access.

Figure 11 represents the relationship between the Regional scenario and the average time of access of new drug approval.

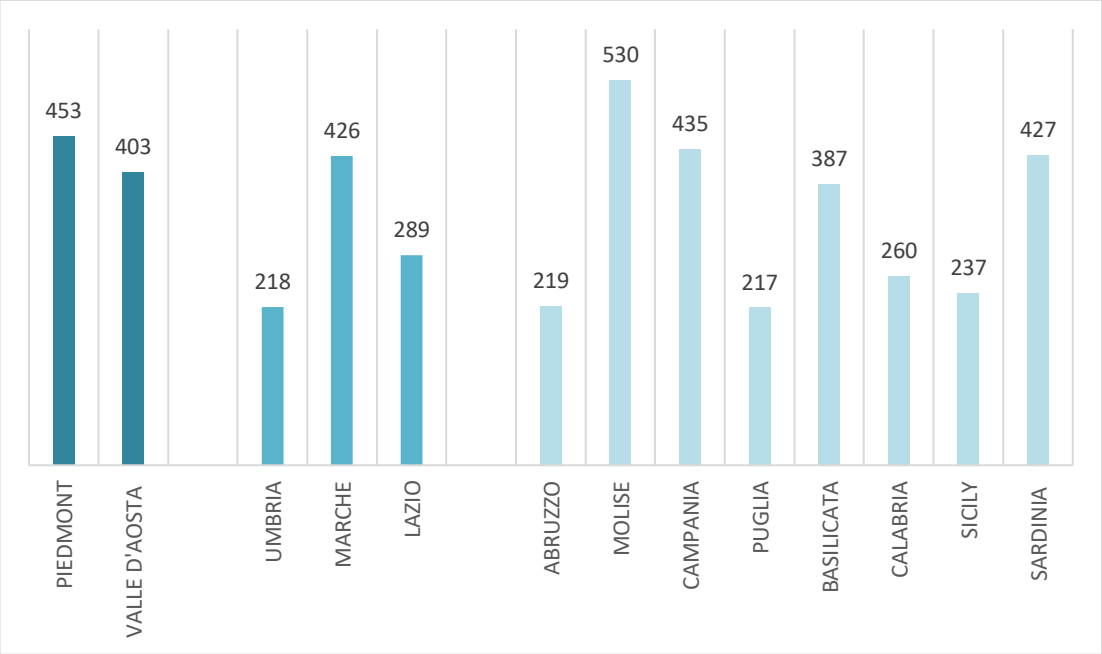
Figure 11: Relationship between average time of access and Regional Therapeutic Handbooks, between 2015 and 2018.



According to the figure above, from a general perspective it is possible to appreciate that Regions with one level have lower time in access than Regions with three levels. In detail, Lombardy presents the lower time access and has one level for introducing the drug in the market (i.e. only HTH level). Lombardy is followed by Friuli V.G. with (244 days), Veneto (275 days), Trento (327 days), Bolzano (342). Three levels Regions instead are Liguria (491 days), E. Romagna (416 days) and Tuscany (360 days). Comparing these two groups, descriptive statistics results are in line with our initial hypothesis, Regions with a leaner structure take less time in introducing new drug in Hospital Therapeutic Handbooks. By reverse, Regions which have more structured steps take more times since they have three steps before the introduction in Regional Handbooks. This is confirmed though the spearman correlation index: Regions with one level are negatively correlated to the days of

access (p-value: 0.00), by reverse Regions with three levels face longer times of drug introduction. This means that the thinner is the system, the faster is the process. Finally, further investigations are needed for two levels since from figure above it is possible to observe a high variance, with some two-tier regions which perform as good as one-tier Regions. In detail, Figure 12 focuses on regions with two levels in order to understand if a North-Southern gradient is present.

Figure 12: Two-tier Regions divided in: North, Centre, South.



Paradoxically, if we look at the two-tier regions, we can see that North works worse in terms of access to drug therapies (i.e. Piedmont and Valle D'Aosta). This may be dictated by geographical issues and centres of excellence availability: Piedmont and the Aosta Valley boast fewer focal points and consequently the bargaining process between the pharmaceutical company and the Region could take place more slowly and, on the other side, they may be less attractive from a competition point of view.

Looking at the central part of Italy, we can observe that it has a faster process that allows for more timely access to treatment, compared to Northern part of Italy. The only outlier is Marche where, however, LTH does not have direct insertion

with the aggravating circumstance that the meetings to decide the insertion of new drug in Handbooks take place on a quarterly basis.

Finally, we can observe a higher heterogeneity in South: Molise is the maximum example of failure with a not binding handbook associated with meeting which take place every 6 months. By reverse virtuous Regions have a "normal" insertion structure while maintaining average times.

The explanations of these effect and variance for the second level may multiple: a) two-tier region represent the wider part of the sample, in this sense variance increases increasing the observations; b) there are some peculiarities for Regions, where some steps are not so rigid and so the process may be faster (e.g. Calabria where the first step is a mere container or Lazio where the HTH insertion is direct and the evaluation is ex- post); c) there are some factors which remain inexplicable since some factors may not be captured by our determinants (e.g. political influence and concrete local organisation within the Local Authorities).

III.I.II – Generalized Linear Model (GLM)

GLM models are run in different combinations between link and family functions: Gaussian-Log, Gamma-Log, Gaussian-Identity, Gaussian-Identity. Below are reported only the baseline model: Gaussian-Log (OLS) and Gamma-Identity.

Table 5: First Step: Timeliness with Gaussian – Log combination (OLS).

TimeAccess	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
RTH2	0.350	0.067	5.23	***	0.218	0.481
RTH3	0.618	0.069	9.02	***	0.483	0.752
Year	0.001	0.021	0.04		-0.040	0.042
NHF	2.59e-11	1.23e-11	2.10	**	1.75e-12	5.00e-11
Repayment Plan	-0.313	0.128	-2.45	**	-0.564	-0.063
Rate of people in bad health	-0.068	0.022	-3.05	**	-0.111	-0.024

Recieveship conditions	0.260	0.109	2.36	**	0.044	0.474
Active Mobility	-6.74e-06	1.80e-06	-3.74	***	-0.000	-3.21e-06
Frequency of meetings	0.002	0.001	2.02	**	0.000	0.003
_cons	5.933	0.100	59.11	***	5.734	6.129

Table 6: Second Step: Inpatient and Outpatient Pharmaceutical expenditures with Gaussian – Log combinations (OLS).

Inaptient Expenditures	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
TimeAccess	-0.002	0.001	-2.05	**	-0.004	-0.000
_cons	20.417	0.354	57.65	***	19.723	21.111

Outpatient Expenditures	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
TimeAccess	-0.002	0.001	-2.14	**	-0.005	-0.001
_cons	20.945	0.393	53.30	***	20.177	21.718

Total Expenditures	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
TimeAccess	-0.002	0.001	-2.42	**	-0.005	-0.001
_cons	21.402	0.353	60.55	***	20.701	22.095

Table 7: First Step: Timeliness with Gamma-Identity combination.

TimeAccess	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
RTH2	138.357	25.247	5.48	***	88.874	187.841
RTH3	218.297	24.423	8.94	***	170.428	266.166
Year	1.441	6.738	0.21		-11.765	14.647
NHF	1.16e-08	3.75e-09	3.09	**	4.24e-09	1.89e-08
Repayment Plan	-129.619	25.812	-5.02	***	-180.209	-79.029
Rate of people in bad health	-24.874	5.815	-4.28	***	-36.272	-13.377
Recieveship conditions	70.643	29.994	2.36	**	11.856	129.430
Active Mobility	-0.002	0.001	-4.36	***	-0.003	-0.001
Frequency of meetings	0.624	0.254	2.46	**	0.127	1.122
_cons	372.443	31.207	11.93	***	311.278	433.609

Table 8: Second Step: Direct and Agreed Pharmaceutical expenditures with Gamma-Identity combination.

Inpatient Expenditures	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
TimeAccess	-866909.5	459065.4	-1.89	**	-1766661	32842.18
_cons	6.60e+08	1.72e+08	3.84	***	3.23e+08	9.97e+08

Outpatient Expenditures	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
TimeAccess	-1428314	637852.9	-2.24	**	-2678483	-178145.4
_cons	9.86e+08	2.45e+08	4.02	***	5.06e+08	1.47e+09

Total Expenditures	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
TimeAccess	-2301093	1041426	-2.21	**	-4342251	-259934.6
_cons	1.65e+09	3.96e+08	4.16	***	8.73e+08	2.42e+09

According to tables above it is possible to appreciate expected relationships at the timeliness level (first step) and the pharmaceutical one (second level). At the timeliness level, in line with our expectations, it is possible to confirm that the more complex is the regional system in drug approval, the longer is the time of drug availability on the market. The reason behind this result may be related to the duplication of procedures before the introduction of the new drug in Therapeutic Handbooks. This results also implies equity effects: therapies are not uniformly available on the national territory, implying non uniformity in care.

The variable *Year* has been introduced to see if there is or not a trend. According to results, no trend has been captured. NHF is positively correlated with time access meaning that increasing the economic funds, also increases the time of approval. Although in contrast with expectations, the effect on the time access is small and maybe affected by the short time horizon and the small sample influence. *Repayment Plan* and *Receivership conditions* are respectively negatively and positively correlated. This result finds it roots in the definition of policies: the first one has the aim to contain costs and to ensure the essential levels of assistance (LEA) in compliance with the national programming and with the DPCM

12/01/2017; the second one instead intervenes when the outcome of Return Plan demonstrates the non-compliance of a region. The "ad acta" Commissioner has the primary aim of achieving balanced budget in order to settle the financial situation. This, consequently, implies less care in new drugs approval. Our results show that Regions with higher *Rate of people in bad health* tend to reduce times for new drug access. This is the effect of the Region attraction: virtuous Regions increase their opportunity of being centres of excellence, which leads to an increment of prestige. Patients in bad health status are attracted by these Regions. This effect may be also captured by the *Active Mobility* variable: the higher is the number of individuals discharged which come from other Regions, the lower is the time access of the drug. Finally, the *Frequency of meetings* influence negatively the time of drug approval: the more infrequent the meeting, the more postponed the inclusion of the drug in the Handbook. Finally, the variable *Time* is not significant in any case, as expected, since days of time access present no variance. They report the average time for a drug to be concretely available on the market for patients between 2010 and 2016.

The second step of the analysis, observes the effect of timeliness on the pharmaceutical expenditures. In both the typologies of expenditures, it is possible to observe a negative relationship: increasing the time of new drug approval (i.e. reduction in Regional timeliness), both *Inpatient* and *Outpatient Pharmaceutical Expenditures* decrease. The explanation is twofold: from one side, a shorter time of new drug approval is typical of regions which are more virtuous and so characterized by high-cost drugs; on the other side, shorter times for a new drug usage implies shorter times to sustain those costs, in other words in a specific span of time, longer times lead to a delay in expenditures. Less timely Regions have also duplicated procedures, more complex systems, less attractive conditions. Availability of new and expensive therapies and latest generation drugs are typical of more timely Regions. These results seem to justify the suspect that the decentralization process allows local committees to adopt their right of veto for the control of spending.

The link test confirmed the appropriateness of the 'link'. Thus, it is possible to conclude that the model is correctly specified, since the squares of the predicted values have no power.

Finally, different robustness checks were run in order to verify the models[19]. In detail, the models were first run with the same structure and the introduction of some indicators of timeliness (Table 9). Then the second step was to replace the same procedure but with the pro-capite NHF in order to see if there are some relevant changes (Table 10).

According to the tale below it is possible to conclude that the specification is robust for all the variables used in the preferred model. We would like to point that with pro-capite specification, the NHF is no more significant. This can be explained by the size effect[20]. In detail this means that the effect can be observed only at the aggregate level. It is in line with the expectations, since the NHF is distributed considering the regional population and the regional transfers; this may imply that the Regional dimension generates timeliness also. Moreover, as reported in Figure 13, pro-capite NHF did not increase a lot.

Furthermore, we run all the robustness checks either with robust standard errors and with clustered errors by regions. According to this procedure, the specificity is reduced in case of clustered errors, but the signs of independent variables remain the same (Table 11 and Table 12).

[19] To be noted, we run more checks than those reported. We decided to insert in the text only the more significant ones.

[20] introducing the weighted population, excluding NHF and people in bad state of health status, the final result does not change, keeping the significance.

Table 9 – Robustness Check – Combinations of indexes.

	Robustness Check 1		Robustness Check 2		Robustness Check 3		Robustness Check 4	
	GLM - Gaussian - Log	*GLM - Gamma - Identity*	*GLM - Gaussian -Log*	*GLM - Gamma - Identity*	*GLM - Gaussian - Log*	*GLM - Gamma - Identity*	GLM - Gaussian -Log	GLM - Gamma - Identity
TimeAccess	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
RTH2	0.311 (0.059) ***	129.162 (22.524) ***	0.358 (0.069) ***	140.075 (26.512) ***	0.317 (0.062) ***	130.364 (23.761) ***	0.251 (0.090) ***	123.456 (30.761) ***
RTH3	0.548 (0.074) ***	203.895 (26.954) ***	0.658 (0.077) ***	221.095 (25.548) ***	0.579 (0.078) ***	206.054 (27.122) ***	0.545 (0.072) ***	203.597 (27.665) ***
Year	-0.004 (0.0188)	-0.552 (6.420)	0.003 (0.021)	2.329 (6.546)	0.001 (0.019)	0.297 (6.158)	0.003 (0.019)	1.815 (6.668)
NHF	5.12e-11 (1.23e-11) ***	1.79e-8 (4.07e-9) ***	2.19e-11 (1.25e-11) *	9.65e-9 (3.99e-19) **	4.73e-11 (1.23e-11) ***	1.58e-8 (4.00e-9) ***	3.24e-11 (1.15e-11) ***	1.28e-8 (3.78e-9) ***
Attraction Index	0.212 (0.001) ***	5.723 (2.533) **			0.021 (0.006) **	5.797 (2.418) **		
Escape Index			0.009 (0.007)	2.207 (1.841)	0.007 (0.006)	2.499 (1.622)		
Cancer Discharge Rate							0.003 (0.001) **	0.578 (0.429)
Repayment Plan	-0.356 (0.124) **	-141.248 (27.732) ***	-0.295 (0.125) **	-122.252 (26.539) ***	-0.340 (0.122) **	-133.601 (27.464) ***	-0.251 (0.132) *	-120.438 (28.009) ***
Rate of people in bad health	-0.051 (0.023) **	-20.299 (6.349) **	-0.067 (0.021) ***	-25.015 (5.789) ***	-0.052 (0.022) **	-19.954 (6.441) **	-0.066 (0.022) ***	-25.761 (5.605) ***
Recieveship conditions	0.237 (0.107) **	62.923 (28.786) **	0.298 (0.103) **	79.163 (26.950) **	0.263 (0.099) **	75.117 (26.585) **	0.235 (0.110) **	66.187 (29.541) **

Active Mobility	-0.000 (2.13e-06) ***	-0.004 (0.001) ***	-7.17e-06 (1.72e-06) ***	-0.002 (0.001) ***	-0.001 (2.07e-06) ***	-0.003 (0.001) ***	-7.19e-6 (1.60e-6) ***	-0.002 (0.001) ***
Frequency of meetings	0.000 (0.001)	0.187 (0.301)	0.003 (0.001) **	0.765 (0.289) **	0.001 (0.001)	0.355 (0.315)	0.002 (0.001) **	0.569 (0.249) **
_cons	6.553 (37.992)	1441.767 (12943.880)	-0.167 (42.074)	-4302.788 (13202.390)	2.915 (38.331)	-250.777 (12416.06)	-2.266 (38.790)	-3356.817 (13447.44)

Table 10 – Robustness Check – Pro-capite NHF with different combinations of indexes.

	Robustness Check 1		Robustness Check 2		Robustness Check 3		Robustness Check 4		Robustness Check 5	
	GLM - Gaussian - Log	*GLM - Gamma - Identity*	*GLM - Gaussian - Log*	*GLM - Gamma - Identity*	*GLM - Gaussian - Log*	*GLM - Gamma - Identity*	GLM - Gaussian - Log	GLM - Gamma - Identity	GLM - Gaussian - Log	GLM - Gamma - Identity
TimeAccess	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
RTH2	0.341 (0.070) ***	125.978 (24.368) ***	0.357 (0.072) ***	125.325 (23.299) ***	0.356 (0.074) ***	128.833 (26.919) ***	0.342 (0.075) ***	126.966 (25.769) ***	0.275 (0.093) **	119.686 (26.288) ***
RTH3	0.508 (0.064) ***	164.000 (0.064) ***	0.485 (0.074) ***	158.192 (29.55) ***	0.573 (0.078) ***	177.265 (24.627) ***	0.547 (0.086) ***	168.784 (30.008) ***	0.461 (0.066) ***	156.456 (24.411) ***
Year	-0.004 (0.024)	-3.007 (7.570)	-0.004 (0.024)	-3.226 (7.533)	-0.002 (0.024)	-2.304 (7.454)	0.001 (0.024)	-2.829 (7.401)	0.001 (0.023)	-2.673 (7.676)
NHF pro capite	0.001 (0.000) *	0.210 (0.153)	0.005 (0.004)	0.201 (0.148)	0.001 (0.000) *	0.243 (0.163)	0.001 (0.001)	0.225 (0.156)	0.001 (0.001)	0.203 (0.154)

Attraction Index			0.005 (0.008)	1.153 (3.742)			0.006 (0.008)	1.987 (3.055)		
Escape Index					0.013 (0.006) **	4.165 (1.917) **	0.012 (0.006) **	4.518 (1.913) **		
Cancer Discharge Rate									0.002 (0.001)	0.269 (0.455)
Repayment Plan	-0.251 (0.122) **	-100.393 (30.669) **	-0.239 (0.120) **	-98.920 (29.713) *	-0.241 (0.116) ***	-101.069 (29.340) ***	-0.226 (0.121) **	-99.153 (28.257) ***	-0.201 (0.129) **	-93.287 (34.385) *
Rate of people in bad health	-0.061 (0.021) **	-19.372 (5.135) **	-0.054 (0.025) **	-18.267 (6.679) **	-0.063 (0.019) **	-20.620 (5.068) ***	-0.055 (0.023) **	-18.385 (6.785) **	-0.058 (0.021)	-19.609 (5.164) ***
Recieveship conditions	0.238 (0.119) **	71.813 (32.767) **	0.223 (0.119) **	69.682 (31.992) **	0.292 (0.105) ***	90.137 (27.337) ***	0.281 (0.103) **	89.876 (27.688) ***	0.226 (0.119) *	68.315 (33.652) **
Active Mobility	-3.17e-06 (6.51e-07) ***	-0.001 (0.000) ***	-3.53e-06 (8.40e-07) ***	-0.001 (0.000) ***	-4.53e-06 (9.17e-07) ***	-0.001 (0.001) ***	-4.96e-06 (1.04e-06) ***	-0.001 (0.002) ***	-2.96e-06 (6.19e-07) ***	-0.001 (0.000) ***
Frequency of meetings	0.001 (0.001)	0.1221 (0.231)	0.001 (0.001)	-0.07 (0.470)	0.002 (0.001) **	-0.052 (0.322)	0.001 (0.001)	0.342 (0.433)	0.001 (0.001)	0.083 (0.234)
_cons	12.263 (48.117)	6077.593 (15117.780)	6.408 (47.383)	6531.425 (15050.090)	10.012 (48.719)	4628.199 (14860.300)	3.246 (48.399)	5707.878 (14760.510)	2.853 (46.001)	5384.622 (15331.770)

Figure 13 – Pro-capite NHF increment across the years of investigation

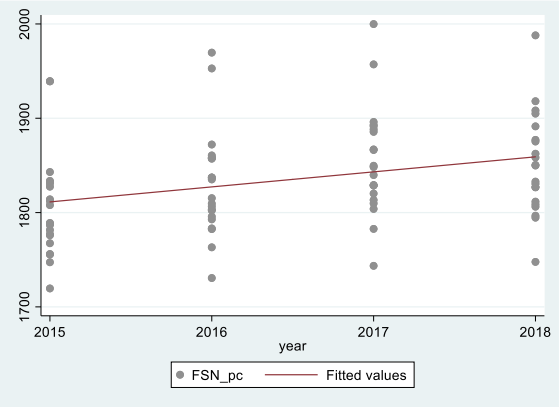


Table 11 – Robustness Check – Combinations of indexes and Clustered Standard Errors.

	Robustness Check 1		Robustness Check 2		Robustness Check 3		Robustness Check 4	
	GLM - Gaussian - Log	*GLM - Gamma - Identity*	*GLM - Gaussian - Log*	*GLM - Gamma - Identity*	*GLM - Gaussian - Log*	*GLM - Gamma - Identity*	GLM - Gaussian -Log	GLM - Gamma - Identity
TimeAccess	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
RTH2	0.311 (0.099) **	129.162 (38.825) ***	0.358 (0.121) **	140.075 (46.661) **	0.317 (0.106) **	130.364 (41.912) **	0.251 (0.158) *	123.456 (52.832) **
RTH3	0.548 (0.141) ***	203.895 (50.824) ***	0.658 (0.147) ***	221.095 (47.509) ***	0.579 (0.147) ***	206.054 (50.829) ***	0.545 (0.132) ***	203.597 (50.335) ***
Year	-0.000 (0.001)	-0.552 (3.760)	0.003 (0.010)	2.329 (3.548)	0.001 (0.008)	0.297 (3.565)	0.004 (0.008)	1.815 (3.376)
NHF	5.12e-11 (2.26e-11) **	1.79e-08 (7.58e-09) **	2.19e-11 (2.30e-11)	9.65e-09 (6.97e-09)	4.73e-11 (2.24e-11) **	1.58e-08 (7.21e-09) **	3.24e-11 (2.10e-11)	1.28e-08 (6.77e-09) *
Attraction Index	0.022 (0.012) *	5.723 (4.687			0.021 (0.012) *	5.797 (3.021)		
Escape Index			0.009 (0.013)	2.207 (3.397)	0.007 (0.011)	2.499 (3.021)		
Cancer Discharge Rate							0.003 (0.002)	0.578 (0.645)
Repayment Plan	-0.356 (0.219)	-141.248 (51.663) **	-0.295 (0.224)	-122.252 (48.206) **	-0.340 (0.216)	-133.601 (50.363) **	-0.251 (0.231)	-120.438 (50.672) **
Rate of people in bad health	-0.051 (0.043)	-20.300 (10.776) *	-0.067 (0.038) *	-25.015 (9.407) **	-0.052 (0.041)	-19.954 (11.012) **	-0.066 (0.041)	-25.761 (9.230) **
Recieveship conditions	0.237 (0.188)	62.923 (49.928)	0.298 (0.188)	79.163 (48.925)	0.263 (0.177)	75.117 (47.470)	0.235 (0.192)	66.187 (51.579)
Active Mobility	-0.000 (4.0e-06) **	-0.004 (0.001) **	-7.17e-06 (3.12e-06) **	-0.002 (0.001) **	-0.000 (3.86e-06) **	-0.003 (0.001) **	-7.19e-06 (2.92e-06) **	-0.002 (0.001) **

Frequency of meetings	0.000 (0.001)	0.187 (0.539)	0.003 (0.002)	0.765 (0.514)	0.001 (0.002)	0.355 (0.545)	0.002 (0.002)	0.569 (0.461)
_cons	6.554 (15.069)	1441.767 (7558.822)	-0.167 (20.717)	-4302.788 (7155.815)	2.915 (16.020)	-253.777 (7173.004)	-2.266 (16.984)	-3356.817 (6809.177)

Table 12 – Robustness Check – Pro-capite NHF with different combinations of indexes with Clustered Robust Standard Errors.

	Robustness Check 1		Robustness Check 2		Robustness Check 3		Robustness Check 4		Robustness Check 5	
	GLM - Gaussian - Log	*GLM - Gamma - Identity*	*GLM - Gaussian - Log*	*GLM - Gamma - Identity*	*GLM - Gaussian - Log*	*GLM - Gamma - Identity*	GLM - Gaussian - Log	GLM - Gamma - Identity	GLM - Gaussian - Log	GLM - Gamma - Identity
TimeAccess	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
RTH2	0.340 (0.113) **	125.978 (42.393) **	0.325 (0.114) **	125.325 (40.074) **	0.356 (0.122) **	128.833 (48.047) **	0.341 (0.122) **	126.966 (45.877) **	0.275 (0.151) *	119.686 (44.080) **
RTH3	0.508 (0.108) ***	164.000 (33.961) ***	0.485 (0.133) ***	158.192 (54.899) **	0.573 (0.140) ***	177.265 (41.973) ***	0.547 (0.158) ***	168.784 (54.325) **	0.460 (0.118) ***	156.456 (42.658) ***
Year	-0.004 (0.014)	-3.007 (4.958)	-0.007 (0.013)	-3.226 (5.498)	-0.003 (0.015)	-2.304 (5.075)	0.001 (0.014)	-2.829 (5.762)	0.001 (0.013)	-2.673 (4.868)
NHF										
NHF pro capite	0.001 (0.000)	0.210 (0.167)	0.001 (0.000)	0.200 (0.139)	0.001 (0.000) *	0.243 (0.179)	0.001 (0.000)	0.225 (0.156)	0.002 (0.001)	0.202 (0.159)
Attraction Index			0.005 (0.015)	1.153 (7.123)		1.153 (7.123)	0.006 (0.136)	1.987 (5.535)		

Escape Index					0.013 (0.012)	4.165 (3.602)	0.013 (0.012)	4.518 (3.676)		
Cancer Discharge Rate									0.002 (0.002)	0.269 (0.741)
Repayment Plan	-0.251 (0.211)	-100.393 (54.700) *	-0.239 (0.202)	-98.920 (51.799) *	-0.240 (0.204)	-101.069 (53.510) *	-0.226 (0.192)	-99.153 (50.622) *	-0.201 (0.211)	-93.287 (58.191)
Rate of people in bad health	-0.061 (0.037) *	-19.372 (8.621) **	-0.054 (0.043)	-18.267 (11.484)	-0.063 (0.034) *	-20.620 (8.444) *	-0.055 (0.040)	-18.385 (11.690)	-0.058 (0.037)	-19.608 (8.844) *
Recieveship conditions	0.238 (0.196)	71.813 (55.385)	0.230 (0.191)	69.682 (52.608)	0.292 (0.182)	90.137 (46.460) *	0.281 (0.175)	89.876 (46.219) *	0.226 (0.192)	68.314 (55.043)
Active Mobility	-3.17e-06 (1.21e-06) **	-0.001 (0.001) ***	-3.53e-06 (1.55e-06) **	-0.001 (0.001) **	-4.53e-06 (1.75e-06) **	-0.001 (0.000) **	-4.96e-06 (1.98e-06) **	-0.001 (0.000) *	-2.96e-06 (1.15e-06) **	-0.001 (0.000) ***
Frequency of meetings	0.001 (0.001)	0.1221 (0.404)	0.001 (0.001)	-0.007 (0.917)	0.002 (0.002)	0.516 (0.591)	0.001 (0.002)	0.342 (0.818)	0.001 (0.001)	0.083 (0.431)
_cons	12.263 (26.915)	6077.593 (9728.709)	6.408 (24.908)	6531.425 (10835.290)	10.012 (28.801)	4628.199 (9960.693)	3.247 (27.611)	5707.878 (11357.480)	2.853 (25.152)	5384.622 (9561.774)

Last check of investigation was regarding the second step, related to the effect of the budget law of 2017. In detail, a dummy was generated to capture a discontinuity between 2017 and 2018. Results are reported in Table 13. It is possible to see that there is discontinuity but only if the two typologies of expenditures are considered separately, by reverse, we find no effect at the aggregate level. This is in line with expectations, since the Budget law of 2017 increased the ceiling of inpatient expenditures (from 3.5% to 6.89%) and reduced the outpatient one (from 11.35% to 7.96%). This is clear from the results since it is possible to observe a negative relationship between the policy and the outpatient pharmaceutical expenditures and a positive relationship with inpatient expenditures. At the aggregate level, instead the effect is null since the ceiling devoted to the pharmaceutical expenditures remained unchanged (14.85%).

Table 13 – Discontinuity investigation – Inpatient, Outpatient and Total Expenditures.

	Robust Std. Err		Clustered Std. Err	
	GLM - Gaussian - Log	GLM - Gamma - Identity	GLM - Gaussian - Log	GLM - Gamma - Identity
Inpatient Expenditures	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
TimeAccess	-0.002 (0.001) **	-760697.9 (415551.8) **	-0.002 (0.002)	-760697.9 (806558.6)
Policy	0.581 (0.174) ***	1.89e+08 (6.38e+07) **	0.581 (0.029) ***	1.89e+08 (4.43e+07) ***
_cons	20.083 (0.358) ***	5.27e+08 (1.62e+08) ***	20.083 (0.659) ***	5.27e+08 (3.10e+08) ***
Outpatient Expenditures	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
TimeAccess	-0.003 (0.001) **	-1359374 (604962.7) **	-0.003 (0.002)	-1359374 (1200033)
Policy	-0.396 (0.194) **	-1.80e+08 (8.64e+07) **	-0.396 (0.343) **	-1.80e+08 (4.79e+07) ***
_cons	21.112 (0.405) ***	1.05e+09 (2.31e+08) ***	21.112 (0.754) ***	1.05e+09 (4.53e+08) **

Total Expenditures	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
TimeAccess	-0.003 (0.001) **	-2301000 (1041511) **	-0.003 (0.002)	-2301000 (2121264)
Policy	0.010 (0.183)	3339588 (1.42e+08)	0.010 (0.005)	3339588 (4494233)
_cons	21.398 (0.364) ***	1.65e+09 (4.03e+08) ***	21.398 (0.719) ***	1.65e+09 (8.07e+08) **

Second investigation on the second step was to understand if Regional structure has an impact on the Pharmaceutical expenditures (Table 14).

Table 14 – Regional Structure effect on Pharmaceutical Expenditures – Inpatient, Outpatient and Total Expenditures.

	Robust Std. Err		Clustered Std. Err	
	GLM - Gaussian -Log	GLM - Gamma - Identity	GLM - Gaussian -Log	GLM - Gamma - Identity
Inaptient Expenditures	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
RTH2	-0.129 (0.278)	4.07e+08 (1.14e+08) ***	-0.129 (0.517)	4.07e+08 (2.13e+08) **
RTH3	0.616 (0.227) **	5.40e+08 (8.94e+07) ***	0.616 (0.227)	5.40e+08 (1.56e+08) **
_cons	20.844 (0.645) ***	9.06e+08 (1.36e+08) ***	20.844 (1.204) ***	9.06e+08 (2.55e+08) ***
Outpatient Expenditures	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
RTH2	-0.166 (0.309)	6.25e+08 (1.38e+08) ***	-0.166 (0.609)	6.25e+08 (2.68e+08) **
RTH3	0.354 (0.230)	7.07e+08 (1.06e+08) ***	0.354 (0.423)	7.07e+08 (1.98e+08) ***
_cons	21.303 (0.786) ***	1.29e+09 (1.87e+08) ***	21.303 (1.548) ***	1.29e+09 (3.67e+08) ***

Total Expenditures	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance	Coef. (Std. Err.) Significance
RTH2	-0.150 (0.279)	1.03e+09 (2.37e+08) ***	-0.150 (0.567)	1.03e+09 (4.82e+08) **
RTH3	0.469 (0.202) **	1.24e+09 (1.73e+08) ***	0.469 (0.411)	1.24e+09 (3.52e+08) ***
_cons	21.787 (0.681) ***	2.20e+09 (3.05e+08) ***	21.787 (1.388) ***	2.20e+09 (6.21e+08) ***

Table 14 shows that with the Gaussian-Log combination no real effects can be observed. On the other side, according to the Gamma- Identity combination is possible to appreciate an effect of regional structure on the pharmaceutical expenditures. Increasing the complexity of the system for new drug market introduction, expenditures, increases also.

III.II – Conclusions

In conclusion, the Riforma Sanitaria Nazionle of 1978 was the first step for moving the NHS toward the federalism with the aim to grant more flexibility and autonomy to Regions. Unfortunately, heterogeneous procedures are fraught of negative consequences in terms of equity, timeliness and market segmentation with a reduction of competitiveness in our country.

This study had the aim to focus on the disparities in health care access in terms of new drug therapies available across Regions. The procedure adopted was first to understand the current Italian scenario mapping, through direct interviews to specialists, the Regional heterogeneous procedures and then to investigate the effects of this heterogeneity on the time of access of new drugs.

The understanding of the Italian policies and Regional structure was not only necessary to interpret the results of the econometric section, but it has also value per se. The work that was done by combining different sources of information allows for a comparative and structured analysis of the regional regulation, namely the number of steps needed to achieve patient access. This section investigation confirmed the complexity of our system. The overall conclusion is that increasing the complexity of the decision-making process, the timing of access increases too. Anyway, we can observe many exceptions without a general pattern.

Through the adoption of a two-steps Generalised Linea Models, the objective in the second section was to first identify how regional characteristics may impact on the timeliness, expressed as days needed for a drug to be available on local market, then to see how timeliness translates on pharmaceutical expenditures.

Descriptive statistics was necessary to highlight which regions deviated from the legal threshold of pharmaceutical expenditures and how much. Furthermore, from data emerged a net distinction between regions with one-tier of approval and Regions with three-tiers, with the first one acting better. Due to the short period of time under investigation, it is not possible to observe a relationship between the number of days for introducing a new

drug in the handbooks and funds devoted to the Regions; however, it emerged that funds are strongly correlated to the pharmaceutical expenditures. From GLM procedures, results showed that, not only the typology and process of RTH insertion of new drug can influence the timing of access, but also political (i.e. return plan, receivership conditions) and demographic characteristics (i.e. people who declare to be in bad health and active mobility) and demographic characteristics.

The limits of this study are related to the sample dimension and the short time horizon of investigation. Further developments could be twofold: to increase the period of investigation, in order to understand if there is also an effect of the Budget Law reform of 2017, and to understand the effect of regional structure on the total hospital expenditures, since an increment in complexity reduces the pharmaceutical expenditures but older therapies may have result into an increment of hospitalization costs.

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Appendix

Appendix A: Outpatient Pharmaceutical Expenditure between 2015 and 2018.

Region	Outpatient Pharmaceutical Expenditure in 2015	Outpatient Pharmaceutical Expenditure in 2016	Outpatient Pharmaceutical Expenditure in 2017	Outpatient Pharmaceutical Expenditure in 2018	Δ%
Piedmont	865,738,772	830,780,766	570,575,549	547,458,393	↓58%
Valle D'Aosta	22,449,037	21,875,133	14,941,875	14,365,918	↓56%
Lombardy	1,933,024,326	1,895,987,037	1,453,861,893	1,463,531,273	↓32%
Bolzano	79,317,141	79,252,681	50,053,458	48,765,537	↓63%
Trento	92,700,481	89,974,215	63,839,173	62,407,088	↓49%
Veneto	881,251,645	834,993,715	582,173,097	558,295,590	↓58%
Friuli V.G.	252,330,782	239,418,731	168,379,334	159,748,176	↓58%
Liguria	333,764,065	316,242,140	217,041,067	209,985,371	↓59%
E. Romagna	824,632,679	781,161,757	488,467,033	475,629,611	↓73%
Tuscany	758,424,783	742,623,475	467,372,505	453,887,655	↓67%
Umbria	181,487,022	183,905,017	126,485,985	124,567,545	↓46%
Marche	337,185,983	328,978,987	231,785,169	211,945,005	↓59%
Lazio	1,329,418,856	1,260,445,977	884,876,643	849,962,960	↓56%
Abruzzi	306,600,636	298,139,369	222,063,965	212,007,331	↓45%
Molise	70,225,335	64,884,274	43,517,934	42,158,055	↓67%
Campania	1,335,392,132	1,296,378,217	875,259,190	859,711,470	↓55%
Puglia	962,299,592	955,647,653	648,763,497	605,910,328	↓59%
Basilicata	125,808,753	121,989,796	82,680,742	82,025,939	↓53%
Calabria	450,789,793	452,350,042	306,588,850	290,207,964	↓55%
Sicily	1,083,250,248	1,050,240,181	689,040,727	664,546,547	↓63%
Sardinia	443,053,703	420,478,882	246,855,907	236,501,666	↓87%

Italy	12,669,145,764	12,265,748,045	8,434,623,595	8,173,619,421	↓55%
Note: Regions which exceeded the celling in all years are highlighted in red: Abruzzi, Campania, Puglia and Calabria. Regions who exceeded the ceiling only in 2017 are highlighted in blue: Marche, Lazio and Sardinia.					

Appendix B: Direct Purchase Expenditure between 2015 and 2018.

Region	***Direct Purchase Expenditure in 2015***	***Direct Purchase Expenditure in 2016***	***Direct Purchase Expenditure in 2017***	***Direct Purchase Expenditure in 2018***	***Δ%***
Piedmont	370,316,357	393,606,713	647,138,694	699,445,021	↑47%
Valle D'Aosta	9,866,703	9,677,403	15,303,111	16,655,317	↑41%
Lombardy	815,774,984	842,312,629	1,278,977,630	1,341,804,933	↑39%
Bolzano	42,446,014	42,876,546	76,938,594	80,588,347	↑47%
Trento	31,617,869	39,106,905	67,524,262	75,759,446	↑58%
Veneto	386,042,856	404,438,754	678,119,758	715,735,718	↑46%
Friuli V.G.	106,330,443	117,793,341	222,603,602	231,143,479	↑54%
Liguria	154,937,751	159,823,474	263,665,022	293,288,894	↑47%
E. Romagna	417,517,438	444,806,283	741,981,840	807,332,821	↑48%
Tuscany	440,914,709	447,170,699	689,671,589	667,276,502	↑34%
Umbria	89,798,916	95,905,128	158,030,493	174,084,362	↑48%
Marche	151,136,402	165,291,445	271,187,379	287,569,700	↑47%
Lazio	476,642,834	490,893,501	896,260,603	983,554,432	↑52%
Abruzzi	133,094,161	133,146,714	212,190,161	247,819,465	↑46%
Molise	24,207,970	25,596,561	49,129,352	52,990,218	↑54%
Campania	520,125,216	523,965,556	924,014,518	1,006,292,899	↑48%
Puglia	405,716,758	393,476,519	727,580,684	804,228,476	↑50%
Basilicata	56,478,796	57,973,651	102,332,900	109,044,282	↑48%
Calabria	183,981,040	177,721,158	326,287,300	368,600,159	↑50%

Sicily	380,589,627	397,703,414	752,599,815	788,031,985	↑52%
Sardinia	173,818,898	161,535,539	315,781,252	331,143,121	↑48%
Italy	5,371,355,742	5,524,821,933	9,361,016,675	10,015,418,856	↑47%
Note: Regions which exceeded the celling in all years are highlighted in red. Regions who exceeded the ceiling only in 2018 are highlighted in blue: Valle D'Aosta.					

Appendix C: Oncological and Non-Oncological Pharmaceutical Expenditure between 2017 and 2018.

Region	***Oncological Pharmaceutical Expenditure in 2017***	***Oncological Pharmaceutical Expenditure in 2018***	***Δ%***	***Non-Oncological Pharmaceutical Expenditure in 2017***	***Non-Oncological Pharmaceutical Expenditure in 2017***	***Δ%***
Piedmont	27.023.545	38.297.776	↑29%	12.228.549	28.010.940	↑56%
Valle D'Aosta	572.569	764.980	↑25%	113.441	634.646	↑82%
Lombardy	56.504.325	80.502.788	↑30%	51.013.294	84.256.779	↑39%
Bolzano	4.005.303	5.537.372	↑28%	862.394	1.766.180	↑51%
Trento	2.654.454	3.367.545	↑21%	543.349	1.990.312	↑73%
Veneto	26.825.160	39.530.864	↑32%	13.271.976	29.827.605	↑56%
Friuli V.G.	10.897.836	11.315.127	↑4%	5.032.710	8.497.368	↑41%
Liguria	13.257.539	21.533.511	↑38%	4.666.216	9.432.703	↑51%
E. Romagna	37.084.710	40.268.803	↑8%	6.265.748	31.322.172	↑80%
Tuscany	34.414.546	41.632.399	↑17%	-2.123.077	31.539.362	↑107%
Umbria	7.017.872	10.428.729	↑33%	3.546.660	4.994.808	↑29%
Marche	12.562.126	16.458.852	↑24%	2.473.132	8.467.784	↑71%
Lazio	41.479.174	69.191.273	↑40%	9.399.837	29.738.111	↑68%
Abruzzi	8.716.647	10.900.135	↑20%	3.550.278	4.389.002	↑19%
Molise	1.669.849	1.437.177	↓16%	94.041	818.561	↑89%

Campania	41.505.274	51.279.743	↑19%	4.593.401	43.652.606	↑89%
Puglia	28.632.697	39.565.578	↑28%	5.262.350	23.219.041	↑77%
Basilicata	3.677.203	4.052.085	↑9%	2.097.593	3.450.108	↑39%
Calabria	8.611.868	11.981.662	↑28%	4.033.489	5.028.074	↑20%
Sicily	24.515.762	28.265.112	↑13%	12.573.824	14.060.956	↑11%
Sardinia	10.980.706	12.951.204	↑15%	4.217.407	3.357.142	↓26%
Italy	402.609.165	539.262.715	↑25%	143.716.612	368.454.260	↑61%

Appendix D: Total Pharmaceutical Expenditure between 2015 and 2018.

Region	***Total Pharmaceutical Expenditure in 2015***	***Total Pharmaceutical Expenditure in 2016***	***Total Pharmaceutical Expenditure in 2017***	***Total Pharmaceutical Expenditure in 2018***
Piedmont	1,236,055,129	1,224,387,479	1.217.714.243	1.246.903.414
Valle D'Aosta	32,315,740	31,552,536	30,244,986	31,021,235
Lombardy	2,748,799,310	2,738,299,666	2,732,839,523	2,805,336,206
Bolzano	121,763,155	122,129,227	126,992,052	129,353,884
Trento	124,318,350	129,081,120	131,363,435	138,166,535
Veneto	1,267,294,501	1,239,432,469	1,260,292,856	1,274,031,307
Friuli V,G,	358,661,225	357,212,072	390,982,935	390,891,655
Liguria	488,701,816	476,065,614	480,706,089	503,274,265
E, Romagna	1,242,150,117	1,225,968,040	1,230,448,874	1,282,962,433
Tuscany	1,199,339,492	1,189,794,174	1,157,044,094	1,121,164,156
Umbria	271,285,938	279,810,145	284,516,478	298,651,906
Marche	488,322,385	494,270,432	502,972,548	499,514,704
Lazio	1,806,061,690	1,751,339,478	1,781,137,246	1,833,517,393
Abruzzi	439,694,797	431,286,083	434,254,126	459,826,795
Molise	94,433,305	90,480,835	92,647,287	95,148,272

Campania	1,855,517,348	1,820,343,773	1,799,273,708	1,866,004,369
Puglia	1,368,016,350	1,349,124,172	1,376,344,181	1,410,138,805
Basilicata	182,287,549	179,963,447	185,013,642	191,070,222
Calabria	634,770,833	630,071,200	632,876,151	658,808,123
Sicily	1,463,839,875	1,447,943,595	1,441,640,542	1,452,578,531
Sardinia	616,872,601	582,014,421	562,637,159	567,644,787
Italy	18,040,501,506	17,790,569,978	17,795,640,270	18,189,038,277
Note: Regions which exceeded the celling in all the years are highlighted in red: Friuli V,G,, Liguria, Tuscany, Umbria, Marche, Lazio, Abruzzi, Molise, Campania, Puglia, Basilicata, Calabria, Sicily and Sardinia, Regions who exceeded the ceiling only in 2018 are highlighted in blue: Piedmont, E, Romagna and Lombardy,				