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Setti Raïs Ali

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UNIVERSITÉ PARIS 1 PANTHÉON SORBONNE
PARIS SCHOOL OF ECONOMICS

T H È S E

pour l'obtention du titre de Docteur en Sciences Économiques

Présentée et soutenue publiquement le 3 juillet 2019 par

Setti RAÏS ALI

**DIAGNOSTIC AND THERAPEUTIC ODYSSEY:
ESSAYS IN HEALTH ECONOMICS**

Préparée sous la direction de Lise ROCHAIX et Sandy TUBEUF

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Glossary

A&E Accident and Emergency.

AATD Alpha-1 Antitrypsin Deficiency Disorder.

ASMR Amélioration du Service Médical Rendu.

ATIH Technical Agency for Information on Hospitalization.

BURQOL-RD Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe.

CBR Child Benefit Records.

CDF Cumulative Distribution Functions.

CE Conformité Européenne.

DALY Disability-Adjusted Life Year.

DELTA Département et Laboratoire d'Economie Théorique Appliquée.

DiD Difference-in-Differences.

EC European Commission.

EHIS European Health Interview Survey.

EHIS Institute for Research and Information in Health Economics.

EMA European Medicines Agency.

EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

EQ-5D EuroQol 5D.

EU European Union.

FDA Food and Drug Administration.

GP General Practitioner.

GUS Growing Up in Scotland.

HR Hazard Ratio.

HTA Health Technology Assessment.

IBD Inflammatory Bowel Disease.

ICD International Classification of Diseases.

ICER Incremental Cost-Effectiveness Ratio.

INSEE National Institute of Statistics and Economic Studies.

INSERM French National Institute for Health and Medical Research.

IPO Initial Public Offering.

KS Kolmogorov-Smirnov.

MA Market Authorization.

MeSH Medical Subject Headings.

MRI Magnetic Resonance Imaging.

NHS National Health Service.

NICE National Institute for Health and Care Excellence.

NIH National Institute of Health.

OD Orphan Drug.

ODA Orphan Drug Act.

OECD Office of Economic Cooperation and Development.

PROMs Patient Reported Outcome Measures.

PS Propensity Score.

QALY Quality Adjusted Life Years.

R&D Research and Development.

RA Reference Ages.

RCT Randomized Control Trials.

ScotGen Scottish Center for Social Research.

SEED Scottish Executive Education Department.

SF-12 12-Item Short Form Health Survey.

UK United Kingdom.

US United States of America.

WHO World Health Organization.

YPLL Years of Potential Life Lost.

General Introduction

Most of us cluster somewhere in the middle of most statistical distributions. But there are lots of bell curves, and pretty much everyone is on a tail of at least one of them. We may collect strange memorabilia or read esoteric books, hold unusual religious beliefs or wear odd-sized shoes, *suffer rare diseases* or enjoy obscure movies.

Virginia Postrel

Rare diseases are a stimulating subject of study for economists because the challenges commonly raised are pushed to the extreme when the disease is *rare*: from the diagnosis to the drug development, and its conditions of accessibility. This strong statement prompted the use of the term "*odyssey*" in the thesis title, as an appreciation of the distinctive nature of rare diseases.

The thesis is structured around three different key actors, all relevant to the diagnostic and therapeutic "*odyssey*" of rare diseases. Part I of the thesis is devoted to *patients and their networks* and considers sources of delays in receiving a diagnosis from the demand side, as well as the spillover effects from patients' health to their direct support systems.

Pharmaceutical firms are the second key actor of the diagnostic and therapeutic "*odyssey*" considered in the thesis. Part II examines how firms' decisions to allocate Research and Development (R&D) investments to rare diseases are impacted by innovation policies in rare disease areas. Finally, *policy makers* are the focus of Part III, which addresses the issues of measuring pharmaceutical innovation benefits along with costs in rare diseases areas, while taking into account the opportunity cost of health care decisions.

In this general introduction, I wish to fulfill two main objectives: the first is to highlight the very specific position of rare diseases regarding access to diagnostic and therapeutic

treatment, justifying the use of the term "*odyssey*." The second is to suggest that adopting a global perspective and comprehensive vision of rare diseases is critical despite the specific nature of each individual disease.

Measuring time period to diagnosis

[Scheuermann et al. \(2009\)](#) defines a diagnosis as the "conclusion of an interpretive process that has as input a clinical picture of a given patient and as output an assertion to the effect that the patient has a disease of such and such a type." The diagnostic workup is thus the final act of an iterative procedure, made of clinical exams and medical history investigation. While this definition chooses to stress the pivotal role of the clinician in the diagnostic workup, it neglects the role played by the patient. Yet, clinical investigation is conditional to the entrance of patients into the health care system in the first place. Their individual care-seeking behaviors and personal health management strategies are likely to induce variations in time period to diagnostic workup attributable to patients.

Multiple factors may explain the postponement of entrance into the health care system. [Ballard et al. \(2006\)](#) conducted qualitative interviews to understand women's experiences in getting a diagnosis of endometriosis, which is a highly prevalent chronic pelvis pain disease. Patients with endometriosis wait on average 11.7 years before obtaining a final diagnosis in the United States of America (US) ([Hadfield et al., 1996](#)). When interviewed, women reported that they experienced symptoms long before their first medical contact. Symptoms were often disruptive to their lives but they did not consider this fact medically alarming. On the contrary, they described themselves as "unlucky," rather than "ill." Social norms and the absence of menstrual education also played an active role in inhibiting women from recognizing that their situation was abnormal. Fear and/or embarrassment prevented them from discussing their condition with family, friends, and medical professionals. Despite the severity of the pain, some women initially coped with symptoms until it became unbearable. In this context, patients delay their access to diagnoses.

Once the step of a first medical consultation was taken, some women reported that they felt the doctors did not believe the severity of their symptoms; this provides evidence that doctors' characteristics are also a potential driver of the time period to diagnosis. Moreover, the symptoms of endometriosis can be intermittently suppressed by hormonal actions. Women would thus experience a temporary recovery, which would lead them to abandon consultation and in doing so, postponing the final diagnosis. Some features of the diseases—whether in the form of the disease's relapsing-remitting nature—or

the generality of its symptoms make it even more difficult to reach a final diagnosis. Lastly, components of the health care system such as poor doctor coordination, absence of diagnostic facilities, or long waiting times for routine procedures are all additional potential explanations of longer time periods to diagnosis.

Beyond the specific features of diseases, potential factors contributing to variations in time to diagnosis thus include the characteristics of patients', doctors, as well as the health care system organization more broadly. Little is known about the relative importance of each criteria in determining time to diagnosis because the literature is scarce in this domain. In addition, most evidence rests on a restrictive definition of time to diagnosis, which begins with the patient's entrance into the health care system. However, we put forward the idea that time to diagnosis should instead be measured from symptom onset.

We discuss the extent to which the increase in time to diagnosis may be attributable to either patients or health professionals, although respective responsibilities cannot be easily assigned. Building on the previous example of doctors' disbelief about symptom severity, responsibility might be imputable to doctors, or to patients, depending on framing. On the one hand, patients may fail to convey their message correctly, because they may lack health literacy or have very heterogeneous perceptions on good and bad health status, or have different expectations from the health care system. On the other hand, doctors may fail to interpret patients' statements. The intrinsic nature of the patient-doctor relationship makes it difficult to single out respective responsibilities in delaying access to diagnostic services and calls for combining patient- and clinician-level sources of delay in diagnoses to consider an aggregate time period to diagnosis from first symptoms to final diagnosis.

We now turn to diagnostic delays in order to consider whether they (1) constitute lost opportunities for patients, and (2) play an important role in the construction of social health inequalities.

Social determinants of time to diagnosis

The French survey Erradiag, conducted in 2016, showed that 25% of patients treated for a rare disease reported their time to diagnosis to be above five years¹. Nearly 60% of patients declared that a lack of diagnosis led to physical harm, psychological distress, avoidable medical treatments, and sick leaves or absence from work. Additionally,

¹Survey conducted by the patient organization "Alliance Maladies Rares." Report available in French: <https://www.alliance-maladies-rares.org/erradiag-enquete-sur-lerrance-diagnostique-dans-les-maladies-rares-2/>.

a systematic literature review on breast cancer found a reduced survival rate when diagnostic delays were between three to six months (Richards et al., 1999). Cancer relapses are shown to be more common if waiting times between diagnosis and treatment are longer (Chen et al., 2008). Results suggest that with a median time period under a month, time periods between diagnosis and treatment planning have a significant impact on tumor size (Jensen et al., 2007). Jensen et al. argue that “if cancer progresses this rapidly after diagnosis, it is not unreasonable to assume it progresses in the time spent establishing a diagnosis.”

This evidence shows the overriding nature of patients’ costs in terms of quality of life, health, and survival, by far the most detrimental aspects of diagnostic delays, and well beyond the potential large costs of avoidable sick leave and medical expenditures. Even in the absence of treatment options, the diagnostic workup is crucial for patients as they value information about their health status *per se*. A diagnostic workup offers labels and legitimizes their suffering. It confirms their inability to pursue their social, familial, and professional ambitions to their full capacity.

The World Health Organization (WHO) defines the social determinants of health as “the conditions in which people are born, grow, live, work and age” (WHO, 2008). The distribution of resources owned by individuals have been shown to determine a wide range of an individual’s health risks and outcomes. A large body of literature brought forth evidence on the existence of a social health gradient, which states that life expectancy is shorter and the prevalence of diseases is higher further down the social ladder in society (Wilkinson and Marmot, 2003; Marmot, 2005). Studies on socioeconomic inequalities in health in the European Union (EU) and the US reveal that avoidable health disparities originate from a large variety of underlying social disadvantages, such as gender or ethnicity (Braveman and Tarimo, 2002).

The extent to which the length of time to diagnosis is determined by social and economic factors remains undocumented. The objective of Chapter 1 of this thesis is to explore the existence of social determinants of time to diagnosis.

Costs and consequences of delays in diagnosis for patients appear to be substantial, yet remain under-documented. Exploring individual variations in time to diagnosis and its socioeconomic determinants may lead us to identify an essential component of social health inequalities. More specifically, the first chapter of the thesis measures the time to diagnosis from first symptoms until final diagnosis for four chronic conditions, and explores the role played by social capital and education in attaining a diagnosis. The diagnostic process,

which can successfully lead to a conclusion or not, is scattered with pitfalls for patients. Still, patients are not single players in their experiences with the disease.

After the final diagnosis, the challenge continues

Health economists demonstrate the specific impact of a condition on patients' health by relying on generic health measures —see for example, the well known EuroQol 5D (EQ-5D) (Kind et al., 1998)—or disease-specific tools such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) in cancers (Aronson et al., 1993). Part of those measures are meant to appraise the multidimensional nature of health by combining a variety of health components. For example, EQ-5D includes dimensions such as mobility, ability with daily activities, pain, and psychological distress. These facilitate a measure of the disease's consequences on patients' health and quality of life. Complementary investigations have endeavoured to describe disease-specific socio-economic costs —see for example, the Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe (BURQOL-RD) (Chevreul et al., 2015). The combination of such tools unveil a key component in patients' treatment management, which largely contributes to the sustainability of their health and their quality of life: the caregivers.

Literature related to caregivers shows that diseases have an impact beyond the patient and impact their informal support system. Caregivers are characterized by their strong commitment to a patient, while often being informal and unpaid (Dwyer et al., 1994). Research has recently moved from a focus on patients only, to a focus on patients within their environment and support structure (Caqueo-Urizar et al., 2009; Dwyer et al., 1994). In this context, an important question is how a cost-effectiveness assessment could factor in the burden to caregivers within health technology appraisals (Tubeuf et al., 2019). Caregiving activities have been shown to have detrimental consequences on caregivers' physical and mental health due to “physical work, emotional pressure, social restrictions, and economic demand arising from taking care of a patient” (Dillehay and Sandys, 1990).

The objective of Chapter 2 is to delineate health spillovers from patients' health to caregivers. With a focus on patients, the first part of this thesis takes chronic diseases as the main example. The choice to focus on chronic diseases is owing to obvious data shortage and the impossibility of collecting patient-level data on rare diseases that is original, rigorously produced, and of sufficient sample size for further quantitative analysis within the time frame of the PhD. The choice of chronic diseases, defined as “conditions that last one year or more and require ongoing medical attention and/or

limit activities of daily living,” which are the leading cause of mortality and morbidity in developed countries (Yach et al., 2004), was motivated by an ambition to reflect the challenges encountered in the diagnostic process of a rare disease.

The first part of the PhD dissertation provides thought-provoking considerations for rare diseases in numerous respects: (1) the diagnosis of rare conditions is complex, and we observe delays in obtaining the diagnostic workup, (2) rare diseases have substantial implications for patients’ professional, family, and/or educational prospects, and (3) the health spillovers on caregivers are significant.

Rare diseases: What they are and their effects

Rare diseases represent a “broad assortment of disorders and constellations of clinical signs and symptoms” (Luzzatto et al., 2015). The term “rare diseases” is transparent enough to refer to diseases that affect a small percentage of the population. But how rare is rare? Everyone seem to have their own answer. A literature review on rare disease terminology found that 58% of rare disease definitions disclosed a prevalence threshold, with an average of 40 people in 100,000 within a defined geographic area (Richter et al., 2015). But the definition of rare diseases is very much a political decision as it determines the scope of diseases that fall within the political framework for action in the field of rare diseases. The Food and Drug Administration (FDA) defines any disease or condition that affects fewer than 200,000 people in the United States as rare (Richter et al., 2015). At the European level, rare diseases are defined by the European Medicines Agency (EMA) as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the EU (Rodwell and Aymé, 2015; European Medicines Agency, 2013). At the aggregate level, rare diseases affect a substantial number of individuals: to date, between 5,000 and 8,000 distinct rare diseases have been documented (European Medicines Agency, 2013), affecting a total of 30 million patients in Europe, and approximately the same number in the US (Griggs et al., 2009).

The difference between a rare and a common disease extends beyond the simple numeric oddity. Average time period until diagnosis is usually dramatically longer in rare diseases as compared to a common disease. We look at the relevant example of Alpha-1 Antitrypsin Deficiency Disorder (AATD) to illustrate all of the challenges encountered through the diagnostic process (Stoller, 2018). Patients suffering from AATD face on average 7 to 8 years before receiving a final diagnosis (Greulich et al., 2013; Stoller et al., 2005, 1994). Results also suggest that patients with longer diagnostic time frames presented clinical sequelae, worse functional status, and advanced symptoms at the time of the diagnosis

(Tejwani et al., 2017). The low occurrence of AATD clinical cases makes it particularly difficult to identify in routine clinical practice. Lack of clinical expertise in rare diseases is acknowledged by a declarative survey where both general practitioners and specialists reported having little or no knowledge of AATD in 64% of cases (Greulich et al., 2013).

We highlighted the lack of expertise on rare diseases by health professionals and its subsequent impact on patient prognoses. With rare diseases, poor disease expertise adds up to few treatment opportunities.

From R&D to diagnosis, and back

Research in rare diseases faces two major obstacles. First, rarity makes research complex. Observed heterogeneity between patients confuses the trace back of the disease's natural history and epidemiology, and hence the definition of specific diagnostic criteria (Auvin et al., 2018; Nestler-Parr et al., 2018). Five new rare diseases are described every week in medical literature (Nestler-Parr et al., 2018): so far there are 5,000 to 8,000 distinct rare diseases that have been documented (European Medicines Agency, 2013). These figures are growing rapidly thanks to DNA-sequencing technological improvements that offer a better understanding of the human genome and facilitate diagnostic success for a number of rare diseases (Boycott et al., 2013). Secondly, there is a lack of incentives to fund R&D into rare diseases. According to many studies, producing orphan drugs is not profitable due to high R&D costs for rare diseases (Buckley, 2008) and market size being insufficiently large to recover fixed costs. One significant item of expenditure is patient recruitment into clinical trials. Given the low prevalence of rare diseases, the recruitment phase is shown to be significantly larger with some recruitment processes spanning more than 17 years (DiMasi et al., 2003). Though, in absence of access to private data on R&D expenditure, the extent to which R&D in rare diseases is financially damaging for pharmaceutical industries remains undocumented.

In response to these challenges, the US and EU enacted beneficial regulation in the field of rare diseases inspired by innovation policies. The Orphan Drug Act (ODA) was implemented in 1983 in the US; it offers 50% taxes credits, FDA approval process fees waivers, grants program for research and technological developments, scientific advice and protocol assistance by the FDA to fulfill the regulatory process for marketing authorization, pre-licensing access, free pricing, and reimbursement at 95% under Medicare for drugs targeting diseases with a prevalence (mean number of people affected by a disease for a period of time) lower than 75 cases over 100,000 in the population. The orphan

drug designation granted by the FDA favors development and market access for some drugs that would not be profitable without the state's incentive. From 1983 to 2016, 503 drugs and biological products were approved for rare diseases and 1,132 drugs obtained an orphan designation ([Hughes and Poletti-Hughes, 2016](#)).

Thousands of patients with rare diseases could then access new therapies and improve their health and living conditions. In 2000, the Orphan Drug (OD) Number 141/2000 of the European Parliament and the Council on orphan medicinal products provided incentives to encourage the R&D of medicines to treat, prevent, or diagnose rare diseases.

One feature of these policies is that these advantages are also granted if the target population is under the rare disease threshold. In that respect, the OD policy may have spurred research into subsets of the patient population classified under non-rare diseases since the criteria for benefiting from supply-side incentives is mainly the targeted population size. Hence, if a particular clinical trial is conducted on relatively small targeted patient population, it could be eligible for orphan drug designation. The increasing trend in precision medicine, defined as drugs relying on genetic, epigenetic, and protein biomarkers has led to specific disease sub-type refinements. These might have been encouraged further by the introduction of the OD policy ([Chandra et al. \(2017\)](#)). Biomarkers are defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”². They are good predictors of clinical response to a treatment.

In the EU, from the inception of the OD regulation through 2015, 133 orphan drugs were granted Market Authorization (MA) ([Giannuzzi et al. \(2017b\)](#)) so that the OD policy is often described as having led to unprecedented investments by manufacturers in R&D targeting rare diseases. However, the study of the indirect impact of the OD legislation on drug development for diseases that are not considered rare has never been studied. In addition, 133 orphan drugs are distributed between 5,000 to 8,000 different rare diseases. The objectives of Chapter 3 and Chapter 4 are (1) to evaluate the innovative policy aiming to foster R&D in rare disease areas, with a special emphasis on non-rare drugs with a OD qualifying indications, and (2) to analyze the distribution of R&D within rare diseases according to disease characteristics and investigate the existence of inequalities in the allocation of R&D resources within rare disease areas. This chapter investigates the impact of innovation policies on pharmaceutical firms' private decisions.

²National Institute of Health (NIH) formed the Biomarker Definition Working Group

Considering the need to tackle the high unmet needs of patients with rare diseases, policy makers introduced supply-side incentives with the objective of fostering firms' decisions to invest in R&D for rare diseases. More than 20 years after the introduction of such policies, numerous orphan drugs have been approved. But is that enough to conclude that it became (1) accessible and, (2) game-changing to patients with rare diseases?

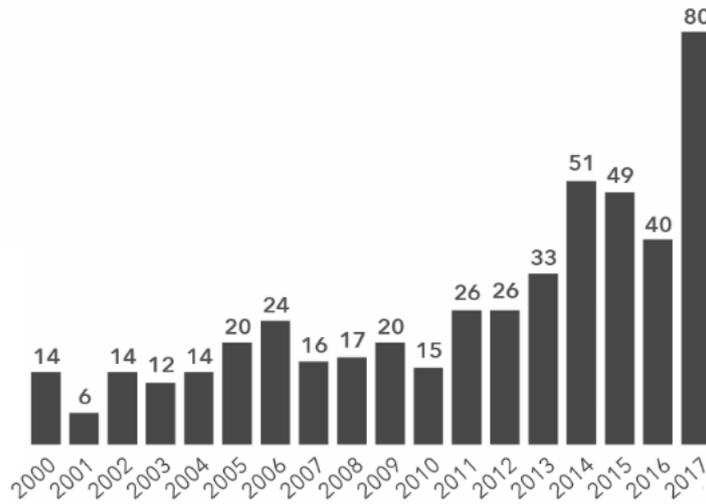
From R&D to access to drugs, and back

Policy makers tasked with allocating resources within the health care system face a major conflict between an unlimited demand of care and limited resources (López-Bastida et al., 2018). Once approved for a rare indication, orphan drugs must undergo a formal Health Technology Assessment (HTA) in a number of regions including North America, Australia, many European countries, and more recently Latin America and Asia (Ciani and Jommi, 2014).

HTA relies on the evaluation of the cost-effectiveness of a new technology and provides guidance on the social benefit of a particular health technology in a given country. Recommendations on medicines and other health technologies are meant to support funding, coverage, and reimbursement decisions or price negotiation about health technologies by the health care system in a specific country (Sorenson et al., 2008). While HTA requires clinical and economic evidence, for a number of reasons it is rarely available for orphan drugs. One reason is that it is impossible to run randomized control trials, which are the gold standard methodology to robustly measure clinical efficacy (Bothwell et al., 2016). Another reason is that clinical trials of rare diseases may not have any control arm, due to ethical considerations, and a comparable technology may not exist (Nicod, 2017). The limited sample size along with heterogeneity in patients' disease progression or clinical sub-type of the disease will ultimately impact the reliability of costs and clinical efficacy estimates (Bothwell et al., 2016).

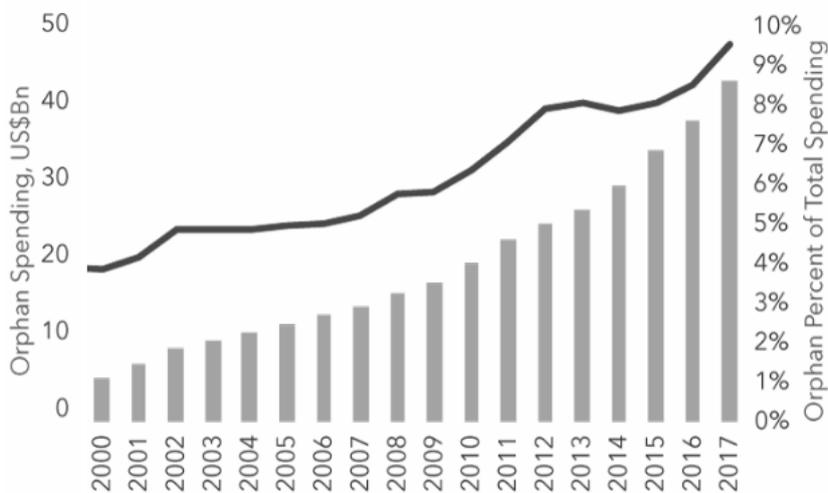
The uncertainty surrounding the benefit of new treatments for rare diseases is not the only issue at stake. The costs of new approved drugs for rare diseases is also a major concern for health services and policy makers worldwide, and thus is the source of much public debate. In recent years, steep prices have been noticed for drugs designed to treat rare diseases. For example, the cost of the treatment of Gaucher's diseases was estimated to be US\$200,000 on average per patient per year Luzzatto et al. (2018). Moreover, the number of approved drugs each year is increasing, along with the share of orphan drugs in total sales each year in the US (see Figure 0.1 and Figure 0.2 below).

Figure 0.1 – NUMBER OF APPROVED ORPHAN INDICATIONS PER YEAR IN THE US



Source: Report IQVIA, Orphan Drugs in the USA — Growth Trends in Rare Disease Treatments, 2018

Figure 0.2 – ORPHAN DRUG EXPENDITURE AND SHARE OF ORPHAN DRUG EXPENDITURE IN TOTAL SALES

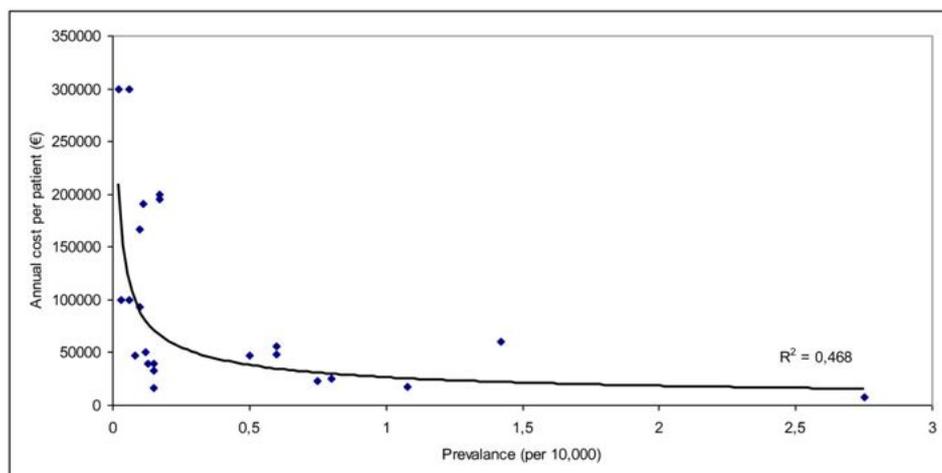


Source: Report IQVIA, Orphan Drugs in the USA — Growth Trends in Rare Disease Treatments, 2018. The dark curve indicates the % share of orphan drug sales in total sales. The bars indicate the orphan spending in US\$Bn.

While one may think that orphan drugs have generated limited sales, we do observe many orphan drugs among blockbusters generating at least US\$1 billion in sales ([Wellman-Labadie and Zhou, 2010](#)), a fact that can be surprising considering that orphan drugs are supposed to target very small populations. According to [Côté and Keating \(2012\)](#), biotechnological and pharmaceutical firms have rapidly adopted strategies to make huge profits out of the orphan drug regulations. An orphan drug may be applicable to either

several rare or non-rare diseases. In such situation, orphan drugs have access to a larger market than expected by the demand side, and sometimes largely recover their R&D fixed costs. Moreover, in case of an extension of indication, pharmaceutical firms may undergo lower fixed costs as most of the research process has been achieved, and thus the firms only bear the cost of undertaking new clinical trials (Côté and Keating, 2012). Lastly, pharmaceutical firms that own an orphan drug designation have been shown to get higher market stock valuations because of a predicted increase in their profits (Gorry and Useche, 2017). Evidence from Belgium on prices suggests that the lower the prevalence of a rare disease, the higher the price of the drug (see Figure 0.3) (Simoens, 2011).

Figure 0.3 – ASSOCIATION BETWEEN ANNUAL BELGIAN COST PER PATIENT OF AN ORPHAN DRUG AND DISEASE PREVALENCE



Source: (Simoens, 2011)

López-Bastida et al. (2018) have investigated the large willingness to pay for orphan drugs using a discrete choice experiment, and the study of the relative importance of attributes used to describe different choice options in five European countries (England, France, Germany, Italy, and Spain). Results show that disease severity and treatment effectiveness are two important dimensions in funding decisions from a social perspective. This confirms the existence of social preference in the funding of drugs. But should we really consider that collective preferences provide clear guidance on funding decisions? What are the implications for society if one invests more in promoting health in the population's subgroups?

Given the high level of uncertainty surrounding orphan drugs costs, efficacy, and the budget constraint, the objective of Chapter 5 is to address the impact of orphan drug approvals on premature mortality, providing evidence on the returns to the large social investments into pharmaceutical innovation for rare diseases. It discusses how challenging it is, notably for policy makers, to estimate the clinical benefit of orphan drugs.

The objective of Chapter 6 is to go a step beyond in the evaluation of orphan drugs, given their specificity, and discuss how they are ultimately made available to patients. We use the interesting example of the National Institute for Health and Care Excellence (NICE) that makes recommendations in terms of health care treatments to patients within the National Health Service (NHS) in the United Kingdom (UK). In the UK, patients are provided with treatments available in the health care basket covered by the nationalized and free health care system. The choice to include a health technology in the health care basket covered by the NHS is based on a combined analysis of the costs and the effectiveness of this new therapy compared to conventional therapeutic strategies and past reimbursement decisions.

Overview of the Chapters

This dissertation is divided into three parts, each of them comprising two chapters.

Part I — THE DIAGNOSTIC QUEST AND ITS PREJUDICE TO PATIENTS AND CAREGIVERS

The first part of the dissertation is devoted to the patient’s diagnostic experience and its consequences for patients’ relatives. Chapter 1 is focused on the determinants of time to diagnosis, and emphasizes the role of patient characteristics, notably social capital, in accessing a final diagnosis. Chapter 2 then evaluates health spillovers and investigates the causal impact of a chronic disease diagnosis on the health of one network member for a patient: the mother.

Chapter 1

In Chapter 1³, we define time to diagnosis as the time span from first symptoms to final diagnosis. We measure time to diagnosis for four chronic conditions (bipolar disorder, Crohn’s disease, multiple sclerosis, and psoriasis), and analyze the role played by patients’

³The chapter is based on a paper co-authored with Paul Dourgnon and Lise Rochaix

education and social networks in explaining time to diagnosis. The data collected are self-reported as part of an online open access questionnaire we designed and administered to a large French social network of patients with chronic conditions. Duration models are used to explain variations in time to diagnosis.

Our findings suggest that social participation and social support reduce the probability of experiencing longer time spans to diagnosis. On the contrary, higher levels of education are associated with an increase in the probability of experiencing longer time spans to diagnosis. We further analyze these results and identify the differences in patients' health care-seeking behavior: more educated patients tend to visit specialists first, which leads to longer time spans to diagnosis as specialists are less likely to refer patients to hospitals for additional tests when needed, compared to general practitioners. While these findings support the WHO's recommendations to enhance individuals' social capital, results on education provide support for reforms aimed at implementing General Practitioner (GP) referral systems.

Chapter 2

In Chapter 2⁴, we investigate the causal impact of a shock on a child's health on the main caregiver's health. We define the shock on a child's health as the onset of a chronic disease resulting in a drop in the child's self-reported health status. We use data from the Growing Up in Scotland (GUS) longitudinal study that includes eight waves of health information on child-mother pairs.

Using a logit fixed effect specification, we find that mothers are significantly more likely to report a lower level of self-reported health as a result of a shock on their child's health. To disentangle the effect on physical and mental health, we use both the SF-12 physical and health indices. The findings suggest that mother's physical health is significantly impacted by a shock on a child's health, while there is no significant effect on their mental health. We further investigate the variation across time and find that the impact of the shock on a child's health on the mother's physical health significantly and constantly increases after the shock on the child's health. This confirms the existence of persistent health spillovers from a child's health onto the mother's health.

Results suggest that the deterioration of health was significantly stronger when the child has a disease that is time-consuming and requires relatively more time resources than

⁴The chapter is based on a paper co-authored with Antoine Marsaudon

money resources from main caregivers. In that case, we see the mothers' probability of reporting a higher health category reduced by 49%, everything else being held constant in the model. This confirms the existence of persistent health spillover effects from child to mother. We finally investigate the impact of a shock on the child's health on the mother's health when the chronic disease is time-intensive and when it is money-intensive. Results suggest that a shock on the child's health is even more detrimental when the chronic disease is time-intensive.

Part II — FIRMS' DECISIONS TO ALLOCATE R&D TO RARE DISEASES

The second part of the dissertation focuses on innovation in rare disease areas and investigates firms' decisions to invest in rare diseases. While Chapter 3 estimates the causal impact of a policy introduced at the European level on R&D into rare diseases, Chapter 4 studies the allocation of R&D between rare diseases.

Chapter 3

Chapter 3 estimates the causal impact of the OD legislation, which was introduced in 2000 at the European level and offers supply-side market incentives to stimulate R&D investment levels in rare diseases. We study the impact of the OD legislation by examining the variation in the number of new clinical trials and new academic publications between 1997 and 2015 using a Difference-in-Differences (DiD) design estimated with a conditional fixed effect Poisson model. We find a causal positive impact on the number of clinical trials from the year 2004 that increases over the 10 years following the legislation. The causal effect of the OD legislation on academic publications was significant and immediate after the introduction of the policy. The policy increased by 52 the count of clinical trials in rare diseases per disease. It appears that the pharmaceutical industry largely responds to financial incentives when allocating R&D resources.

Chapter 4

Chapter 4⁵ investigates the existence of inequalities in the allocation of R&D resources within rare diseases and identifies the characteristics of rare diseases that appear to lead R&D investments. Rare diseases are generally underserved by drug development because pharmaceutical industries consider R&D investment into rare diseases too costly and risky in comparison with the low expected returns due to the small population involved. 80%

⁵The chapter is based on a published paper co-authored with Sandy Tubeuf: (Raïs Ali and Tubeuf, 2019)

of rare diseases are not part of pharmaceutical firms' R&D agendas and such limited R&D investment might impact the access to treatment for patients with rare diseases, thus leading to further health inequalities in the population.

There have been considerable discussions within the philosophical and political economy literature about the welfare state's role in promoting equity in the provision of goods and services, especially the need for public health actors to tackle health inequalities and prioritize the most disadvantaged groups. Combining data from Orphanet and PubMed and calling upon non-parametric methods such as stochastic dominance and bilateral tests, we show that rare diseases in children and with a smaller prevalence are underserved by R&D. R&D efforts appear to be concentrated in more profitable research areas with potentially larger sample sizes for trial designs and adult population.

Part III — REGULATORS' CHALLENGES IN DEFINING THE CONDITIONS OF ACCESS TO INNOVATIVE DRUGS

The third part of the dissertation covers the issues facing policy makers in measuring the health benefits of innovative health technologies and addressing the opportunity costs of health care resources while defining the conditions of access to pharmaceutical innovation for patients with rare diseases. Chapter 5 examines the causal impact of pharmaceutical innovation and academic publications on longevity, and Chapter 6 evokes the equity perspectives in the economic evaluation of health technologies, especially in the nationalized English and Welsh health care systems.

Chapter 5

In this chapter, we measure the causal impact of pharmaceutical innovation and academic publications on premature mortality from rare diseases using a two-way fixed effect model. We then investigate how pharmaceutical innovation impacts longevity over time. We appraise premature mortality by computing Years of Potential Life Lost (YPLL) at ages 65, 70, 75, 80, and 85 from longitudinal data containing all US death certificates from the period 1999-2015. We control our results for variation in diagnostic ability that may lead us to underestimate the impact of pharmaceutical innovation on premature mortality caused by rare diseases. Results suggest that pharmaceutical innovation, as measured by the cumulative number of lagged approved drugs, significantly reduces the number of YPLL at 65 by an average of -455 years per disease. The investigation of the time variation in the impact of drug approval on premature mortality suggests that drug

approval significantly decreases the number of YPLL at 65 and YPLL at 70 between two and four years after approval.

Chapter 6

Chapter 6⁶ discusses how the NICE, which is responsible for recommending treatments and health care for patients within the NHS in England and Wales, evaluates health care technologies. The NICE has a dual objective of clinical excellence and a balanced budget, which is at the forefront of decisions and recommendations regarding treatments made available within the basket of goods and services. As part of NICE's health technology assessment process, health gains and induced costs are compared by calculating an Incremental Cost-Effectiveness Ratio (ICER) expressing the cost per Quality Adjusted Life Years (QALY). The value of the ICER is then compared to a cost-effectiveness threshold for health technologies defined by NICE in 2000. This cost-effectiveness threshold of health technologies is an interval between £20,000 and £30,000 per QALY; below this range, an innovative health technology is considered highly cost-effective, within the range it is cost-effective, and over £30,000 per QALY, the new treatment is deemed too expensive compared to the expected gain in health.

The case of NICE is of utmost interest to this thesis for two reasons: (1) unlike NICE, most countries do not use an explicit threshold for their decisions in health care resources, and (2) NICE adopts a more flexible approach to the use of the threshold for some particular decisions, including the health care treatment for rare diseases. This chapter offers a critical discussion of the methodological foundations of the cost-effectiveness threshold in the evaluation of health technologies and it highlights the gaps between the reference model and the actual practice as well as the apparent equity issues for NHS patients.

⁶The chapter is based on a paper co-authored with Sandy Tubeuf

Présentation de la thèse en français

Most of us cluster somewhere in the middle of most statistical distributions. But there are lots of bell curves, and pretty much everyone is on a tail of at least one of them. We may collect strange memorabilia or read esoteric books, hold unusual religious beliefs or wear odd-sized shoes, *suffer rare diseases* or enjoy obscure movies.

Virginia Postrel

Les maladies rares sont des objets d'étude stimulants pour les économistes tant les défis soulevés à l'ordinaire par les maladies sont poussés à leur paroxysme lorsque la pathologie considérée est *rare*. Ce constat nous a conduit à utiliser le terme d'*Odyssée* afin d'apprécier la nature très particulière des maladies rares.

Cette thèse de doctorat est structurée autour de trois acteurs au coeur de l'*Odyssée* diagnostique et thérapeutique des patients atteints de maladies rares. La partie I est dédiée aux patients et ses interactions sociales. Cette partie s'intéresse à l'effet des caractéristiques des patients sur le délai d'obtention de son diagnostic, parmi lesquelles le capital social. Cette partie évoque également les externalités négatives affectant la santé des mères aidantes informelles dans le cas d'un diagnostic d'une pathologie chronique infantile.

L'industrie pharmaceutique est le second acteur de l'*Odyssée* diagnostique des patients atteints de maladies rares. La seconde partie de la thèse est dédiée à l'industrie pharmaceutique et s'intéresse aux décisions d'investissements de R&D ciblant les maladies rares. Enfin, la Partie III est dédiée aux décideurs publics et discute des enjeux d'évaluation des bénéfices de l'innovation thérapeutique et de la définition des conditions d'accès à cette innovation.

Dans cette introduction générale, je souhaite poursuivre deux objectifs. Le premier est de souligner la spécificité des maladies rares dans l'accès au diagnostic et au traitement justifiant par là l'usage du terme d'*Odyssée*. Le second est d'expliquer qu'il est crucial d'inscrire les maladies rares dans une réflexion globale, et ce en dépit de la nature très singulière de chaque pathologie rare.

Mesurer le temps d'accès au diagnostic

[Scheuermann et al. \(2009\)](#) définissent le diagnostic comme la “conclusion d'un processus interprétatif qui a pour début le tableau clinique d'un patient donné et comme fin une affirmation selon laquelle le patient a une maladie de tel type”. Le diagnostic est donc l'acte final d'une procédure itérative, constituée d'examen cliniques et d'une enquête sur les antécédents médicaux. Alors que cette définition souligne le rôle central du clinicien dans l'établissement du diagnostic, elle néglige par la même le rôle central occupé par le patient. En effet, l'investigation clinique est conditionnelle à l'entrée du patient dans le système de santé. Le comportement individuel du patient en matière de recherche de soins et sa stratégie de gestion de sa santé sont des éléments susceptibles d'induire du délai dans l'obtention de son diagnostic, imputable aux patients.

Plusieurs facteurs peuvent expliquer le report de l'entrée du patient dans le système de santé. [Ballard et al. \(2006\)](#) ont mené des entretiens qualitatifs afin de comprendre les expériences des femmes en matière de diagnostic de l'endométriose, une maladie chronique occasionnant des douleurs chroniques du bassin. Les patientes atteintes d'endométriose attendent en moyenne 11,7 ans avant d'obtenir un diagnostic définitif de la pathologie ([Hadfield et al., 1996](#)). Lorsqu'elles ont été interrogées, les femmes ont signalé qu'elles avaient présenté des symptômes bien avant leur premier contact médical. Ces symptômes perturbaient souvent leur vie quotidienne, sans que cela les alarme sur le plan médical. Au contraire, loin d'envisager un diagnostic médical, elles se considéraient comme “malchanceuses” plutôt que “malades”. Les normes sociales et l'absence d'éducation menstruelle ont joué un rôle dans l'impossibilité des femmes à reconnaître la nature véritable de leur situation. La peur et l'embarras les ont dissuadées d'aborder leur problème de santé avec leur famille, leurs amis et des professionnels de la santé. En dépit de la sévérité de la douleur, certaines femmes ont déclaré avoir supporté l'insupportable avant de se décider à consulter un avis médical. Dans ce contexte, les patients se révèlent être eux-mêmes une source de délai de diagnostic.

Une fois la première consultation médicale dépassée, certaines femmes ont déclaré avoir le sentiment que les médecins ne mesuraient pas la gravité de leurs symptômes. Cela

prouve que les caractéristiques des médecins sont également une autre source de délai de diagnostic. De plus, les symptômes de l'endométriose peuvent être supprimés par intermittence, sous l'action des hormones. Les femmes connaîtront ainsi un rétablissement temporaire, ce qui pourrait les inciter à repousser la consultation médicale, et ce faisant, à reporter l'obtention du diagnostic final. Certaines caractéristiques de la maladie —de son caractère cyclique composé de phases de rétablissement et de rechute ou de la généralité de ses symptômes présentés —complexifient davantage encore l'établissement d'un diagnostic final. Enfin, les caractéristiques propres au système de santé telles que le niveau de coordination des médecins, l'existence de tests diagnostic ou la durée des délais d'attente pour les procédures de routine, sont autant d'explications possibles au retard diagnostic.

Au-delà des caractéristiques spécifiques des maladies, les facteurs potentiels contribuant aux variations du temps nécessaire pour converger au diagnostic incluent donc les caractéristiques des patients, des médecins, ainsi que l'organisation du système de santé au sens large. L'importance relative de chaque critère dans la détermination du délai de diagnostic est mal connue, car la littérature est rare dans ce domaine. En outre, la plupart des preuves reposent sur une définition restrictive du délai de diagnostic, qui commencerait avec l'entrée du patient dans le système de santé. Cependant, nous avançons ici l'idée que le délai de diagnostic devrait plutôt être mesuré dès l'apparition des symptômes de la pathologie.

Nous avons discuté de la mesure dans laquelle l'augmentation du délai de diagnostic pouvait être attribuée aux patients ou aux professionnels de la santé, bien que les responsabilités respectives ne puissent être facilement distinguées. Les patients peuvent ne pas transmettre correctement leur message ou celui-ci peut-être incorrectement interprété. Les patients peuvent également avoir des perceptions très hétérogènes de ce qu'est un bon ou un mauvais état de santé, ayant en conséquence des attentes différentes envers le système santé. La nature intrinsèque de la relation patient-médecin rend difficile l'identification des responsabilités respectives en ce qui concerne le retardement de l'accès au diagnostic final.

Les retards de diagnostic (1) constituent-ils une perte de chance pour les patients et; (2) jouent-ils un rôle crucial dans la construction des inégalités sociales de santé ?

Déterminants sociaux du délai de diagnostic

L'enquête française Erradiag, menée en 2016, a montré que 25% des patients traités pour une maladie rare déclaraient un délai de diagnostic supérieur à cinq années⁷.

Près de 60% des patients ont déclaré que l'absence de diagnostic avait entraîné pour eux des dommages physiques, une détresse psychologique, des traitements médicaux évitables, des congés de maladie ou des absences du travail. En outre, une revue systématique de la littérature sur le cancer du sein a mis en évidence un taux de survie réduit lorsque les délais de diagnostic étaient compris entre trois et six mois. La littérature suggère également que la récurrence dans le cancer est plus fréquente si les délais entre le diagnostic et le traitement sont allongés (Chen et al., 2008). Les résultats suggèrent qu'avec une période médiane inférieure à un mois, les délais entre le diagnostic et l'initiation du traitement ont un impact significatif sur la taille de la tumeur (Jensen et al., 2007). Jensen et al. (2007) ajoutent que "si le cancer progresse aussi rapidement après le diagnostic, il n'est pas déraisonnable de supposer qu'il progresse dans les temps passés à établir le diagnostic."

Ces résultats soulignent les coûts supportés par les patients en termes de qualité de vie, de santé et de survie, qui sont de loin les aspects les plus préjudiciables d'un retard diagnostic, bien au-delà des coûts pourtant élevés des congés de maladie et des dépenses médicales évitables. Même en l'absence de traitement, l'établissement du diagnostic est crucial pour les patients car ceux-ci valorisent les informations relatives à leur état de santé *per se*. L'établissement du diagnostic met un libellé sur leur maladie et légitime leur souffrance. Dans le cas d'une pathologie invalidante, cela confirme leur incapacité à poursuivre pleinement leurs ambitions sociales, familiales et professionnelles.

L'Organisation Mondiale de la Santé (OMS) définit les déterminants sociaux de la santé comme "les conditions dans lesquelles les personnes naissent, grandissent, vivent, travaillent et vieillissent" (WHO, 2008). La répartition des ressources entre individus détermine un large éventail de risques et de résultats de santé. De nombreux travaux ont mis en évidence l'existence d'un gradient social de santé, selon lequel l'espérance de vie est de plus en plus courte et la prévalence des maladies de plus en plus élevée dans la société à mesure que l'on descend dans la hiérarchie des revenus (Wilkinson and Marmot, 2003; Marmot, 2005). Des études sur les inégalités socio-économiques en matière de santé aux États-Unis et en Europe révèlent que les disparités évitables en matière de santé découlent d'une grande variété de désavantages sociaux sous-jacents, tels que le sexe ou l'origine ethnique, (Braveman and Tarimo, 2002).

⁷Enquête réalisée par l'Association de patients "Alliance Maladies Rares". Rapport disponible en français: <https://www.alliance-maladies-rares.org/erradiag-enquete-sur-lerrance-diagnostique-dans-les-maladies-rares-2/>

La mesure dans laquelle le délai diagnostique est déterminé par des facteurs sociaux et économiques reste non documentée. L'objectif du chapitre 1 de cette thèse est d'explorer l'existence de déterminants sociaux au délai de diagnostic.

Les coûts et les conséquences des retards de diagnostic pour les patients semblent être substantiels, mais restent sous-documentés. L'exploration des variations inter-individuelles de délai de diagnostic et de ses déterminants socio-économiques pourrait nous conduire à identifier une composante essentielle des inégalités sociales de santé. Plus spécifiquement, le premier chapitre de la thèse mesure le temps nécessaire au diagnostic, du premier symptôme au diagnostic final pour quatre pathologies chroniques, et explore le rôle occupé par le capital social et l'éducation dans l'obtention du diagnostic. Le processus de diagnostic, qui peut aboutir ou non à une conclusion, est semé d'embûches pour les patients. Néanmoins, les patients ne sont pas les seuls acteurs à souffrir de l'expérience de leur maladie.

A l'issue du diagnostic, le défi perdure

Les économistes de la santé démontrent l'impact spécifique d'une maladie sur la santé des patients en s'appuyant sur des mesures génériques de la santé. Voir, par exemple, les outils bien connus de l'EQ-5D (Kind et al., 1998), —tels que EORTC QLQ-C30 dans les cancers (Aaronson et al., 1993). Une partie de ces mesures intègre le caractère multidimensionnel de la santé en combinant diverses composantes de cette dernière. Par exemple, l'EQ-5D inclut des dimensions telles que la mobilité, la capacité à effectuer des activités quotidiennes, la douleur et la détresse psychologique. Celles-ci permettent de mesurer les conséquences de la maladie sur la santé et la qualité de vie des patients. Des enquêtes complémentaires ont tenté de décrire les coûts socio-économiques spécifiques à une maladie —voir, par exemple, les BURQOL-RD (Chevreul et al., 2015). La combinaison de ces outils révèle un élément clé de la gestion du traitement des patients, qui contribue largement à leur santé et leur qualité de vie : les aidants.

La littérature relative aux aidants montre que les maladies ont un impact bien au-delà du seul patient en affectant notamment leur système de soutien informel. Les aidants se caractérisent par leur engagement fort envers le patient, tout en étant souvent informels et non rémunérés (Dwyer et al., 1994). La recherche académique est récemment passée d'une emphase mise uniquement sur les patients à la prise en compte de son environnement et sa structure de soutien (Caqueo-Urizar et al., 2009; Dwyer et al., 1994). Dans ce contexte, une question importante est de savoir comment une évaluation coût-efficacité pourrait prendre en compte le fardeau imposé aux soignants lors des évaluations des

technologies de santé (Tubeuf et al., 2019). Les résultats suggèrent en effet que l'aide informelle auraient des conséquences néfastes sur la santé physique et mentale des aidants en raison du "travail physique, de la pression émotionnelle, des restrictions sociales et économiques découlant de la prise en charge d'un patient".

Le chapitre 2 a pour objectif de définir les retombées négatives sur la santé des aidants d'un diagnostic d'une pathologie chronique. En se concentrant sur les patients, la première partie de cette thèse prend comme exemple principal les maladies chroniques. Le choix de se concentrer sur les maladies chroniques répond à l'impossibilité de collecter des données auprès de patients atteints de maladies rares qui seraient originales, produites de manière rigoureuse, et qui offriraient un nombre d'observations suffisant pour permettre une analyse quantitative approfondie dans les délais impartis pour la thèse. Le choix des maladies chroniques, définies comme "des affections qui durent un an ou plus et nécessitent des soins médicaux continus et / ou une limitation des activités de la vie quotidienne", principales causes de mortalité et de morbidité dans les pays développés (Yach et al., 2004), est motivé par l'ambition de refléter les défis rencontrés par les patients atteints de maladies rares, aussi bien dans l'établissement du diagnostic, que dans son rapport à l'aidant, dans un contexte où une grande majorité des maladies rares sont infantiles.

La première partie de la thèse offre des considérations pour les maladies rares à de nombreux égards : (1) le diagnostic de maladies rares est complexe et l'on constate des retards dans l'obtention du diagnostic final, ainsi qu'une grande incertitude sur celui-ci, (2) des maladies rares ont des implications substantielles pour les patients et leurs perspectives professionnelles, familiales et / ou scolaires, et (3) les retombées sur les aidants sont importantes.

Les maladies rares: quelles sont-elles ? Qu'impliquent-elles ?

Les maladies rares représentent un "large éventail de troubles et de constellations de signes et de symptômes cliniques" (Luzzatto et al., 2015). Les termes "maladies rares" sont suffisamment transparents pour faire référence à des maladies qui touchent un faible pourcentage de la population. Mais à quel point rare est-il rare ? Une revue de la littérature sur la terminologie des maladies rares révèle que 58% des définitions de maladies rares indiquaient un seuil de prévalence, avec une moyenne de 40 personnes sur 100 000 dans une zone géographique définie (Richter et al., 2015). Mais la définition des maladies rares est une décision politique dans la mesure où elle détermine la portée des maladies qui entrent dans le cadre l'action politique dans le domaine des maladies rares. La FDA définit toute maladie ou affection affectant moins de 200 000 personnes aux États-Unis

comme une maladie rare (Richter et al., 2015). Au niveau européen, les maladies rares sont définies par l'EMA comme des maladies représentant un danger de mort ou une incapacité chronique n'affectant pas plus de 5 personnes sur 10 000 en EU (Rodwell and Aymé, 2015; European Medicines Agency, 2013). Globalement, les maladies rares touchent un nombre important d'individus : à ce jour, 5 000 à 8 000 maladies rares distinctes ont été documentées (European Medicines Agency, 2013), touchant un total de 30 millions de patients en Europe et à peu près le même nombre aux US (Griggs et al., 2009).

La différence entre une maladie rare et une maladie commune va au-delà de la simple bizarrerie numérique. Le délai moyen jusqu'au diagnostic est généralement considérablement plus long dans les maladies rares. Nous examinons l'exemple de l'AATD pour illustrer tous les défis rencontrés au cours du processus de diagnostic (Stoller, 2018). Les patients atteints de AATD font face en moyenne 7 à 8 ans avant de recevoir un diagnostic final (Greulich et al., 2013; Stoller et al., 2005, 1994). Les résultats suggèrent également que les patients avec des délais de diagnostic plus longs présentaient des séquelles cliniques, un statut fonctionnel plus mauvais et des symptômes avancés au moment du diagnostic (Tejwani et al., 2017). La faible occurrence de cas cliniques de l'AATD rend son identification particulièrement difficile en pratique clinique de routine. Le manque d'expertise clinique dans les maladies rares est reconnu par une enquête déclarative dans laquelle les médecins généralistes et les spécialistes ont déclaré n'avoir que peu ou pas de connaissances sur AATD dans 64% des cas (Greulich et al., 2013).

Nous avons souligné le manque d'expertise des professionnels de la santé sur les maladies rares et son impact sur les pronostics des patients. Dans le cas des maladies rares, une faible expertise en matière de maladies se conjugue avec peu de possibilités de traitement.

De la R&D au diagnostic, et vice versa

La recherche sur les maladies rares se heurte à deux obstacles majeurs. Premièrement, la rareté rend la recherche complexe. L'hétérogénéité observée entre les patients complexifie la compréhension de l'histoire naturelle et de l'épidémiologie de la maladie et ainsi, la définition de critères diagnostic spécifiques (Auvin et al., 2018; Nestler-Parr et al., 2018). Cinq nouvelles maladies rares sont décrites chaque semaine dans la littérature médicale (Nestler-Parr et al., 2018): jusqu'à présent, 5 000 à 8 000 maladies rares distinctes ont été documentées (European Medicines Agency, 2013). Ces chiffres augmentent rapidement grâce aux améliorations technologiques du séquençage de l'ADN qui permettent de mieux comprendre le génome humain et facilitent l'établissement du diagnostic pour

un certain nombre de maladies rares (Boycott et al., 2013). Deuxièmement, il y aurait un manque cruel d'incitations à financer des investissements de R&D dans les maladies rares. Selon de nombreuses études, la production de médicaments orphelins n'est pas rentable en raison des coûts élevés liés aux maladies rares (Buckley, 2008) et à la taille du marché insuffisante pour permettre la récupération des coûts fixes de R&D. Un élément de dépense important est le recrutement de patients dans les essais cliniques. Compte tenu de la faible prévalence des maladies rares, la phase de recrutement s'avère nettement plus longue, certains processus de recrutement s'étendant sur plus de 17 ans (DiMasi et al., 2003). Bien que, en l'absence d'accès aux données privées sur les dépenses de R&D, la mesure dans laquelle la R&D dans les maladies rares est financièrement risquée pour les industriels du médicament reste peu documentée.

En réponse à ces défis, les US et l'EU ont promulgué des réglementations dans le domaine des maladies rares inspirées par les politiques d'innovation. L'ODA a été introduite en 1983 dans le répertoire US; cette politique offre 50% de crédits d'impôt sur la conduite des essais cliniques, des dispenses de frais de processus d'autorisation de mise sur le marché, un programme de subventions pour la recherche et le développement technologique, des conseils scientifiques et une assistance au protocole par la FDA afin de respecter le processus réglementaire d'autorisation de mise sur le marché et de licence préalable. Elle cible des maladies dont la prévalence (nombre moyen de personnes atteintes d'une maladie pendant une période donnée) est inférieure à 75 cas sur 100 000 dans la population. La désignation de médicament orphelin accordée par la FDA favorise le développement et l'accès au marché de certains médicaments qui ne seraient pas rentables sans l'incitation de l'État. De 1983 à 2016, 503 médicaments et produits biologiques ont été approuvés pour le traitement de maladies rares et 1 132 médicaments ont obtenu une désignation orpheline (Hughes and Poletti-Hughes, 2016).

Des milliers de patients atteints de maladies rares pourraient alors avoir accès à de nouveaux traitements, cultivant ainsi l'espoir de voir leur santé et leurs conditions de vie s'améliorer. En 2000, au niveau Européen, la Commission européenne a introduit des incitations pour encourager la des médicaments dits orphelines et traitant, prévenant ou diagnostiquant les maladies rares.

L'une des caractéristiques de ces politiques est que ces avantages sont également accordés si la population cible d'une pathologie se situe dessous le seuil de prévalence des maladies rares. À cet égard, la politique OD pourrait inciter à la recherche sur des sous-ensembles de population de patients, le critère pour bénéficier des incitations étant principalement la taille de la population ciblée. Par conséquent, si un essai clinique donné est mené sur une population de patients relativement restreinte et ciblée, il pourrait être éligible à la désignation orpheline. La tendance croissante de la médecine de précision, définie comme reposant sur des biomarqueurs génétiques, épigénétiques et protéiques, a conduit à des raffinements diagnostics par sous-types de maladies. Celle-ci aurait pu être davantage encouragée par l'introduction de la politique OD (Chandra et al., 2017). Les biomarqueurs sont définis comme "une caractéristique objectivement mesurée et évaluée en tant qu'indicateur de processus biologiques normaux, de processus pathogènes ou de réponses pharmacologiques à une intervention thérapeutique". Ils sont de bons prédicteurs de la réponse clinique à un traitement.

Depuis l'entrée en vigueur du règlement OD jusqu'en 2015, 133 médicaments orphelins ont été mis sur le marché (Giannuzzi et al., 2017b), de sorte que la politique en vigueur est souvent décrite comme ayant conduit à des investissements sans précédent ciblant les maladies rares. Cependant, l'étude de l'impact indirect de la législation sur le développement de médicaments pour des maladies qui ne sont pas considérées comme rares n'a jamais été étudiée. En outre, 133 médicaments orphelins sont répartis entre 5 000 et 8 000 maladies rares différentes. Les objectifs des chapitres 3 et 4 sont (1) d'évaluer la politique innovante visant à favoriser la R&D dans les domaines des maladies rares, en mettant l'accent sur les médicaments non rares présentant des indications qualifiantes et (2) analyser la distribution de la R&D au sein de maladies rares en fonction des caractéristiques de la maladie et mettre en évidence des inégalités dans l'allocation des investissements de R&D dans les maladies rares. Ce chapitre étudie l'impact des politiques d'innovation sur les décisions privées des entreprises pharmaceutiques.

Compte tenu de la nécessité de répondre aux besoins non satisfaits des patients atteints de maladies rares, les décideurs ont mis en place des mesures incitatives dans le but de favoriser l'investissement en faveur des maladies rares. Plus de 20 ans après l'instauration de telles politiques, de nombreux médicaments orphelins ont été approuvés. Mais est-ce suffisant pour conclure qu'ils sont devenus (1) accessibles et (2) qu'ils présentent des bénéfices pour les patients atteints de maladies rares ?

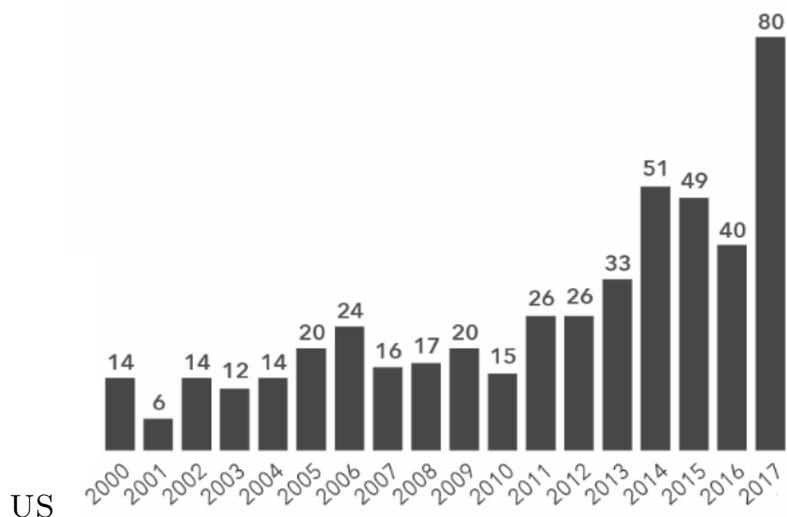
De la recherche à l'accès aux thérapies

Les décideurs politiques chargés d'allouer des ressources au sein du système de santé sont confrontés à un conflit majeur entre une demande de soins illimitée et des ressources limitées (López-Bastida et al., 2018). Une fois approuvés pour une indication rare, les médicaments orphelins doivent se conformer à une évaluation ou HTA, comme observé dans plusieurs régions, dont l'Amérique du Nord, l'Australie, de nombreux pays européens, et plus récemment l'Amérique latine et l'Asie (Ciani and Jommi, 2014).

L'HTA se fonde sur l'évaluation du rapport coût-efficacité d'une nouvelle technologie de santé et offre des indications sur les bénéfices collectifs d'une technologie de santé donnée dans un pays donné. Les recommandations sur les médicaments et autres technologies de santé sont supposées soutenir le système de santé d'un pays donné (Sorenson et al., 2008) dans ses décisions de financement, de couverture, de remboursement ou de négociation des prix des technologies de la santé. Bien que l'HTA nécessite des preuves cliniques et économiques, cette évaluation est rarement disponible pour les médicaments orphelins pour un certain nombre de raisons. L'une des raisons est qu'il est impossible d'effectuer des essais contrôlés randomisés, qui constituent la méthode de référence par excellence pour mesurer l'efficacité clinique d'un traitement (Bothwell et al., 2016). De plus, les essais cliniques dans les maladies rares peuvent ne pas comporter de bras de contrôle, pour des raisons éthiques, ou peuvent de pas avoir de comparateur (Nicod, 2017). La taille limitée de l'échantillon, ainsi que l'hétérogénéité de la progression de la maladie ou du sous-type clinique de la maladie, auront une incidence sur la fiabilité des estimations de coût et d'efficacité clinique (Bothwell et al., 2016).

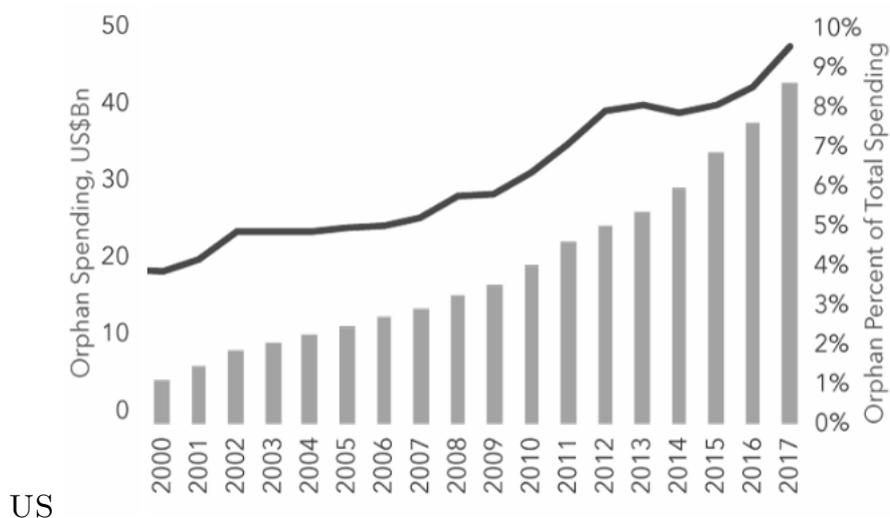
L'incertitude sur les bénéfices d'un traitement innovant dans les maladies rares n'est pas le seul enjeu. Les coûts des nouveaux médicaments approuvés pour les maladies rares constituent également une préoccupation majeure pour les services de santé et les décideurs du monde entier, et sont à l'origine de nombreux débats publics. Ces dernières années, des prix élevés ont été observés pour les médicaments conçus pour traiter les maladies rares. Par exemple, le coût du traitement des maladies de Gaucher a été estimé à 200 000 USD en moyenne par patient et par an (Luzzatto et al., 2018). De plus, le nombre de médicaments approuvés augmente chaque année, de même que la part des médicaments orphelins dans les ventes totales chaque année aux États-Unis (voir la Figure 1 et la Figure 2 ci-dessous).

FIGURE 1 — NOMBRE DE MÉDICAMENTS ORPHELINS APPROUVÉS PAR ANNÉE AUX



Source: Report IQVIA

FIGURE 2 — DÉPENSES DÉDIÉES AUX MÉDICAMENTS ORPHELINS ET PART DES DÉPENSES DÉDIÉES AUX MÉDICAMENTS ORPHELINS DANS LE TOTAL DES DÉPENSES,

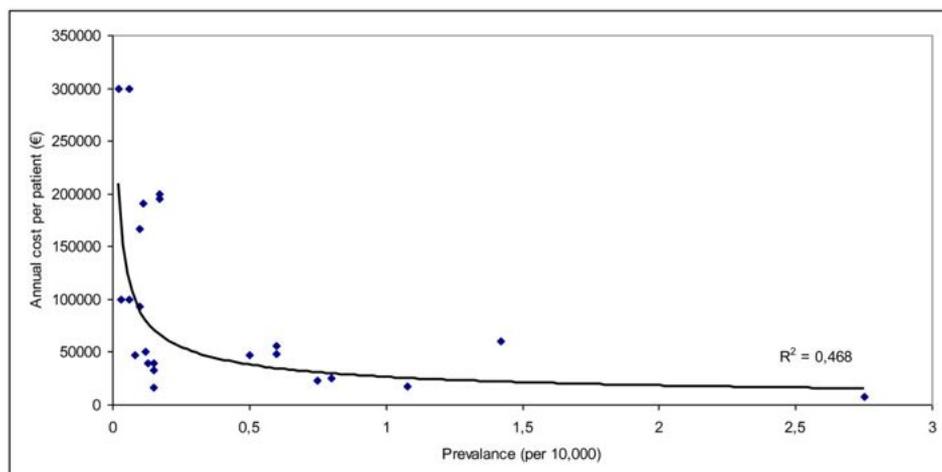


Source: Rapport IQVIA, Médicaments orphelins aux États-Unis — Croissance du nombre de traitements ciblant les maladies rares, 2018. La courbe en noir indique la part de % des ventes de médicaments orphelins dans les ventes totales. Les barres indiquent les dépenses en médicaments orphelins en milliards de dollars américains.

On pourrait penser que les médicaments orphelins génèrent des ventes limitées, mais nous observons de nombreux médicaments orphelins parmi les blockbusters générant au moins 1 milliard de dollars US de ventes. Selon [Côté and Keating \(2012\)](#), les entreprises biotechnologiques et pharmaceutiques ont rapidement adopté des stratégies leur permettant de réaliser des profits importants grâce à la réglementation sur les

médicaments orphelins. Un médicament orphelin peut traiter plusieurs maladies rares ou non-rares. Dans une telle situation, les médicaments orphelins ont accès à un marché plus vaste que prévu et récupèrent parfois en grande partie leurs coûts fixes de R&D. En outre, en cas d'extension d'indication, les sociétés pharmaceutiques peuvent être confrontées à des coûts fixes moins élevés, la plupart des processus de recherche étant terminé, elles ne supportent donc que le coût de la réalisation de nouveaux essais cliniques (Côté and Keating, 2012). Enfin, des résultats suggèrent que les entreprises pharmaceutiques possédant une désignation orpheline obtiendraient des valorisations boursières plus élevées en raison de l'augmentation attendue de leurs bénéfices (Gorry and Useche, 2017). Les données belges sur les prix suggèrent que plus la prévalence d'une maladie rare est faible, plus le prix du médicament est élevé (voir Figure 3) (Simoens, 2011).

FIGURE 3 — ASSOCIATION ENTRE LE COÛT ANNUEL BELGE PAR PATIENT D'UN MÉDICAMENT ORPHELIN ET LA PRÉVALENCE DE LA MALADIE



Source: (Simoens, 2011)

López-Bastida et al. (2018) ont étudié la volonté à payer pour des médicaments orphelins en utilisant une expérience de choix discrets, et ont exploré l'importance relative des attributs utilisés pour décrire différentes options de choix dans cinq pays européens. Les résultats montrent que la gravité de la maladie et l'efficacité du traitement sont deux dimensions importantes des décisions de financement d'un point de vue social. Cela confirme l'existence d'une préférence sociale dans le financement des médicaments. Mais devrions-nous vraiment considérer que les préférences collectives fournissent des

indications claires sur les décisions de financement ? Quelles sont les implications pour la société si l'on décide d'investir davantage dans la promotion de la santé de certains sous-groupes de la population ?

Compte tenu du niveau élevé d'incertitude sur le coût, l'efficacité et la contrainte budgétaire associés aux médicaments orphelins, le chapitre 5 a pour objectif de traiter de l'effet de l'innovation pharmaceutique dans les maladies rares sur la mortalité prématurée des patients atteints de maladies rares. Il souligne à quel point il est difficile, notamment pour les décideurs, d'estimer les bénéfices cliniques des médicaments orphelins.

L'objectif du chapitre 6 est de franchir une étape supplémentaire dans l'évaluation des médicaments orphelins, compte tenu de leur spécificité, et de discuter de la manière dont ils sont finalement mis à la disposition des patients. Nous utilisons pour cela l'exemple du NICE. Au Royaume-Uni, les patients bénéficient des traitements disponibles dans le panier de soins de santé couvert par le système de santé nationalisé et gratuit. Le choix d'inclure une technologie de la santé dans le panier de soins couvert par le NHS repose sur une analyse combinée des coûts et de l'efficacité de la nouvelle thérapie par rapport aux stratégies thérapeutiques conventionnelles et aux décisions de remboursement antérieures. Nous discuterons de l'usage des outils d'évaluation en santé, notamment pour les médicaments orphelins.

Part I

THE DIAGNOSTIC QUEST AND ITS PREJUDICE TO PATIENTS AND CAREGIVERS

The first part of this thesis focuses on patients and their support system. Diagnostics are a key element of a patient's trajectory. As discussed in the general introduction, patient characteristics may affect the length of time to receive a diagnosis, which can impact disease management in the long-run. Delays in receiving a diagnosis generate costs for patients, and in turn, for society. A better understanding of patient characteristics and how they may be associated with a greater length of time to diagnosis is crucial to alleviate social inequalities in access to diagnostic services. Chapter 1 is focused on the patient's experience and delays in receiving a diagnosis, addressing how social capital may impact time to a diagnostic workup. Chapter 2 documents the existence of spillover effects from patients' health to their main caregiver's health.

Chapter 1

Social Capital or Education: What Matters Most in Reducing Time to Diagnosis?

1 Introduction

Uncertainty surrounding the incidence of disease and efficiency of treatment has been formalized by [Arrow \(1963\)](#) as a major economic issue in medical care. However this uncertainty is preceded by another: uncertainty surrounding the correct diagnosis of the pathology.

The diagnostic workup can be conceived of as a double agency problem due to the presence of information asymmetry between health providers, patients, and a third party—the insurance provider. First, health providers collect and evaluate information provided by the patient in order to converge on a final diagnosis based on their training and medical expertise. They thus act in the interest of the patient in a conventional principal-agent problem. However insurance providers require the efficient use of limited resources, and require health providers to rationalize costs in their decision-making process. As such, efficiency requires that health providers take into account the effect of their actions on overall health care budgets, which in turn makes doctors “double-agents” ([Blomqvist, 1991](#); [Rochaix, 1997](#)). Ensuring appropriateness of care aims to prevent both waste in the use of health care resources and harm to patients.

When analyzing this double agency problem, neither the uncertainty surrounding the incidence of the disease nor the uncertainty of the diagnostic workup should be treated as exogenous. First, the probability of being a patient is greatly influenced by social factors. Second, the patient’s role must be acknowledged: the first medical decision in the model is that undertaken by the patient himself, when seeking care and medical expertise upon falling sick. Most papers in economics emphasize the time period following a patient’s entry into the health care system and the first medical consultation, while the decision to seek care is determined endogenously as a function of health and socio-economic variables. However a patient’s behavior may delay access to diagnostic. In economics the role of the patient has mostly been viewed as passive and models usually fail to acknowledge the active role patients play in determining their health care pathway, and thus the incidence and course of the disease.

A popular example of how patients’ social characteristics affect diagnostic and treatment is tonsillectomy. This procedure has unusually high rates of take-up in high-income households. A study by [Glover \(2008\)](#) showed that beliefs in high-income households about the advantages of the surgery for their children was the main driver of this higher

take-up. [Burton \(2008\)](#) summarizes the decision-making process of patients by stating that they “made-up their mind about what they want to have done beforehand.” Social effects are at stake in the construction of these beliefs about the appropriateness of a test and/or treatment. While supply-induced demand has been widely investigated in health economics, the “demand-induced supply,” which designates the excess supply of services due to an increase in demand initiated by patients, is much less documented ([Shih and Tai-Seale, 2012](#)).

While the patient’s role must be acknowledged to investigate the question of access to diagnostics, the behavior of doctors and their decision-making processes are likely relevant sources of observed variations of time to diagnosis.

[Glover \(2008\)](#) observes variations in doctors’ practices that cannot be fully explained by professional guidelines or differences in professional training. Health providers apply a rule of thumb decision-making process. First, they tend to specialize in areas in which they perform better, and also learn over time about private costs and benefits of diagnostic strategies and treatment options using availability heuristics to process and reuse information when needed. Doctors’ preferences and availability heuristics appear to favor patients and increase the likelihood of an appropriate diagnosis and medical treatment if a patient’s disease is aligned with the health provider’s medical expertise. Otherwise, the lack of medical adequacy may lead to delays in the diagnostic workup and lead to inefficient outcomes, especially in a situation in which the absolute number of diseases is growing along with their complexity.

Variations in time to diagnosis may reflect supply-side effects such as the health care system’s responsiveness to a symptom’s onset, as well as demand-side effects driven by patients’ characteristics and health care seeking behavior. The main purpose of this chapter is to identify factors from the supply side (doctors’ rules-of-thumb) and the demand side (patient characteristics) influencing time period to diagnosis. Specifically, this chapter investigates whether convergence to a final diagnosis is determined by the patient and/or physicians in the health production function.

We study the pre-diagnosis stage of a health condition from the patient’s perspective. The main variable of interest is time to diagnosis as defined by the time elapsed between the first symptom’s appearance and the final diagnosis.

We use data obtained from an online survey we administered to patients registered in a social network for chronic conditions. Data were collected for the purpose of this study. We describe time to diagnosis among patients treated for four chronic diseases: bipolar disorder, Crohn’s disease, multiple sclerosis, and psoriasis. We then explore socioeconomic factors that may explain differences in time to diagnosis between patients. We especially consider the importance of an individual’s social capital and education since these variables have been shown to have important causal effects on health status, health behaviors, and health utilization behaviors (Li and Powdthavee, 2015; Hummer and Lariscy, 2011; Kawachi et al., 2008).

This chapter is organized as follows. Section 2 reviews the literature on diagnosis workup, and on the channels through which social capital and education may influence time to diagnosis. Section 3 presents the questionnaire along with the data and the methods. Section 4 presents our main results and a final discussion is provided in Section 5.

2 Literature Review

In this section, we review the existing literature on time to diagnosis and the links between health and health care utilization.

As was pointed out in the general introduction, delays in diagnosis may have a detrimental impact on patients in terms of health and health expenditures. Despite innovative diagnostic technologies and the standardization of diagnosis and treatment protocols, the time elapsed between the onset of symptoms and the final diagnosis can vary substantially between patients. The French survey Erradiag, conducted by the Alliance for Rare Diseases association in 2016, showed that 25% of patients treated for a rare disease reported a time to diagnosis of over five years (Alliance Maladies Rares, 2016). Nearly 60% of patients declared that the lack of diagnosis led to physical harm, psychological distress, and avoidable medical treatments. Beyond rare diseases, several medical studies conducted on cancer patients have shown that time to diagnosis is negatively correlated to survival time (Richard et al., 2000; Facione, 1993; Ramos et al., 2007). The pre-diagnosis period has important consequences on prognosis and disease progression and if linked to social status, it may play an important role in the construction of social health inequalities. However it has thus far received very little, if no attention at all, in economics.

The time elapsed between first symptoms and first medical visit varies with symptom specificity and illness severity. If the symptoms are nonspecific to a disease, the patient may interpret them as transient episodes of tiredness or anxiety. Conversely, severe symptoms, sometimes combined with disabilities, will spur a patient's likelihood to seek care and thereby reduce time to first contact with a health care professional (Fajardy and Michel, 2012).

A thorough examination is critical in getting a diagnosis following a patient's first medical visit. The role of health care professionals is to identify the optimal diagnosis strategy, weighing the benefits and costs associated with additional tests, including direct and indirect costs to the patient such as invasive procedures and anxiety (Fuat et al., 2003).

The time elapsed from the first medical visit to the final diagnosis will also vary with the nature of the symptoms (specific or not) and the disease stage and form. For example, illnesses such as multiple sclerosis or lupus are characterized by relapsing-remitting forms for which symptoms may suddenly disappear. In complex or rare diseases, a diagnosis is harder to finalize and errors are more frequent. When symptoms are common to more than one disease, health professionals may misdiagnose the actual illness. According to the results of the survey conducted in 2012 by the French Observatory for rare diseases, 90% of health care professionals lack knowledge of rare diseases. Moreover, health care professionals, who are increasingly specialized, are less likely to adopt a global approach to patients' health when faced with a case presenting comorbidities.

While increased specialization may have positive effects on health care and health outcomes for diseases within the same area of specialization, it has been shown to lead to failure in coordination when multiple medical disciplines are involved (Baicker and Chandra, 2004).

Patient characteristics have been shown to influence health care seeking behaviour. An extensive literature has established the link between education and health, often referred to as the "health education gradient." Results indicate that more educated people have healthier lifestyles, a better health status, and a higher life expectancy (Grossman, 1972; Cutler and Lleras-Muney, 2010; Johnston et al., 2015). The study shows higher ability means patients are able "to gain access, understand and use information in ways that promote and maintain good health," a result often referred to as "health literacy" (Nutbeam and Kickbusch, 2000; Nutbeam, 2008). The more educated tend to adopt

healthier lifestyles, adhere to and comply with medical decisions and treatment, and so enjoy the benefits of improved medical technology (Goldman and Smith, 2002, 2011) and health campaigns (Cooper et al., 2003; Gordon et al., 2006). Education is associated with better access to both health services and financial support (Oreopoulos, 2006; Devereux and Hart, 2010).

Furthermore, education is associated with better health-related behavior such as lower cigarette consumption and higher levels of physical exercise (De Walque, 2007). An additional year of schooling appears to reduce the average daily cigarette consumption by 1.6 for men and 1.1 for women, and to increase physical exercise by 17 minutes on average (Wolfe et al., 2002; Kenkel, 1991).

Moreover, socio-anthropological studies show that more educated individuals also have different perceptions of their body and their health care needs, and seem to experience and report pain differently (Bonham, 2001). These results explain why less educated people may under-use health care services, even when provided freely (Després et al., 2011).

Studies on the patient-doctor interaction suggest that the social proximity between patients and doctors influence the diagnosis process, health care provision, and information sharing (Balsa and McGuire, 2003; Balsa et al., 2005; Kelly-Irving et al., 2011). Balsa and McGuire (2003) analyze the way in which interactions between doctors and patients may contribute to social disparities and suggest that the patient's relative social position affects doctors' interpretations and decisions during the diagnosis process. All an illustration of this, studies conducted before acute coronary crises showed that doctors had undertaken more investigations for better educated patients (Lang et al., 1998, 2011; Gerber et al., 2010). Patients' education, therefore, appears to affect both health care seeking behaviors and health care professionals' responses. The pre-diagnosis time span thus appears crucial in the construction of social health inequalities.

Beyond education, social relationships and networks may also play an important role in inequalities in time to diagnosis. Social capital, developed by (Coleman, 1988; Bourdieu, 1980; Putnam, 1995) is of growing interest for different fields, from sociology to political science, to economics and epidemiology. In the health economics literature, social capital has been assessed at the individual and the collective level (society, communities). At the collective level, social capital corresponds to "features of the social organizations such

as trust, norms, and networks that can improve the efficiency of society by facilitating coordinated actions” (Putnam, 1995).

In this chapter, we refer to social capital at the individual level, meaning it represents an “individual’s social characteristics that enable private returns via interaction with others that can be accumulated or transmitted across generations” (Glaeser et al., 2002; Rocco et al., 2014; Rocco and Fumagalli, 2014). Intensive interactions provide patients with privileged channels of information transmission; the opportunity to share past experiences on health facilities, health services, and health professionals; and this may reduce patients’ information costs (d’Hombres et al., 2010) as well as provide them with social and/or financial support (Hawe and Shiell, 2000).

Rocco et al. (2014) present four different mechanisms that may account for the link between social capital and health: (1) social capital may provide easier access to health relevant information as a result of more intense social interaction; (2) social capital may facilitate the provision of informal health care and psychological support; (3) social capital may facilitate people’s lobbying efforts to obtain health-enhancing goods and services; (4) social capital may induce rational people to reduce their risky behavior by increasing the expected value of life. In the time span to diagnosis, returns to social capital may enhance patients’ health-seeking behavior and facilitate interactions between health care professionals.

The role of individual preferences in decision-making has been widely investigated in economics (Anderson and Mellor, 2008; Gafni and Torrance, 1984). Attitudes toward risk (Charness et al., 2013) and time preferences, such as the preference for immediate over delayed satisfaction (Kahneman and Frederick, 2002), capture part of individual heterogeneity and are useful concepts for understanding and predicting individual behavior. Various approaches have been suggested to elicit individual preferences but relatively little attention has been paid to their contribution to health and health care seeking disparities. Studies suggest that individuals with lower time preferences or who are less risk-averse are more likely to undergo screening procedures (Picone et al., 2004; Jusot and Khlal, 2013). There is also evidence that time preferences and risk aversion are correlated with risky behaviors such as smoking. Jusot and Khlal (2013) show a reduction of the educational gradient in smoking after controlling for time preferences and risk aversion, supporting their role as partial mediators.

Regarding access to health care, results from (Picone et al., 2004) suggest that individuals with lower time preferences tend to delay care seeking and be less proactive during the period when their diagnosis is made because they underestimate the future losses associated with delayed access. Similarly, risk averse individuals may fear the final diagnosis and be less proactive during the period of their diagnosis development, and experience a longer time span to diagnosis.

The literature shows strong associations between education, social capital or individual preferences, with respective health and health behaviors. Verba et al. (1995) show that more educated people engage more often in collective activities while Putnam and Helliwell (1999) show that education levels increase levels of trust, one of the commonly used proxies for social capital. Regarding individual preferences, the less educated are more likely to engage in riskier behaviors (Murphy and Topel, 2006). While many studies examine the isolated effect of education, social capital, and individual preferences, few have considered these variables together.

3 Data and Methods

3.1 Data

To understand the role of patients' preferences in explaining time to diagnosis, we must adopt a patient's perspective and rely on patients' reported outcomes. Although the use of the Patient Reported Outcome Measures (PROMs) is a growing field of interest, no information is jointly collected on PROMs and patient characteristics. Our study is therefore the first to link these two dimensions. It is based on patients' self-assessments of time elapsed from first symptoms to final diagnosis. This information was collected from an online survey conducted between May and July 2015 on a French social network called Carenity, dedicated to patients with chronic conditions. ¹

The response rate was estimated at 23%, with no significant differences between diseases. This response rate should be considered the lower bound as the questionnaire was sent to all patients in the entire database, including those who were not active for more than six months, which overestimates the pool of potential respondents. As individual health characteristics are not systematically recorded in Carenity, it was not possible to explore

¹Carenity is a social network dedicated to patients with chronic health conditions (see the UK version of the website at <https://www.carenity.co.uk/who-we-are>).

which factors determined individual participation.

The collected data were self-reported and retrospective. We checked the patients' response consistency by comparing values for age, age of symptom onset, date of first symptoms, and final diagnosis date reported. A total of 659 completed questionnaires (78%) fulfilled the aforementioned coherence tests. Since the study focused on the impact of education and social capital on time to diagnosis, patients aged less than 18 years old at the time of first symptoms were excluded. While reducing the sample size to 503 patients, this enables us to concentrate on patients with autonomous behavior in health management and to exclude patients diagnosed at birth or in their childhood.

The questionnaire draws from the French health, health care, and insurance surveys, which is the main French health and insurance interview survey.² Questions on the pre-diagnosis time period were designed to describe patients' experience from symptom appearance to final diagnosis. The questionnaire was piloted on a sub-sample of 21 patients. The sample is not designed to be nationally representative and suffers from the usual selection biases relating to patient participation in social networks, both in terms of social and health characteristics. Previous work conducted on the Carenity patient database to explore its representativity suggests that compared to a nationally representative sample of patients, Carenity's sample has fewer seniors and more women, but displays no significant differences in geographical representation (Raïs Ali et al., 2017). Additionally, with the survey being administered online along with open access and no control over a respondent's environment, we suspect patients with expanded pre-diagnostic periods may be more likely to share their experience online. Respondents to the opening question, "What has been your experience of the health care system from symptoms' appearance to final diagnosis?" were more likely to have experienced poorly integrated care.

Regarding memory bias, the literature suggests that the period preceding final diagnosis is usually well remembered by patients (Talarico et al., 2004; Berney and Blane, 1997), in particular if the illness entails a substantial and durable change in social and professional life. From our analysis, this is likely to be the case for patients suffering chronic conditions: multiple sclerosis, bipolar disorder, psoriasis, or

²The French health, health care, and insurance surveys were conducted by the Institute for Research and Information in Health Economics (EHIS) from 1988 to 2014. They now form the basis of the European Health Interview Survey (EHIS).

Crohn's disease. We chose to focus on heterogeneous conditions, both in terms of severity and progression, for which clinical diagnoses are difficult to establish given the non-specificity of symptoms. Another key criterion that mattered when selecting the conditions was that they had severe impacts on functional health and patients' daily lives, as well as their relative importance in the database, to ensure a large enough sample.

Multiple sclerosis is an inflammatory disease of the central nervous system characterized by sensation disorders and mobility impairments. The diagnosis is based on imaging analysis such as a Magnetic Resonance Imaging (MRI) scan. Prognosis is unpredictable, with long remission periods (McDonald et al., 2001).

Bipolar disorders are characterized by maniac phases, or recurring hypo-mania, and major depressive episodes. Addictions, isolation, divorce, or unemployment are commonly associated with bipolar disorders. The risk of suicide is 15 times higher than that of the general population in France (Goodwin and Jamison, 2007). There is on average a ten-year lag between the onset of bipolar disorder symptoms and the start of treatment (Hättenschwiler et al., 2009).

Psoriasis is a long-lasting autoimmune disease characterized by patches of abnormal skin. The diagnosis of psoriasis is typically based on the symptoms and is difficult to establish; it is associated with an increased risk of psoriatic arthritis, lymphomas, cardiovascular disease, Crohn's disease, and depression. Psoriatic arthritis affects up to 30% of individuals with psoriasis (Gelfand et al., 2005).

Crohn's disease is a type of Inflammatory Bowel Disease (IBD) characterized by inflammatory and remission phases. Symptoms include abdominal pain, diarrhea, fever, and weight loss. Diagnosis is based on the addition of several tests including biopsy and bowel wall examination. Delayed diagnosis may lead to severe complications (Van Assche et al., 2010).

Variables used in the analysis

The variable *Time To Diagnosis* (in months) captures the time elapsed between the first symptoms to the final diagnosis. It is calculated from respondents' self-reported date of first symptoms and final diagnosis.

The variable *Education* represents the highest educational attainment reported by pa-

tients, grouped into three categories: neither diploma nor technical degree, baccalaureate (corresponding to the high school final degree in France), and undergraduate level or higher.

We used two variables to proxy the level of social capital: *Social Participation* is a dummy variable that measures patients' reported participation in collective activities such as voluntary-charity work, training courses, sport-social clubs, religious organizations, and political-community organizations. It is one of the most commonly used variables to capture individual social capital (Scheffler et al., 2007; Olsen and Dahl, 2007). *Social Support* is a dummy variable that indicates whether the respondent reported being able to rely on support from family or friends during the pre-diagnostic period. This question was tailored to the particular context of the pre-diagnostic period and to the measurement of the pre-diagnostic social capital level. Information on symptom severity was also collected to control for clinical symptoms using a categorical variable *Symptoms Severity* corresponding to mild, moderate, or severe symptoms.

Individual preferences were collected using standardized questions developed and validated by EHIS for the French Health Healthcare and Insurance Survey 2008. The *Time Preference* and *Risk Aversion* variables were derived from scores assessed by respondents on a 0 to 10 scale. These scales were defined in the National Institute of Statistics and Economic Studies (INSEE) / Département et Laboratoire d'Economie Théorique Appliquée (DELTA) survey (Arrondel et al., 2004b, 2007) which aimed to measure time and risk preference measures (Arrondel et al., 2004a; Arrondel and Masson, 2014). Following Jusot and Khlal (2013), we respectively transformed the scores into two binary variables for time preference ([0;1] versus [2/3;10]) and for risk aversion ([0;7] versus [8;10]).

In spite of the GP reform in 2004 in France that led to GPs becoming gatekeepers, the health system still allows patients to freely choose between four entry points when seeking care: a GP, a specialist outside the hospital, a specialist based within the hospital, or Accident and Emergency (A&E) Departments. The variable *First Medical Visit* in the dataset therefore coded as one of these four possible first contacts.

Table I.1.1 displays respondents' socioeconomic characteristics by type of disease. Table I.1.2 reports the distribution of time to diagnosis by disease and displays large discrepancies both between and within illnesses. As is shown in Table I.1.1, women represent the majority of the sample (77%): this feature is consistent with the over-representation of

women in online social networks (Correa et al., 2010), and the higher incidence of multiple sclerosis (Chwastiak et al., 2002) and bipolar disorder (Llorca et al., 2013) among women. Carenity respondents are on average more educated and younger than the general population (Correa et al., 2010; Raïs Ali et al., 2017), which corresponds to the general findings on social media participation rates. Looking at the distribution of time to diagnosis, we observe very skewed distributions toward 0 (less than 1 month of time to diagnosis) with very large extreme values (with a maximum value of 20 years of time to diagnosis for psoriasis and 35 years for bipolar disorder). We do observe large variations in time to diagnosis within and between each of the four chronic conditions.

3.2 Methods

We studied the links between time to diagnosis (in months) and our two main variables of interest, education and social capital, accounting for demographics as well as risk and time preferences, and differences in self-assessed symptoms' severity between respondents. We used a Cox proportional hazard model (Cox, 1992) to analyze time to diagnosis, using the Breslow method for ties. Time to diagnosis was used as our time scale (in months).

This semi-parametric procedure enabled us to compute the baseline hazard function $h(t)$, which is the probability that an individual will experience an event (here, the diagnosis workup) within a small time interval, given that the individual has survived up to the beginning of the interval, without any restrictive distributional assumptions (see Equation 1.1). The Cox model assumes that covariates are related to the hazard (i.e., proportional hazard assumption) in a multiplicative way but this hypothesis appears to be contradicted for *Age Class*, as young patients experience, on average, a shorter time span to diagnosis compared to older patients in our sample.

We therefore used an extension of the Cox model to deal with non-proportional hazards by stratifying over the covariate *Age Class*, which does not satisfy the proportional hazard assumption. The extension allows for multiple strata with distinct baseline hazard functions but common values for the coefficient vector. Our model specifies four strata corresponding to the four categories of *Age Class*: 18-34 years old; 35-44 years old; 45-54 years old; >55 years old (as displayed in Table I.1.1).

The model for each strata is written:

$$h_g(t) = h_{0g}(t) \exp[\beta_1 X_1 + \dots + \beta_p X_p] \quad (1.1)$$

with $g \in \{1, 2, 3, 4\}$, strata defined from Age Class

Using this specification, we measure the effect of both education and social capital on the probability of survival, which here represents the probability of remaining without a diagnosis (the event of the survival analysis being ‘obtaining the final diagnosis’). The fully adjusted models include controls for gender, marital status, and symptom severity. We added controls and clustered errors for medical conditions to account for heterogeneity across diseases. The vector X hence includes the following variables: *Education*, *Social Participation*, *Social Support*. It also includes the aforementioned control variables: gender, marital status, symptom severity, and medical condition.

We also assess heterogeneity in the results by conducting sub-sample analysis by pathology. The regressions are estimated separately and provided as additional results in the chapter [Appendix](#). While our primary objective is to estimate the average impact of patient characteristics on time period to diagnosis and not the heterogeneity of the impact given disease specificity (i.e., medical skills and/or equipment needed to converge on a diagnosis, natural history of the disease, complexity and specificity of symptom onset, etc.), we present sub-sample analysis to remove our implicit constraint on our coefficient to be the same for all four illnesses.

That being said, it is difficult to estimate and discuss results on models by disease given the limited number of observations and the likely low statistical power. A small sample reduces the chance of detecting a true effect and also reduces the likelihood that a statistically significant result reflects a true effect.

4 Results

Table [I.1.3](#) reports estimates for models (1), (2), and (3). The results from Cox stratified models show that social capital, as measured by social participation and social support, is significantly associated with shorter time to diagnosis. Patients reporting social support or social participation exhibit Hazard Ratio (HR) superior to 1, meaning that social support significantly increases the probability of obtaining a diagnosis by 21-27% (Table

I.1.3 Model (1), HR respectively 1.21, $p < 0.05$ and 1.27, $p < 0.000$). This finding is robust to the inclusion of control variables accounting for time and risk preferences (Table **I.1.3** Model (2) and Model (3)).

More educated patients have a higher probability of experiencing a longer time to diagnosis compared to patients without diplomas. More specifically, it significantly reduces the probability of obtaining the diagnostic by 5% (Table **I.1.3**, Model (1), HR 0.95 for individuals with a college degree, $p < 0.01$).

After controlling for individuals' risk aversion and time preferences (Table **I.1.3**, Model (2)), coefficients for *Education* remain constant and significant. Preference for the present appears to significantly increase the probability of longer time to diagnosis and significantly increases the time waited by 5% (Table **I.1.3**, Model (2), HR 0.95, $p < 0.05$), while the coefficient for risk aversion remains insignificant.

Consulting a specialist first, rather than a GP, significantly increases the probability of having a longer time to diagnosis (Table **I.1.3**, Model (3), HR 0.60, $p < 0.01$). This increases the probability of experiencing a longer time period to diagnosis by 40%. Moreover, after controlling for the type of first medical visit, the coefficient for *Education* becomes insignificant, providing evidence that education was previously associated with the probability of having a longer time to diagnosis when choosing specialists as a first medical visit.

This result is robust to the inclusion of control variables accounting for individual risk and time preferences. It is also robust to the exclusion of the 3% extreme values of our sample, which reduces the maximum value of time to diagnosis from 420 months to 262 months (see Table **I.1.4** in **Appendix**, Model (4)). We also remove from the sample recently diagnosed individuals (defined as diagnosed within the past 1 or 2 years) to avoid the risk of misdiagnoses. The results are robust to this check (see Table **I.1.4** in the **Appendix**, Model (5)). Finally, the hypothesis of proportional hazard of our stratified Cox model proportionality of hazard was not rejected ($p > 0.67$), and this confirms the chosen specification.

Stronger social participation and social support significantly reduce time to diagnosis, increasing the probability to obtain the diagnostic by 25%-31% (Table **I.1.3**, Model (3): HR respectively 1.25, $p < 0.001$; 1.31, $p < 0.000$). Social interactions may allow patients to gather health information as well as information from other patients, thereby reducing time to diagnosis. Social capital also facilitates access to social and financial support.

Regarding individual preferences, only strong preferences for the present were associated with a higher probability of longer time to diagnosis, reducing the probability of obtaining the diagnosis by 25% (Table I.1.3, Model (3): HR 1.25, $p < 0.001$). This result on time preferences is in line with previous findings (Picone et al., 2004): patients with a stronger preference for the present are substantially more focused on current well-being and may be less proactive in the diagnosis-seeking process. Such patients may undervalue future losses associated with postponing medical care or a less proactive behavior during the pre-diagnosis period. They may also favor procrastination, i.e. value ignorance over awareness, postponing examinations they fear may reveal an unknown pathology (Rapp, 2014).

Higher levels of education increase by 5% the probability of longer time to diagnosis (Table I.1.3, Model (1), HR on college degree: 0.95, $p < 0.01$). Even after controlling for risk aversion and preference for the present (Table I.1.3, Model (2)), the coefficients for *Education* remain constant and significant.

We identify three possible channels to account for this result:

1. More educated patients tend to challenge medical doctors' assessments (Lupton, 1997; Smith et al., 2009), and may seek second opinions. Besides, doctors may behave differently when patients are more educated, knowing that they are more proactive and may challenge their diagnosis (Willems et al., 2005). Recent evidence indeed shows that doctors have implicit biases which influence their response to patients' demands (Chapman et al., 2013). As a result, doctors may attempt to gather more evidence before giving their final diagnosis, to reduce further the probability of diagnosis errors.
2. Educated patients may retrospectively assess symptoms' appearance earlier, and differences in biases regarding self-reported dates may partly drive the results on education. More educated patients have been shown to have higher expectations about their health status (Allin et al., 2010; D'Houtaud and Field, 1984) and socioeconomic variations in pain tolerance have also been established (Bonham, 2001).
3. In France, patients have the freedom to choose between GPs and specialists, who are both paid on a fee-for-service basis. Although gate keeping was implemented in 2004, it is not binding (Groenewegen et al., 2013), and some patients continue to access specialist care directly despite higher out-of-pocket expenditures. As more educated patients consult specialists more readily than GPs, this freedom of choice may have induced social disparities in diagnostic trajectories due to differences in individual preferences, health literacy, and economic resources (Le Fur and Yilmaz, 2008; Gouyon, 2010). Ambulatory

care specialists, unlike GPs, tend to delay referring patients to hospitals or emergency services (Friedberg et al., 2010; Foot et al., 2010; Johnson et al., 2008). This can, in turn, increase the time to a final diagnosis.

We provide in the [Appendix, I.1.5, I.1.6 and I.1.7](#) additional results with sub-sample analysis and replication of the empirical strategy for each of the four diseases considered. Given the limited number of observations and the subsequent loss of statistical power, we lose significance for most of the results. Still, signs of the coefficients remain consistent with the full sample analysis. Most of the variation between the full sample and sub-sample analyses is observed with the variable capturing the severity of the symptoms during the pre-diagnostic period; it suggests that an analysis incorporating precise information on the course of the disease would be necessary to fully account for the heterogeneity in diseases and the specificity of the symptoms. The objective would be to identify whether or not the symptoms of the disease are conclusive enough to more quickly converge on a diagnosis.

A number of papers have investigated socioeconomic inequalities in waiting times. Prolonged waiting times may also (1) postpone benefits from treatment and (2) induce a deterioration of the patient's health status and/or quality of life. Literature on waiting times suggests that even in publicly funded health systems, nonprice allocation of services does not guarantee equality of access by socioeconomic status.

[Laudicella et al. \(2012\)](#) also use Cox models to estimate the effects of education and income deprivation on waiting times. Results suggest that patients in the first quintile with the least deprivation in education wait 9% less than patients in the second quintile, and 14% less than patients in the third-to-fifth quintiles. Patients in the fourth and fifth income-deprived quintile wait about 7% longer than patients in the least deprived quintile. Our results show similar magnitude for the education coefficient, even if the effect here is mediated by different health behavior between less educated and more educated patients. Moreover, comparing the magnitude of coefficients, social capital—not investigated in the literature on waiting times—and the first medical contact show larger impact on diagnostic delays than in [Laudicella et al. \(2012\)](#).

No information was collected on patients' or doctors' actual behavior during the study period, which does not allow for further investigations on the first and second channels. However based on the available data, we can further document the third hypothesis. Results suggest differences in health care-seeking behavior as the coefficient on *Education*

loses significance (Table I.1.3, Model (3): HR respectively 0.94, $p > 0.1$) while the coefficient associated with specialists becomes significant (Table I.1.3, Model (3): HR 0.60, $p < 0.01$). More educated patients tend to visit specialists first, and this is correlated with a longer time to diagnosis since specialists are less likely than GPs to refer patients to hospitals for additional tests when needed.

Our study suffers from several limitations. First, since questionnaires were kept reasonably short to ensure a high response rate and avoid undue burden for respondents, we did not include questions on disease history or symptom evolution. As a result, controls for disease severity lack precision since they are based on patients' perception of symptom severity in the disease early phase, to measure time to diagnosis. Moreover, beyond education, no other socio-economic characteristics of patients were collected (e.g., income).

To address the issue of possible reverse causality, we chose to remove patients with symptoms occurring before 18 years of age, which ensures the inclusion of patients with autonomous health decisions. Yet this method only partially answers the endogeneity issue since the time to diagnosis may have an impact on educational achievements. Finally, we lacked data to model and estimate the determinants of a patient's decision to seek care, which would contribute towards understanding their disease management strategies.

The survey only includes patients who have ever received a diagnosis. A large proportion of patients may have symptoms that (1) are not correctly identified or (2) have not been reported to doctors and so remain undiagnosed. It is plausible that these patients have lower socioeconomic status and thus are less prone to consult specialists as a first medical contact, and have lower levels of social capital and education. The overall impact on external validity of the non-random selection of the sample, and the absence of undiagnosed patients, is questionable. The results will hold if the sample includes sufficiently diverse socioeconomic groups however if the patients in the dataset are highly selected, the results will not have external validity. It would be reasonable to suspect that patients with expanded pre-diagnostic periods will be more prone to sharing their experience online since the study explicitly referred to delays in accessing a diagnosis. The information collected in the opening question, "What has been your experience of the health care system from symptoms' appearance to final diagnosis," showed that those who responded were more likely to have experienced poorly integrated care. This is a limitation in the estimation if socially deprived categories of patients are not represented in the analysis.

Still, as displayed in descriptive statistics, we observe variations in socioeconomic statuses.

Finally, we undertook another robustness check related to the likelihood of incorrect diagnosis by removing from the sample recently diagnosed individuals, here defined as those diagnosed within the past two years. The results were robust to this restriction.

5 Discussion and Conclusion

The full diagnostic timespan, from the initial onset of symptoms to final diagnosis, has received very little attention since most of the data collection begins after a patient's first medical visit. Only anecdotal evidence has been gathered on variations in time to diagnosis, indicating that more educated patients or those with strong social networks experience a shorter diagnostic time frame.

For a number of diseases, depending on disease severity and symptoms' evolution, delays in accessing diagnostic services can have important implications for survival. The consequences associated with delays in receiving a diagnosis may be irreversible for patients. Implications for quality of life resulting from the lack of a diagnosis, especially in the case of an acute pathology, is likely to be physically and psychologically damaging. When patients are asked about the difficulties experienced during the pre-diagnostic period, 39%³ reported that they experienced important challenges in their professional life and even has to quit work, or substantially reorganize their working schedule. Regarding family problems, 34%⁴ reported having separated from their partner, and/or abandoning family projects during the pre-diagnostic period.

This chapter offers the first measure of this time prior to diagnosis. Despite data restrictions, we were able to document large variations between patients and between conditions.

Our results provide evidence that the first medical visit plays an important role in explaining time to diagnosis. Patients who first seek care from GPs experience shorter time spans as compared to those seeking who see a specialist for their first medical

³Statistics reported are computed on the full sample of 503 patients. Percentages vary between 31% for Crohn's disease and 48% for multiple sclerosis. These statistics must be taken with caution as we do not have information on work status at the time of the diagnosis.

⁴Statistics reported are computed on the full sample of 503 patients. Percentages vary between 22% for psoriasis and 40% for bipolar disorder. These statistics must be taken with caution as we do not have precise information on family life.

visit. This may be due to the fact that specialists are less likely than GPs to refer patients to hospitals for additional tests when needed. These results provide support for public policies aimed at establishing coordinated and streamlined health care pathways, continuing to use GPs as gatekeepers.

Regarding social networks (social participation and social support), we find that they reduce the probability of experiencing a longer time to diagnosis and confirm the WHO's recommendations to enhance individual social capital.

Higher levels of education seem to increase the probability of longer time spans. We further analyze this unexpected result by identifying differences in patients' health care seeking behavior and found that more educated patients tend to seek care from specialists first, leading to longer time spans. Two alternative channels are offered for this result on education, based on 1) specialists' implicit biases regarding educated patients or 2) differences in patients' ability to identify and report dates of first symptoms. None of these two alternative channels can be further investigated using our data.

While our results on social networks are likely to apply to most health care systems, those on education may not hold for health care systems in which gatekeeping is fully implemented. Carrying out similar studies in countries where higher education or stronger social networks may influence time to diagnosis would shed light on these issues. Our results point to the important role of the pre-diagnostic period in the construction of differentiated access to diagnoses. Yet delays in time to diagnosis are an under-documented aspect of inequalities in health and health care. Potential leverage for inequality reduction must be further explored in academic research to refine health care practices and design health care reforms.

6 Appendix

Table I.1.1 – PATIENTS’ SOCIO-DEMOGRAPHIC CHARACTERISTICS

	Medical conditions				
	Psoriasis Col %	Multiple sclerosis Col %	Bipolar trouble Col %	Crohn’s disease Col %	Total Col %
Gender					
Male	36.6	19.9	24.3	17.5	23.3
Female	63.4	80.1	75.7	82.5	76.7
Age group					
18-34	4.9	12.4	8.7	33.8	13.7
35-44	15.9	22.1	26.1	27.5	22.9
45-54	31.7	33.2	39.1	18.8	32.0
>55	47.6	32.3	26.1	20.0	31.4
Couple					
No	42.7	37.6	50.4	37.5	41.4
Yes	57.3	62.4	49.6	62.5	58.6
Education					
No diploma	40.2	32.3	20.0	35.0	31.2
Baccalaureate	14.6	22.1	20.9	12.5	19.1
Bac+2 and +	45.1	45.6	59.1	52.5	49.7
Social participation					
No	82.9	75.2	82.6	82.5	79.3
Yes	17.1	24.8	17.4	17.5	20.7
Social support					
No	46.3	38.1	53.9	40.0	43.3
Yes	53.7	61.9	46.1	60.0	56.7
N	82	226	115	80	503

Source: Author’s data.

Table I.1.2 – TIME TO DIAGNOSTIC WORKUP BY DISEASE (IN MONTHS)

Disease	N	Mean	SD	p25	p50	p75	Min	Max
Psoriasis	82	35.5	71.1	2	4	34	0	366
Multiple sclerosis	226	37.3	64.1	3	10	46	0	386
Bipolar disorder	115	90.5	90.8	7	68	150	0	420
Crohn’s disease	80	24.6	44.0	3	6.5	26.5	0	239
Total	503	47.2	73.6	3	12	57	0	420

Source: Author’s data.

Table legend: Time to diagnosis is defined as the time span between symptoms’ first appearance and final diagnosis, expressed in months. Statistics displayed are: (1) Number of observations; (2) Mean ; (3) Standard deviation; (4) First quartile; (5) Median; (6) Third quartile; (7) Minimum; (8) Maximum.

Table I.1.3 – ESTIMATED COEFFICIENTS AND 95% CONFIDENCE INTERVALS FOR CO-VARIATES' INCIDENCE ON TIME TO DIAGNOSTIC WORKUP USING COX MODEL STRATIFIED BY AGE CLASS.

	(Model 1)	(Model 2)	(Model 3)
Female	-0.138 (-1.64)	-0.148 (-1.91)	-0.123 (-1.78)
Couple	0.0506 (0.49)	0.0403 (0.40)	0.0835 (0.87)
Education (Ref=No diploma)			
Baccalaureate	-0.0237 (-0.89)	-0.0471*** (-3.98)	-0.0476 (-0.64)
Bac+2 and +	-0.0548** (-2.74)	-0.0714** (-3.13)	-0.0601 (-1.55)
Social support	0.189* (2.34)	0.199** (2.82)	0.221*** (3.31)
Social participation	0.240*** (4.93)	0.244*** (4.81)	0.268*** (4.01)
Disease (Ref=Psoriasis)			
Multiple sclerosis	-0.0659 (-0.63)	-0.0560 (-0.56)	-0.143 (-1.26)
Bipolar disorder	-0.660*** (-30.95)	-0.640*** (-18.13)	-0.715*** (-19.25)
Crohn's disease	0.0469 (0.85)	0.0650 (1.15)	-0.0507 (-0.63)
Symptoms' severity (Ref=Mild)			
Moderate	-0.0397 (-0.17)	-0.0662 (-0.26)	-0.0338 (-0.15)
Severe	-0.0654 (-0.39)	-0.101 (-0.51)	-0.0915 (-0.47)
Risk aversion		-0.147 (-0.90)	-0.159 (-0.87)
Pref. for present		-0.0551* (-1.96)	-0.0706*** (-5.42)
First medical contact (ref=GP)			
Hospital specialist			-0.0871 (-1.15)
Ambulatory specialist			-0.513** (-2.65)
Emergency service			-0.126 (-0.50)
Observations	503	503	503

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table I.1.4 – ROBUSTNESS CHECKS: MODEL (4) COEFFICIENTS FOR MODEL (3) WITHOUT 3% TOP VALUES AND MODEL (5) DISPLAYS COEFFICIENTS FOR MODEL (3) RESTRICTING FOR PATIENTS DIAGNOSED WITHIN THE 2 PREVIOUS YEARS

	(Model 4)		(Model 5)	
Female	-0.0976	(-1.53)	-0.158	(-1.93)
Couple	0.101	(0.88)	0.0606	(0.64)
Education (Ref=No diploma)				
Baccalaureate	-0.0946	(-1.17)	-0.0504	(-0.47)
Bac+2 and +	-0.0587	(-0.85)	-0.0520	(-1.07)
Social support	0.154***	(4.74)	0.248***	(4.05)
Social participation	0.174*	(2.52)	0.278***	(3.87)
Disease (Ref=Psoriasis)				
Multiple sclerosis	-0.355***	(-5.17)	-0.135	(-1.11)
Bipolar disorder	-1.037***	(-11.01)	-0.695***	(-18.67)
Crohn's disease	-0.374***	(-4.13)	-0.0562	(-0.66)
Symptoms' severity (Ref=Mild)				
Moderate	-0.0149	(-0.09)	-0.0821	(-0.35)
Severe	0.000401	(0.00)	-0.139	(-0.75)
Risk aversion	-0.0877	(-0.51)	-0.219	(-1.27)
Pref. for present	-0.236***	(-3.42)	-0.0420*	(-2.43)
First medical contact (ref=GP)				
Hospital specialist	-0.0672	(-0.83)	-0.120	(-1.38)
Ambulatory specialist	-0.413*	(-2.55)	-0.536**	(-2.95)
Emergency service	-0.000556	(-0.00)	-0.148	(-0.54)
Observations	489		474	

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Additional results

Table I.1.5 – SUB-SAMPLE ANALYSIS (1): ESTIMATED COEFFICIENTS AND 95% CONFIDENCE INTERVALS FOR COVARIATES' INCIDENCE ON TIME TO DIAGNOSTIC WORKUP USING COX MODEL STRATIFIED BY AGE CLASS.

	(1)	(2)	(3)	(4)
	P	MS	BD	CD
Female	-0.269 (-0.99)	-0.246 (-1.31)	-0.0531 (-0.22)	-0.224 (-0.61)
Couple	0.341 (1.24)	0.0351 (0.24)	-0.198 (-0.93)	0.108 (0.41)
Education (Ref=No diploma)				
Baccalaureate	-0.122 (-0.30)	-0.0218 (-0.11)	-0.232 (-0.70)	-0.311 (-0.66)
Bac+2 and +	-0.0277 (0.11)	-0.0420 (-0.26)	-0.126 (0.47)	-0.0561 (-0.20)
Social support	0.294 (0.98)	0.353* (2.24)	0.264 (1.16)	0.132 (0.49)
Social participation	0.465 (1.12)	0.269 (1.50)	0.235 (0.86)	0.270 (0.78)
Symptoms' severity (Ref=Mild)				
Moderate	-0.466 (-1.31)	0.212 (1.00)	-0.190 (-0.39)	0.0345 (0.05)
Severe	-0.436 (-1.22)	0.0705 (0.35)	0.184 (0.40)	-0.0967 (-0.14)
Observations	82	226	115	80

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Caption: P refers to psoriasis, MS refers to multiple sclerosis, BD refers to bipolar disorder, CD refers to Crohn's disease.

Table I.1.6 – SUB-SAMPLE ANALYSIS (2): ESTIMATED COEFFICIENTS AND 95% CONFIDENCE INTERVALS FOR COVARIATES' INCIDENCE ON TIME TO DIAGNOSTIC WORKUP USING COX MODEL STRATIFIED BY AGE CLASS.

	(1)	(2)	(3)	(4)
	P	MS	BD	CD
Female	-0.269 (-0.95)	-0.225 (-1.18)	-0.00414 (-0.02)	-0.395 (-1.03)
Couple	0.291 (1.04)	0.0554 (0.37)	-0.205 (-0.97)	0.0831 (0.31)
Education (Ref=No diploma)				
Baccalaureate	-0.0210 (-0.05)	-0.00456 (-0.02)	-0.231 (-0.70)	-0.258 (-0.53)
Bac+2 and +	-0.101 (-0.37)	-0.0245 (-0.15)	-0.169 (-0.62)	-0.138 (-0.47)
Social support	0.225 (0.74)	0.343* (2.16)	0.258 (1.11)	0.0260 (0.09)
Social participation	0.630 (1.48)	0.258 (1.42)	0.239 (0.89)	0.215 (0.62)
Symptoms' severity (Ref=Mild)				
Moderate	-0.509 (-1.33)	0.243 (1.12)	-0.418 (-0.79)	0.186 (0.26)
Severe	-0.454 (-1.23)	0.0989 (0.48)	-0.0570 (-0.11)	-0.111 (-0.16)
Risk aversion	-0.410 (-0.86)	-0.188 (-0.93)	-0.350 (-1.07)	-0.652 (-1.49)
Pref. for present	-0.551 (-1.18)	-0.0208 (-0.09)	-0.0432 (-0.14)	-0.398 (-0.65)
Observations	82	226	115	80

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Caption: P refers to psoriasis, MS refers to multiple sclerosis, BD refers to bipolar disorder, CD refers to Crohn's disease.

Table I.1.7 – SUB-SAMPLE ANALYSIS (3): ESTIMATED COEFFICIENTS AND 95% CONFIDENCE INTERVALS FOR COVARIATES' INCIDENCE ON TIME TO DIAGNOSTIC WORKUP USING COX MODEL STRATIFIED BY AGE CLASS.

	(1)	(2)	(3)	(4)
	P	MS	BD	CD
Female	-0.200 (-0.69)	-0.165 (-0.84)	-0.0787 (-0.31)	-0.372 (-0.92)
Couple	0.364 (1.25)	0.129 (0.84)	-0.0331 (-0.16)	0.0235 (0.08)
Education (Ref=No diploma)				
Baccalaureate	0.00513 (0.01)	-0.0618 (-0.30)	0.478 (1.30)	0.271 (0.57)
Bac+2 and +	0.0109 (0.04)	-0.0256 (-0.16)	0.170 (0.58)	-0.130 (-0.42)
Social support	0.304 (0.97)	0.336* (2.13)	0.232 (0.94)	-0.0170 (-0.06)
Social participation	0.579 (1.37)	0.312 (1.72)	0.152 (0.54)	0.121 (0.33)
Symptoms' severity (Ref=Mild)				
Moderate	-0.422 (-1.06)	0.301 (1.38)	-0.189 (-0.36)	-0.00355 (-0.00)
Severe	-0.326 (-0.83)	0.149 (0.72)	0.0709 (0.14)	-0.218 (-0.32)
Risk aversion	-0.473 (-0.98)	-0.200 (-0.98)	-0.285 (-0.85)	-0.571 (-1.27)
Pref. for present	-0.521 (-1.05)	-0.0499 (-0.21)	-0.0435 (-0.14)	-0.500 (-0.81)
First medical contact (ref=GP)				
Hospital specialist	-0.539 (-1.63)	-0.0536 (-0.28)	-0.190 (-0.69)	0.0124 (0.04)
Ambulatory specialist	-0.860* (-2.31)	-0.323* (-2.49)	-1.005* (-2.26)	-0.265* (-2.45)
Emergency service	-0.242 (-0.41)	-0.552 (-0.22)	0.550 (1.09)	-0.366 (-0.92)
Observations	82	226	115	80

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Caption: P refers to psoriasis, MS refers to multiple sclerosis, BD refers to bipolar disorder, CD refers to Crohn's disease.

Chapter 2

My Baby Brings Me Down:

Children's Health Shock

Externalities on Mothers' Health

1 Introduction

Traditional models of health capital specify an individual utility function to define individual preferences for goods or services. In contrast, collective models allow for the inclusion of the utility of other individuals as an argument in the representation of individual behavior. Multiple arguments can be put forward to call upon the use of collective models and interdependence of utilities.

[Manski \(2000\)](#) identifies several channels through which individual levels may affect each other resulting from the existence of (1) constraints on shared resources; (2) interactions with peers and updates on beliefs associated with marginal costs or benefits of adopting a specific health behavior; (3) direct impact on others' preferences when, for example, one derives utility from consuming the same goods or services.

Collective models are appropriate when we observe repeated and regular cooperation between individuals; they especially apply to intra-household interactions. In the field of household economics, assumptions are made about families' decision-making processes to achieve efficiency in consumption and production decisions as household members individually affect future outcomes at household level.

Altruism is a common feature of decision-making models when considering the preferences and strategic behavior of family members, and particularly within nuclear family units. The axiomatic theory of *pure altruism* refers to a situation by which an individual derives utility from his or her descendants' overall utility aside from his or her own consumption of goods and services ([Galperti and Strulovici, 2017](#); [Becker, 1974](#); [Kimball, 1987](#)). Parents who care for the well-being of their offspring are assumed to invest household production time and market goods into their child's health at every stage of life; such investment in turn has contemporaneous and long-term effects on their own health.

[Basu and Meltzer \(2005\)](#) offer a collective theoretical framework that demonstrates spillover effects of illness on family members by adjusting the individual's utility by the utility value associated with the family.

They indicate that the total effect of an adverse health state may be decomposed into three components: (1) the effect of the illness on the patient's health status and

survival that together affects his quality-adjusted life expectancy; (2) the effect of a patient's utility on the effects of being taken care of in the household; (3) the effect on family member's utility. It consists of the direct effect of time and health expenditure on the parent's health status utility due to the change in health status of a household member.

Total effect of an adverse health state = Direct effect on a patient's utility + indirect effect on a patient's utility through family members' utility + direct effect on family members' utility

Empirical attempts to capture parental preferences use contingent valuation methods to estimate the marginal rate of substitution between health outcomes experienced by the child and parent. Results suggest that parents are willing to pay some amount when there is a risk reduction to their child that actually exceeds their willingness-to-pay for such gains to themselves. [Dickie and Messman \(2004\)](#) estimated the marginal rate of substitution is about two for a 9-year-old child, implying that parents value their children's acute illnesses twice as highly as their own.

While we have indifferently considered mothers and fathers as equal in altruism, there might be reason to think that, everything else being equal, the well-being of children has a larger weight in the mother's utility function. First, mothers often serve as the primary care provider for their children, and spend more time with them ([Craig, 2006](#)). Second, results suggest that children benefit more when cash transfers are made to mothers rather than fathers ([Kornrich, 2016](#); [Gertler, 2004](#)). Finally, behavioral economics and investigations into gender differences in decision-making studies have repeatedly found that women are, on average, more altruistic than men ([Brañas-Garza et al., 2018, 2016](#); [Dreber et al., 2014](#)).

Several challenges may arise when estimating spillovers effects from the child's health to the mother's health. First, there may be unobservable factors that affect both the mother and the child's health: this would lead to an over estimation of the impact of child's health. An estimation must therefore address this endogeneity issue. Second, a causal estimation must address the likelihood of a selection effect in caregiving. Mothers in poorer health are more likely to be unemployed and so will have more free time to provide informal care to their child. Moreover, several observable and unobservable

individual characteristics including, for example, preferences for leisure or income will be correlated with the decision to provide informal care as well as the mother's health status.

To investigate the impact of a child's health on his or her mothers' health, we rely on a shock in the child's health. The health shock is measured using a combination of two events in longitudinal data. First, the child is recorded as having a longstanding illness or disability. Second, the child's self-reported health status drops at least one category in the ordered discrete health measure.

In this chapter, we investigate the spillover effects of a shock on the child's health on the mother's health using mother's self-reported general, physical, and mental health, while addressing endogeneity and selection issues. We explore the heterogeneity of this effect across two types of diseases [Gould \(2004\)](#): time intensive diseases and money intensive diseases.

The chapter is organized as follows: Section 2 introduces the background literature; Data and descriptive statistics are presented in Section 3; Section 4 presents the empirical strategy; Section 5 presents our main results and robustness checks; and Section 6 concludes.

2 Background Literature

Chronic diseases are the leading cause of mortality and morbidity in Europe. Depending on how the term is defined, anywhere from 13% to 27% of children are affected by chronic conditions ([Van Cleave et al., 2010](#)). This figure has increased dramatically in the last four decades, primarily from four classes of common conditions: asthma, obesity, mental health conditions, and neurodevelopmental disorders ([Perrin et al., 2014](#)).

Chronic conditions have large consequences on a child's daily life. In particular, chronic conditions have been shown to cause serious limitations, reduce quality of life, as well as increase physical and cognitive impairments ([Pomerleau et al., 2008](#)). In the long run, chronic diseases significantly affect educational attainment and career prospects ([Currie, 2009](#)).

While studies usually emphasize the impact of such conditions on children's health and future prospects, most of them neglect the spillover effects on relatives and caregivers, especially their quality of life and health. The intergenerational transmission of health

from parents to children is well documented in the health economics literature and suggests that mothers' socioeconomic status directly impacts the child's health, while fathers' social status has an indirect impact through social status as an adult (Trannoy et al., 2010). Mothers tend to play the dual role of parenting expert and caregiver when their child has poor health. As a consequence, children's health is likely to affect their mother's health.

One transmission channel from the child's health to mother's health is the direct effect of caregiving activities on her physical health and immune system. As she increases her caregiving duties to her child, the mother may turn her attention away from the promotion of her own health (e.g., Nicholl and Begley (2012)). Moreover, she may be physically impaired by the change in her daily life. Emotional pressure may arise in response to growing concerns about her child's health and growing responsibilities with regards to the management of her child's health (e.g., Desai and Alva (1998); Murphy et al. (2007); Byrne et al. (2010)).

Reduction in leisure time may have social implications for the mother and result in social isolation. Due to the reshuffling of family routines and time schedule, family cohesion may be affected and cause marital turmoil (e.g., Repetti et al. (2002); Cohen (2004)).

Finally, a health shock may raise childcare costs due to transportation to doctor and therapists, with extra costs for specialized childcare (e.g., Anderson et al. (2007); Stabile and Allin (2012); Mailick Seltzer et al. (2001)). Gravestock et al. (2011) estimate the average extra childcare costs due to cancer to be of £524 per month or £6,286 per year in the UK. Yet, this does not include loss of income due to a change in working status or in working hours.

The impact of a child's chronic disease on the mother's labor supply has been studied by Gould (2004). The author builds a theoretical model in which the impact of the child's ill health on the mother's work supply depends on the characteristics of the child's disease. Relying on interviews with medical expert focus groups, her research divided pediatric chronic diseases into two groups: (1) money intensive chronic diseases that require relatively more money than time from main caregivers and (2) time intensive chronic diseases that require relatively more caregiving time than money. The latter are likely to cause a decrease in the mother's labor supply, while money intensive diseases are likely to cause an increase in the mother's labor supply.

The research question investigated in this chapter is at the intersection of two research topics in health economics: caregiving and health shocks. On the first, caregivers and caregiving activities have been widely studied, notably in the context of care arrangements for the disabled elderly. This literature acknowledges the existence of spillover effects on caregivers' health and their quality of life (Carmichael and Charles, 2003; Caqueo-Urizar et al., 2009; Bonsang, 2009; Fontaine et al., 2009). Moreover, there is a broad range of spillover domains from emotional health to physical health that are affected when the spouse has a health condition (Wittenberg et al., 2013). All this evidence confirms the existence of spillovers on caregivers' health and suggests that its magnitude varies depending on the relationship between the caregiver and the person she cares for.

Secondly, the literature on acute health shocks offers guidance on the identification strategy to purge endogeneity issues raised by the two-way causal relationship between mother's health and child's health (García-Gómez et al., 2013; Clark and Etilé, 2002). We follow this literature in choosing an exogenous variation in self-reported health status (Riphahn, 1999; García-Gómez, 2011; Sundmacher, 2012). This identification strategy assumes that this variation is unanticipated. Any significant difference in the outcome¹ under consideration is, therefore, attributable to the health shock.

3 Data and Descriptive Statistics

The main purpose of the GUS² project is to provide large national longitudinal health information on children and their families. This survey was an appropriate source of data to better understand how children's health impacts mothers' health, as data are collected on pairs of mothers and children. In 2005, a birth cohort of more than 5,000 children (sweep 1) was established from families randomly selected from the Child Benefit Records (CBR)³. Since then, other mothers and children (sweeps 2 to 8) have been added to this initial survey. Mothers provided personal information as well as child outcomes

¹In the cited literature, the outcomes are all related to labor market behaviors.

²The reader can refer to the cohort [website](#) for more information. This dataset was commissioned by the Scottish Executive Education Department (SEED), and managed by the Scottish Center for Social Research (ScotGen).

³This is a payment that families can claim for their children, regardless of their income levels. The amount received by families is 20.70 pounds (per week) per child and 13.70 pounds for any additional children. To increase participation and engage families in the data collection, a weekly financial incentive scheme was implemented.

through a face-to-face computer-assisted interview at home. The analysis is based on the longitudinal dataset and includes data from sweeps 1 to 8.

It is worth noting that the GUS dataset is representative of the CBR. To be eligible for the CBR, families had to be responsible for a child under the age of 16 and live in the United Kingdom⁴. In 2017, 562,960 families received the Child Benefit, covering 930,375 children in Scotland. Families can decide to opt out of receiving this benefit. This could be the case for those who have to pay the High Income Child Benefit charge. Being liable for this charge does not affect a child's entitlement, but any Child Benefit recipient is liable to repay some or all of their Child Benefit back if their individual income is more than 50,000 pounds per year. In 2017, fewer than 50,000 families decided not to receive the Child Benefit⁵. Therefore, the CBR is not representative of the whole Scottish population; it does not include people without children, nor families that have decided to be opt out of the program.

3.1 Variables of Interest

We rely on a self-reported measure of health for mothers. This variable is based on the survey question, "How is your health in general?" asked to mothers and assorted with five possible answers: excellent, very good, good, fair, and poor. This variable appears to be a good proxy for both future and present health. Evidence suggests that it has predictive power of mortality and functional decline (Lee, 2000; Idler and Benyamini, 1997), higher risk of fatal and nonfatal coronary heart disease (Møller et al., 1996; Manor et al., 2001), developing chronic diseases (Manor et al., 2001; Wu et al., 2013), hospitalization, out-of-hospital medical services, and drug prescriptions (Idler and Benyamini (1997); Devaux et al. (2008); Doiron et al. (2015); Guillemin et al. (2017)).

To investigate how a child's health shock impacts mothers' health in greater depth, in addition to using a general health measure, we also employ physical and mental health indices. More specifically, mothers respond to 12 questions related to both their physical and mental health. We use the 12-Item Short Form Health Survey (SF-12) developed by Ware Jr et al. (1996)⁶. It contains six questions on physical health⁷ and six questions on

⁴For more information on eligibility criteria, the reader can refer to the government [website](#).

⁵For further information on Child Benefit statistics by geographical area, the reader can refer to the [National Statistics Publication](#).

⁶This scale is an abbreviated version of the original one that contains 36 items (Ware Jr and Sherbourne, 1992)

⁷Questions rely on an individual's ability to complete moderate activities (e.g., moving a table, climbing

mental health⁸. These two indices range from 0 to 100 with all questions having equal weight. The lower the score, the lower the physical (mental) health; the higher the score, the higher the physical (mental) health.

We consider that the child experiences a health shock if he or she falls at least one category in the below-mentioned scale, and if he or she has any longstanding illness or disability as compared to the previous wave. More precisely, we combine the following two questions: “Does [Childname] have any longstanding illness or disabilities⁹?” and “How is [Childname]’s health in general?” Mothers then rate their perception of their child’s health on a five-point scale. This scale ranks from 1 to 5 (1 and 2 stand for being in very bad or bad health; 3, 4 and 5 stand for being in fair, good, and very good health, respectively). We remove from our analysis any child that had a longstanding illness or disability but had no change in the child health scale variable. In other words, such individuals belong to neither the treatment nor the control group.

We exploit the richness of the panel by using a broad set of covariates in our analysis. *Age* is discrete variable of four age groups (16 to 24-years-old; 25-34; 35-44; and 45+). *Educational attainment* is a discrete variable of five different qualification levels (no qualifications; vocational qualifications; degree or equivalent; standard grade; higher grade). *Income* designates the quintile of equalized¹⁰ total net household annual income. *Working status* is a binary discrete variable equal to 1 if the mother is currently working, 0 otherwise, and *Job Hours* is the average number of worked hours per week. *Couple* is a binary discrete variable equal to 1 if the mother is a part of a couple, 0 otherwise. *Rural vs. Urban* is a binary discrete variable equal to 1 if the mother lives in a rural area, 0 otherwise. *Child’s gender* is a binary discrete variable in which a boy is coded as 1 and 0 otherwise. Finally, *Child age* is computed in years.

stairs).

⁸Questions on mental health are, for example, “Have you felt calm and peaceful the past four weeks?; How much have your emotional problems interfered with your social activities?”

⁹The question provides greater detail by adding that, “by longstanding we mean anything that has troubled him/her over a period of time or that is likely to affect him/her over a period of time.”

¹⁰Equalization is based on an adjustment of a household’s income for size and composition using the “Modified Office of Economic Cooperation and Development (OECD) equivalence scale”, in which an adult couple with no children is taken as the benchmark with an equivalence scale of one. Each child aged 0-13 has an equivalence scale of 0.20; each child aged 14-18 has an equivalent scale of 0.33; and any subsequent adult is weighted at 0.33 as well. This produces an equalized income scale; we use quintiles of this scale. Therefore our variable contains five categories: 1 stands for the lowest income, 5 for the highest.

4 Empirical Strategy

4.1 Model

We aim to estimate the impact of a child’s health shock on his or her mother’s health using a natural experiment. In this setup, having a child with a health shock is similar to treatment; therefore mothers with a child having a health shock are treated while those who have a child who does not experience a health shock are used as controls. The treated individuals are likely to have specific characteristics that make them different from the mothers in the control group (see Table I.2.1). In order to take into account the non-randomness of the occurrence of health shocks, we rely on the following fixed effect model to estimate the causal effect of a child’s health on his or her mother:

$$H_{it} = \gamma \cdot Child\ Shock_{it} + \Xi \cdot X'_{it} + \delta \cdot X'_j + \sigma_i + \sigma_t + \epsilon_{it} \quad (2.1)$$

In Equation (2.1), H_{it} refers to the three measures of mothers’ health (i.e., general health, physical health, and mental health). These measures are available for a set of mothers indexed by $i = 1, \dots, N$, which are observed during eight years indexed by $t = 1, \dots, T$. For each year in which H_{it} is observed, we observe a matrix of covariates X'_{it} and X'_j , respectively, describing the characteristics of mother i in year t , and the characteristics of her child j .

These covariates were described in the previous sub-section. The shock on the child’s health is a dummy variable equal to 1 from the year after the shock, and continuously for the rest of the waves for individuals in the treatment group, 0 otherwise; σ_t denotes unobserved time-varying characteristics (i.e., time fixed effects); σ_i denotes mother fixed characteristics; and ϵ_{it} is a time-varying error term that is assumed to be orthogonal to all characteristics.

By using this two-way fixed effect econometric method (De Chaisemartin and D’Haultfœuille, 2018), we remove both unobservable individual specific effects that are constant over time (e.g., genetic factors, educational attainment, distance to hospitals), and common time effects such as drug prices or exposure to preventive policies. Further, as our main endogenous variable, with general self-reported measure of health being an ordinal indicator, we rely on a fixed effect ordered logit model (Baetschmann et al., 2015). For the other measures of health we rely a fixed effect linear model (e.g., Laporte and Windmeijer (2005); Chandra et al. (2010)).

Further, we analyze mothers' physical and mental health evolution over time to document the duration of the effect. More precisely, we compare the mother's physical (mental) health in the treatment group with those in the control group. We therefore analyze whether there are differences in health status between groups according to time¹¹.

Finally, we investigate the heterogeneity of the spillover effects by estimating (2.1) on two different sub-samples composed of time-intensive and money-intensive diseases, respectively. To do so, and relying on the typology of [Gould \(2004\)](#), we consider that mothers who significantly reduce their work supply (increase their work supply) after the health shock belong to the time-intensive group (the money-intensive group). We thus compare work supply two years before the shock to work supply observed two years after the shock by using t-tests to compare the means of *Job Hours*.

To be able to compare the impact of a child with a time-intensive disease versus a money intensive disease on mothers' health, we rely on a Propensity Score (PS) matching methodology [Rosenbaum and Rubin \(1983\)](#); [Rosenbaum and Rubin \(1984\)](#); [Rubin and Thomas \(2000\)](#). The PS is the probability that a mother has a child with a chronic disease given her observed characteristics.

PS matching consists of calculating the average difference between the mean outcome of the treated mothers characterized by a specific PS, and the mean outcome of the control mothers characterized by a similar PS. PS matching implies pairing each treated mother with a comparable control mother. For our matching to be robust, it implies that selection is based solely on observable individual characteristics, and that all variables that influence both treatment assignment (i.e., experiencing health shocks) and outcomes (i.e., mothers' health) are observed. This, however, is unlikely to be the case. For example, unobservable variables—such as mother's lifestyles—may influence both the probability that her child had a health shock and her own health.

We apply a 1-nearest neighbor matching to guarantee precision in the comparability of the two groups. This procedure selects, for each treated mother, the closest control (i.e.,

¹¹To do so, we create a dummy variable for each time period. More precisely, we create dummy variables to compare the evolution of mothers' health. Such dummies are set to 1 for years -4 and -3 (before the occurrence of the shock), 0 otherwise; 1 for years -2 and -1, and 0 otherwise; 1 for the year of the shock, 0 otherwise; 1 for years +1 and +2 (after the shock), 0 otherwise; 1 for years +3 and +4, 0 otherwise; 1 for years +5 and above, and 0 otherwise.

those that have the closest PS but did not experience the shock). The choice of the nearest neighbor is bounded by the common support range¹². We calibrate the maximum difference in the PS between matched and control subjects to be at 0.1¹³. This ensures that matched mothers have very similar PS. Our matching is also performed with no replacement so that the same control mother cannot serve as the nearest neighbor for multiple treated mothers.

4.2 Identification

Our identification approach exploits the occurrence of a child facing a severe health shock (defined as a combination of a longstanding disease and a drop in the self-reported child's health variable). The focus of this specific type of health event is motivated by its severity because it is, in most cases, unanticipated. Even if mothers might anticipate that their child will experience a similar health shock (e.g., due to unfavorable genetic factors or due to past family health history), some uncertainty remains, if not on the occurrence, then on the time of potential occurrence.

For the main coefficient of interest, γ , to measure the causal impact of health shocks on mothers' health, there should be no endogeneity issues. We are not able, however, to state with certainty that this is not the case.

A child's health shock and mothers' health may be either correlated with measurement errors, subject to reverse causality, or both. With regards to reverse causality, mothers' health during pregnancy or during the first years of his or her child's life can impact the probability that this child will suffer from health shocks in the future (Goldberg et al., 2002; Barouki et al., 2012; Jusot et al., 2013). Regarding measurement error, both types of self-reported measures of health may suffer from desirability bias and may also depend on the mother's personality traits as she reports her child's health status.

Regarding our investigation into money-intensive versus time-intensive diseases, the first underlying identification assumption in PS matching is the assumption of unconfoundedness (or the assumption of selection on observables). It assumes that selection to treatment

¹²Treatment observations whose score is higher than the maximum or less than the minimum score of the controls are discarded.

¹³This means, for example, that a treated mother with a PS of 0.6 is matched with a mother in the control group with a PS of 0.7 or 0.5.

is based only on observable characteristics (i.e., all variables that influence both treatment assignment and outcomes are observed). To ensure non-violation of the unconfoundedness assumption, all variables that influence both treatment assignment and the outcome variable must be included in the PS. The second requirement is the common support (or overlap) condition. This ensures that individuals with the same observable variables have a similar probability of being both treated and non-treated [Heckman et al. \(1999\)](#).

5 Results

5.1 Descriptive statistics

Table [I.2.1](#) displays descriptive statistics. We observe 8,037 individuals in our unbalanced panel dataset. In this sample, 31.8% of the children have ever faced a health shock ($n=2,553$). Individuals in the treatment group (i.e., mothers with a child who has experienced a health shock) have specific characteristics that are not shared with those in the control group. For instance, they are significantly more likely to have lower education attainment, report lower levels of income, and are less likely to live in couple, than mothers in the control group. Importantly, mothers in the treatment group are also more likely to report a lower level of health than those in the control group. This provides the first evidence that mothers who have a child experiencing a health shock have a lower health status.

Furthermore, looking at the within variations of treated mothers' characteristics reveal that a child's health shock seems to significantly reduce a mother's general health. A health shock also significantly reduces mothers' working status (i.e., they are less likely to report being working), but has no impact on income. Additional descriptive statistics can be found in Table [I.2.1](#). Figures [I.2.1](#), [I.2.2](#), [I.2.3](#), and [I.2.4](#) show average differences in health status between treatment and control, and before and after the shock in the treatment group, for both the mother's and the child's health status.

5.2 Main Results

Table [I.2.2](#) shows the effect of health shocks on lifestyles using a fixed effect ordered logit model described in Equation [2.1](#). We report the results as follows. Column 1 gives the difference between the treated and control groups in mothers' general health only when controlling for individual and time fixed effects. In columns 2 and 3, the estimated

models respectively add the mother- and child-specific control variables. The results of the full model are presented in column 4. Compared with mothers in the control group, mothers of children who experienced a health shock have a 27,23% reduced probability of reporting being in a higher health category, everything else in the model held constant¹⁴. The full results with control variable coefficients are displayed in Table I.2.6 as additional results in [Appendix](#).

Table I.2.3 displays the effect of a child's health shock on the physical and mental health of their mothers using a linear fixed effect model, as described in Section 4. Column 1 reports the effect of the health shock on the mother's physical health, and column 2 on the mother's mental health. Both columns include mother and child control variables along with individual and time fixed effects. Results show that mothers in the treatment group reduce their physical health, but not their mental health, as compared to mothers in the control group. Mothers lose 0.62 points in their index of physical health on average as a result of the child's health shock. The full results with control variable coefficients is displayed in Table I.2.7.

Furthermore, Figure I.2.5 provides an estimation of the duration of the effect. It shows that physical health declines significantly after the shock in the child's health and the impact of this shock increases constantly in magnitude even five years after. After five years, the mother's physical health index is on average reduced by 1.7 points as a result of the shock on the child's health. Mental health, however, does not appear to be affected by a shock in the child's health.

Finally, results on the heterogeneous impact of the child's health shock for time-intensive versus money-intensive diseases are reported in Table I.2.4. Results now rely on the matching procedure and sub-samples estimations, therefore the number of observations is reduced to 9,537 observations in the money-intensive group and 3,189 observations in the time-intensive group; this suggests that we have a higher proportion of children having an illness with a strong financial component ([Gould, 2004](#)). In that case, mothers need to increase their working time to deal with the substantial costs of childcare ([Blau and Robins, 1989](#); [Mason and Kuhlthau, 1992](#)).

¹⁴The coefficients given in Table I.2.2 are ordered log-odd. To interpret these coefficients as percentages, we apply the following formula: $[1-(\exp(\text{coefficient}))]$.

Results suggest that the deterioration of health was significantly larger when the child has a time-consuming disease. Mothers in the treatment group see their probability of reporting a higher health category reduced by 49%, everything else in the model held constant. The full results with control variable coefficients are displayed in Table I.2.8.

5.3 Robustness Checks

To check the validity of our empirical results, we perform several types of robustness checks, which are displayed in Table I.2.5. The baseline results are reported in column 1.

First, the mother's past health status is likely to influence the mother's current health, as health status is strongly state dependent (Tubeuf et al., 2012). Part of the impact of the shock on the child's health could also capture health deterioration before the shock and selection into caregiving. If this is the case, we would observe a decrease in mothers' health status due to the selection of mothers with poor health into a caregiving role. To ensure that this is not the case, we control for the lagged mother's health status. We provide an estimation using a dynamic model as it includes a lagged level of the dependent variable as an independent variable. By including the lagged health status in the model, the strict exogeneity assumption is violated because the lagged dependent variable is correlated with the independent variable. We circumvent this problem by relying on the Arellano-Bond specification (Arellano and Bond, 1991). This result is displayed in column 2 of Table I.2.6. It shows a negative and significant relationship between a child's health shock and mothers' health. More precisely, a child's health shock reduces mothers' health by 0.229 ($p=0.001$), once controlling for her past health.

Second, we are not working with a balanced panel dataset. Only 2,633 (32.75% of our sample) mothers are present during the whole period (i.e., for the entire eight years). To control for this issue, we restrict our analysis to mothers who are recorded over the full period. By doing so, we are analyzing the impact of the shock of the child's health on mothers' health using a balanced panel dataset. Such results can be found in column 3 of Table I.2.5. Results indicate that the child's health shock reduces mothers' health by 0.251 ($p=0.001$). This result might also control for non-random attrition in our sample (i.e., mothers that would be selected out due to specific personal characteristics).

Third, we check if our results are robust to a change in the definition of mothers' health. To do so, we discretize our dependent variable into two categories. The new discrete

variable equals 1 for mothers who report being in good or excellent health, 0 otherwise. Results are displayed in column 4 of Table 5. Mothers' health is decreasing by 0.303 ($p=0.001$) if her child faces a health shock. Our baseline result is, therefore, robust to a change in a broader definition of mothers' health.

Fourth, we check if our results still hold after changing the definition of a shock in the child's health. We relax the definition for health shock to include all children who have dropped by at least one category of health during the past year. This finding can be seen in column 5 of Table I.2.5. It shows that mothers with children facing a health shock experience a reduction of 0.229 ($p=0.001$) in their health. Such results indicate that no matter the definition of child health shock, our baseline results still hold.

Fifth, we proceed in a similar manner and now define a health shock as the health of the child dropping by more than two categories in the reported health status variable. The control group is mothers whose child's health has not worsened regarding self-reported health (even if they have a chronic disease). This proxy of health shock is similar to the one used in the literature on the impact of health shocks on labor market outcomes (e.g., [Lechner and Vazquez-Alvarez \(2004\)](#); [García Gómez and López Nicolás \(2006\)](#); [García-Gómez \(2011\)](#)). Results are displayed in columns 5 and 6 of Table I.2.5. Coefficients of these regressions report that our result is robust to the severity of the child's health shocks. It does so by keeping the same magnitude: -0.258 ($p=0.001$) and -0.246 ($p=0.100$) for columns 5 and 6, respectively.

To ensure the quality of the matching procedure when estimating the heterogeneous effect of money-intensive versus time-intensive diseases, we graph in Figure I.2.6 the differences in the distribution of PS scores before and after matching. Figure I.2.6 shows the PS scores distribution for the treated (continuous line) and control (dashed line) individuals before (left-hand side), and after (right-hand side) the matching procedure. While some overlap in the distribution is visible before matching, post-matching distributions exhibit better fit.

Figure I.2.7 highlights that a PS value is available for both groups and displays the common support region to ensure that the overlap between both groups is sufficient to make comparisons. The histogram displays the PS for the treatment and control cases. Control and treated individuals span the full range of the PS, which gives further support to the identification strategy ([Blundell and Dias, 2002](#); [Imbens and Wooldridge, 2009](#);

Lechner and Wunsch, 2013; Tubeuf and Bell-Aldeghi, 2016; Lechner and Strittmatter, 2017).

Overall, our robustness checks provide evidence that our analysis is robust to both an alternative modeling method and resampling.

6 Discussion and Conclusion

This chapter shows that a child's health shock generates negative spillover effects onto their mothers' general health. As a consequence of the health shock, a mother's probability of reporting being in a higher health category reduces by 27.23%, everything else in the model held constant. When investigating the impact of a child's adverse health event on maternal physical and mental health, results suggest a significant impact of the child's health shock on the mother's physical health, only.

On average, we observe a 0.7 point reduction in the mother's SF-12 physical index as a consequence of the child's health shock. After five years, the mother's physical health index is on average reduced by 1.7 points. Mental health, however, does not appear to be affected by a shock on the child's health.

Two recent papers use similar methods to estimate the impact of informal care in the context of loss of autonomy in old-age. Bom et al. (2018) estimated that caring for parents significantly reduces the physical health SF-12 score by 0.07 points, and the mental health SF-12 score by 0.45 points, using Dutch data during the period 2010 to 2013. Schmitz and Westphal (2015) found no reduction at all in physical health SF-12 scores as a consequence of caring for old parents, while the SF-12 mental health score significantly decreases by 2 points on average. They used German data from 2002 to 2010 and included in their sample only daughters who provide informal caregiving at least 2 hours per day to their old parents.

We add to this literature showing that the effect of a child's health shock is much more detrimental on a caregiver's health than long-term care. This is due to the specificity of the mother-child relationship. While our estimated coefficients on maternal mental health are comparable in magnitude to those estimated by Bom et al. (2018), we do not find any significant impact of the child's adverse health shock on mental maternal health.

The result could be driven by (1) the existence of internalized social pressures, and (2) the development of effective coping strategies (Kim et al., 2003). Mothers are most of the time the ones making decisions regarding the health of their children, even in the absence of chronic diseases. Evidence from behavioral economics also suggests that women are expected to behave altruistically, and are often blamed for failing to be altruistic to a much greater extent than men (Rand et al., 2016). As a result, women may internalize altruism as their intuitive response, especially in the case of motherhood (Rand et al., 2016). The internalization of the responsibility for the child along with other responsibilities in the family such as balancing family life or maintaining relationships, may drive this result. Prior evidence shows that mothers are “minimizing consequences” to keep themselves going (Ray, 2002).

The stock of hedonic capital owned by a mother may also be of importance for the result. Hedonic capital is defined as the stock of psychological resources available to an individual (Graham and Oswald, 2010)¹⁵. If mothers have an important stock of hedonic capital, they might be insured against the negative effects of their child's health shocks (Hastings and Brown, 2002; Gould, 2004; Corcnan et al., 2005).

One limitation of the work is the lack of information about other caregivers, as we suspect that both relatives (e.g., a partner, family members, or friends) and medical professionals are at stake to influence mother's health. The fact that we do not observe the amount of time dedicated to childcare prevents us from disentangling the “family effect” from the “caregiver effect.” The first effect refers to the effect of *caring about* a relative, while the second refers to the effect of *caring for* someone who is ill (Bobinac et al., 2010). Bobinac et al. (2010) found that both effects exist and may be comparable in size. While this distinction is relevant for our research question, we were unable to draw any conclusions on the size of the family effect versus the caregiver effect.

If our results are confirmed in different settings and in different countries, they call for a refinement of informal care policy strategies for sustaining maternal health in the context of children's chronic diseases. This could include, for example, career breaks or the opportunity to be given advice by medical staff and social workers. By doing so, such

¹⁵More precisely, the authors define hedonic capital as “social relationship with partners, friends, and colleagues; health; self-esteem; status; and meaningful work [. . .]. These aspects are considered as a stock in that they rely on past inputs and are carried across the time period.”

policies could jointly improve the mother's and child's health.

As similar schemes exist in some countries, cross-country comparisons could investigate the performance of these regimens to sustain mothers' health. Future research could also focus on caregiving allocation within the household when a child experiences a health shock, especially the division of work and care tasks between fathers and mothers and the transition into lower paying jobs for mothers.

7 Appendix

Table I.2.1 – SUMMARY STATISTICS BY GROUP

	Treated and control groups			Treated group		
	Treatment group (1)	Control group (2)	Difference (3)	Before (4)	After (5)	Difference (6)
<i>Mothers' health</i>						
Excellent	.039 (.002)	.020 (.001)	-.020*** (0.002)	.022 (.001)	.047 (.002)	-.025*** (.002)
Very good	.144 (.003)	.085 (.002)	-.059*** (.003)	.094 (.004)	.152 (.002)	-.058*** (.004)
Good	.304 (.004)	.265 (.003)	-.038*** (.005)	.271 (.005)	.310 (.002)	-.039*** (.006)
Fair	.361 (.004)	.406 (.003)	.046*** (.005)	.401 (.005)	.349 (.003)	.052*** (.006)
Poor	.151 (.003)	.223 (.003)	.071*** (.004)	.211 (.004)	.141 (.002)	.070*** (.005)
Mental health	48.664 (.127)	50.512 (.080)	- 1.848*** (.143)	52.314 (.086)	51.597 (.084)	-.717*** (.123)
Physical health	51.928 (.102)	53.510 (.060)	- 1.581*** (.111)	49.049 (.104)	48.502 (.112)	-.547*** (.155)
<i>Educational Attainment</i>						
No qualification	.079 (.002)	.061 (.001)	-.018*** (.003)			
Technical degree	.410 (.004)	.376 (.003)	-.033*** (.005)			
Degree	.304 (.004)	.333 (.003)	.029*** (.005)			
Standard grade	.143 (.003)	.151 (.002)	.008*** (.004)			
Higher grade	.064 (.002)	.078 (.002)	.014*** (.003)			
Observations	13,218	24,503	37,721	5,608	7,610	13,218

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: This table shows the differences in means of all covariates and outcome variable between the treated and the control group (column 3). It shows the same differences between the treatment group, before and after the onset of a health crisis (column 6). Interpretation: Overall groups differ in age, marital status, educational attainment, health, income, and working status. Looking only at the treatment group indicates that health shocks have an impact on health, education decisions, and marital status.

Table I.2.1: SUMMARY STATISTICS BY GROUP (CONTINUED)

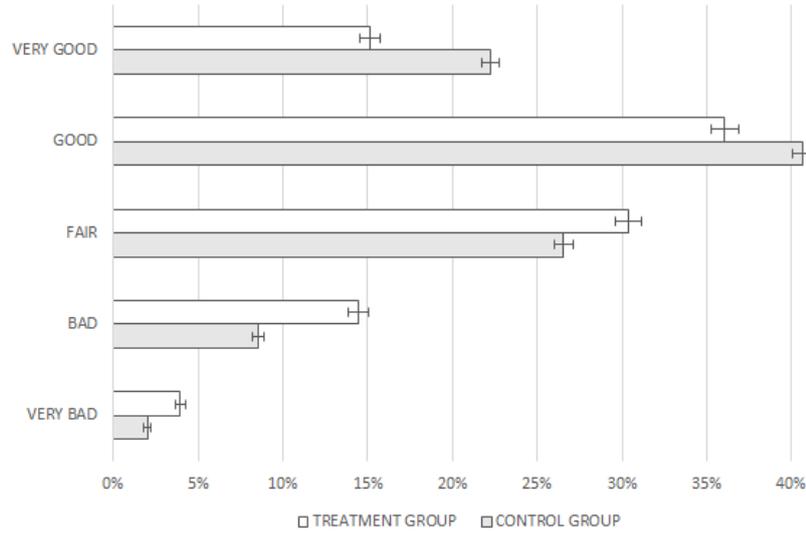
	Treated and control groups			Treated group		
	Treatment group	Control group	Difference	Before	After	Difference
	(1)	(2)	(3)	(4)	(5)	(6)
Being in a couple	.806 (.003)	.840 (.002)	.034*** (.004)	.838 (.004)	.792 (.002)	.045*** (.004)
Living in rural area	.230 (.003)	.233 (.004)	.002 (.004)	.234 (.005)	.222 (.002)	.012** (.005)
Currently working	.841 (.003)	.864 (.002)	.023*** (.004)	.866 (.004)	.814 (.002)	.052*** (.005)
Income above or equal to the 5th quintile	.561 (.004)	.609 (.003)	.048*** (.005)	.603 (.006)	.549 (.003)	.054*** (.006)
Mother is more than 34-years-old	.523 (.003)	.535 (.003)	.013** (.005)	.530 (.003)	.530 (.005)	.001 (.006)
Child age	4.053 (.005)	3.977 (.005)	-.076*** (.008)	3.616 (.014)	4.371 (.012)	-.755*** (.019)
Child is female	.439 (.004)	.516 (.003)	.078*** (.005)	.501 (.005)	.442 (.003)	.059*** (.006)
Child health = Very good	.566 (.004)	.823 (.002)	.256*** (.004)	.797 (.002)	.478 (.005)	.319*** (.002)
Good	.315 (.004)	.157 (.002)	-.158*** (.004)	.176 (.005)	.357 (.002)	-.181*** (.005)
Fair	.106 (.001)	.019 (.003)	-.086*** (.004)	.026 (.001)	.144 (.004)	-.119*** (.003)
Bad or very bad	.106 (.001)	.019 (.003)	-.086*** (.004)	.026 (.001)	.144 (.004)	-.119*** (.003)
Observations	13,218	24,503	37,721	5,608	7,610	13,218

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

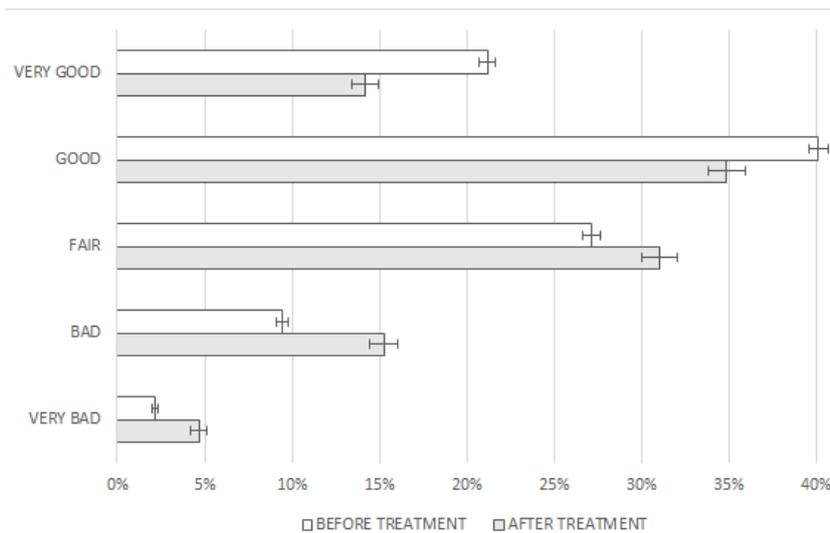
Note: This table shows the differences in mean of all covariates and outcome variables between the treated and the control group (column 3). It shows the same differences between the treatment group, before and after the onset of a health crisis (column 6). Interpretation: Overall groups differ in age, marital status, educational attainment, health, income, and working status. Looking only at the treatment group indicates that health shocks have an impact on health, education decisions, and marital status.

Figure I.2.1 – DIFFERENCES IN MOTHERS' HEALTH STATUS — TREATMENT VS. CONTROL



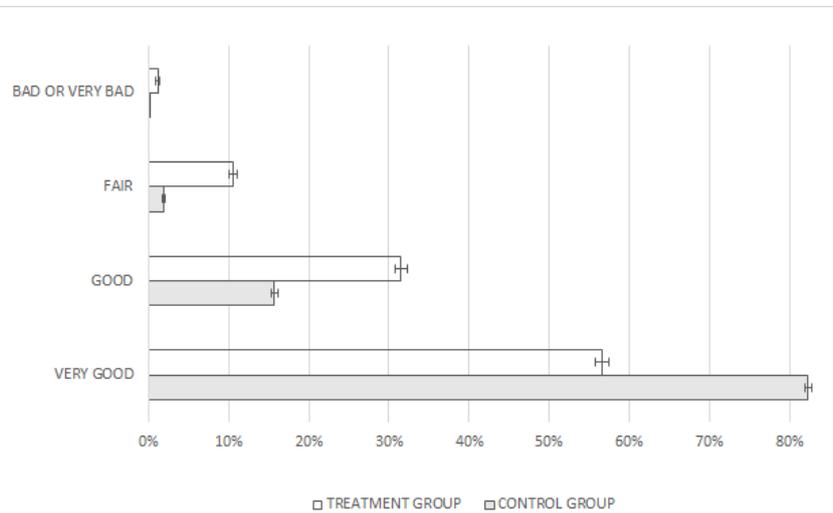
Note: This figure shows the differences in mothers' health status between the treated and the control group. The figure displays proportion in percentages by health status categories.

Figure I.2.2 – DIFFERENCES IN MOTHERS' HEALTH STATUS — BEFORE AND AFTER TREATMENT



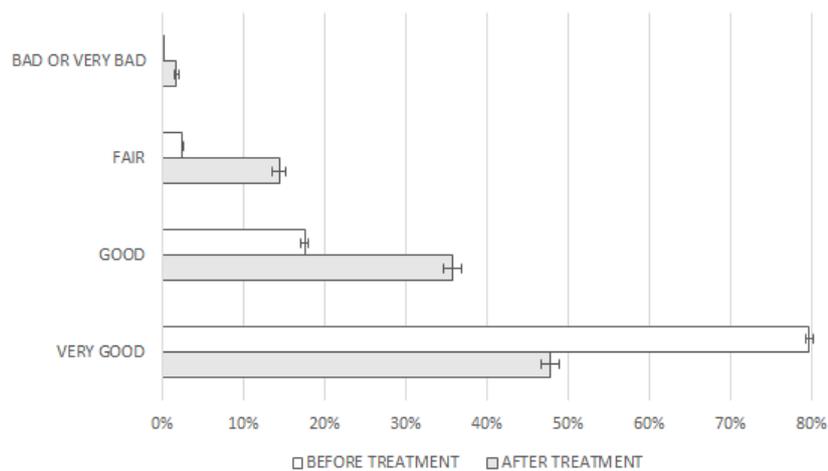
Note: This figure shows the differences in mothers' health status in the treatment group before and after treatment. The figure displays proportion in percentages by health status categories.

Figure I.2.3 – DIFFERENCES IN CHILDREN’S HEALTH STATUS — TREATMENT VS. CONTROL



Note: This figure shows the differences in child’s health status between the treated and the control group. The figure displays proportion in percentages by health status categories.

Figure I.2.4 – DIFFERENCES IN CHILDREN’S HEALTH STATUS — BEFORE AND AFTER TREATMENT



Note: This figure shows the differences in child’s health status in the treatment group before and after treatment. The figure displays proportion in percentages by health status categories.

Table I.2.2 – IMPACT OF CHILD'S HEALTH SHOCK ON MOTHER'S SELF-REPORTED GENERAL HEALTH

	(1)	(2)	(3)	(4)
	Mother's health	Mother's health	Mother's health	Mother's health
Child health shock	-0.348*** (0.094)	-0.318*** (0.099)	-0.348*** (0.094)	-0.318*** (0.099)
Mother controls	No	Yes	No	Yes
Child controls	No	No	Yes	Yes
Mother fixed effects	Yes	Yes	Yes	Yes
Time fixed effects	Yes	Yes	Yes	Yes
Observations	37721	37721	37721	37721

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: Mother's health status designates self-reported health status in 5 categories. We report coefficients from a fixed effect ordered logit model.

Table I.2.3 – IMPACT OF CHILD'S HEALTH SHOCK ON MOTHER'S PHYSICAL AND MENTAL HEALTH

	(1)	(2)	(3)	(4)	(5)	(6)
	Physical health	Physical health	Physical health	Mental health	Mental health	Mental health
Child health shock	-0.830*** (0.058)	-0.727*** (0.061)	-0.673*** (0.062)	-0.426 (0.072)	-0.284 (0.075)	-0.404 (0.076)
Mother controls	Yes	Yes	Yes	Yes	Yes	Yes
Child controls	Yes	Yes	Yes	Yes	Yes	Yes
Mother fixed effects	No	Yes	Yes	No	Yes	Yes
Time fixed effects	No	No	Yes	No	No	Yes
Observations	19271	19271	19271	19271	19271	19271

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: Mother's health status designates SF-12 physical or mental indices. We report coefficients from a fixed effect linear model. We report coefficients from a fixed effect linear model.

Table I.2.4 – HETEROGENEITY IN THE IMPACT OF A CHILD’S HEALTH SHOCK ON THE MOTHER’S SELF-REPORTED GENERAL HEALTH STATUS

	(1) Mother’s Health Money intensive diseases	(2) Mother’s Health Time intensive diseases
Child health shock	-0.094 (0.153)	-0.399** (0.175)
Mother controls	Yes	Yes
Child controls	Yes	Yes
Individual fixed effects	Yes	Yes
Time fixed effects	Yes	Yes
Observations	9537	3189

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: The table displays sub-sample analysis and distinguishes between time-intensive and money-consuming chronic diseases. Mother’s health status designates self-reported health status in 5 categories. We report coefficients from a fixed effect ordered logit model.

Table I.2.5 – ROBUSTNESS CHECKS OF THE BASELINE RESULTS

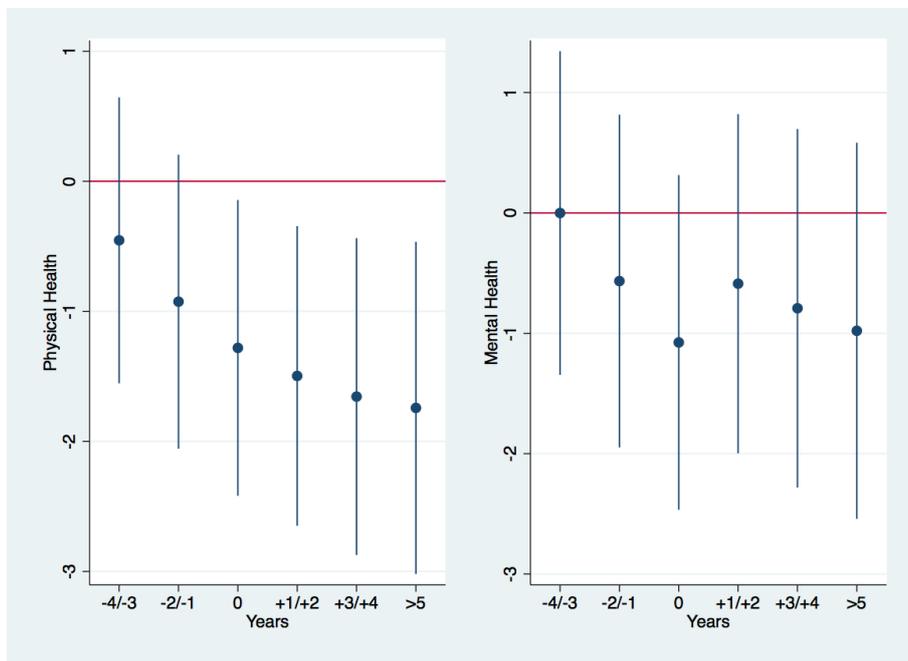
	(1) Mother’s health	(2) Mother’s health	(3) Mother’s health	(4) Mother’s health	(5) Mother’s health	(6) Mother’s health	(7) Mother’s health
Child health shock	-0.261*** (0.839)	-0.229*** (0.212)	-0.251*** (0.112)	-0.303*** (0.099)			
Lag mother’s health		0.118*** (0.125)					
1 year shock					-0.229*** (0.532)		
2 year shocks						-0.258*** (0.909)	
Child severe health shock							-0.246* (0.209)
Mother controls	Yes						
Child controls	Yes						
Mother fixed effects	No	Yes	Yes	No	Yes	Yes	Yes
Time fixed effects	No	No	Yes	No	No	Yes	Yes
Observations	50,152	29,815	29,570	20,862	41,273	28,602	29,688

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

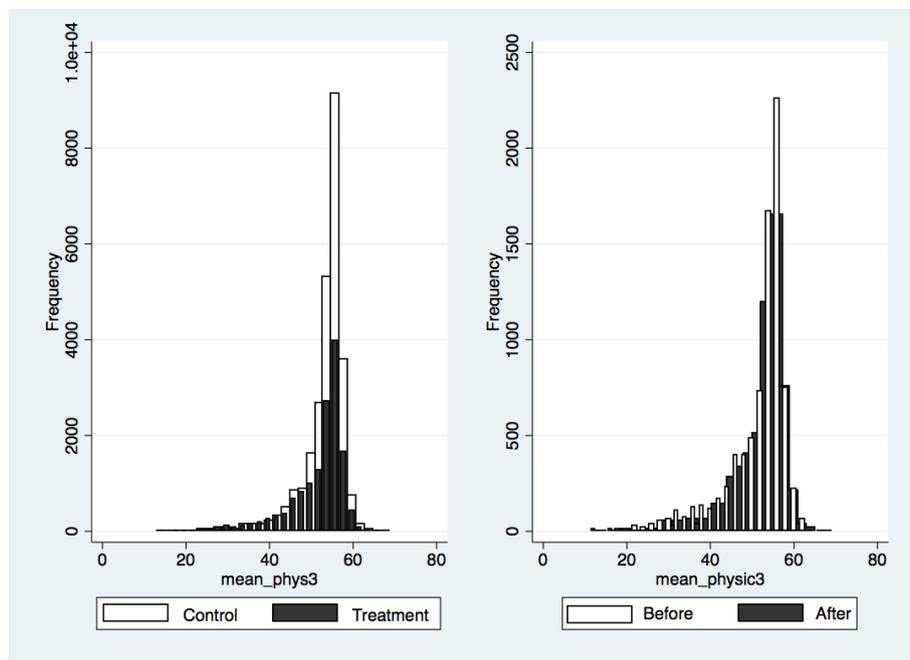
Note: Mother’s health status designates self-reported health status in 5 categories. We report coefficients from a fixed effect ordered logit model.

Figure I.2.5 – EVOLUTION OF PHYSICAL AND MENTAL HEALTH OVER TIME



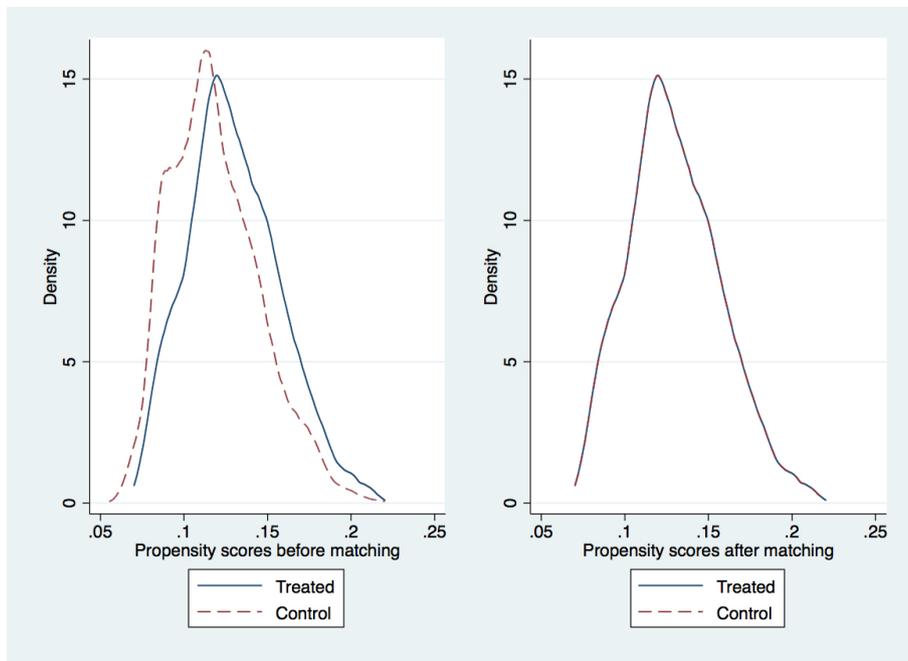
Note: The child's health shock reduces mothers' physical health for at least five years after the occurrence of the shock. Such an effect is not found for mothers' mental health.

Figure I.2.6 – DISTRIBUTION OF PHYSICAL HEALTH BY GROUPS AND WITHIN THE TREATMENT GROUP



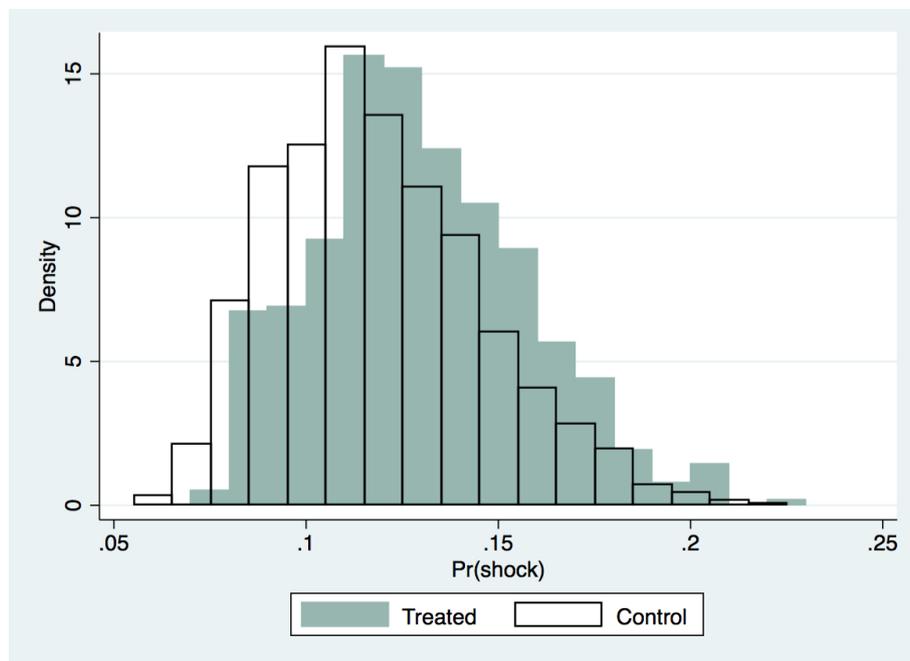
Note: This figure shows the distribution of physical health for both the control and the treatment group (left-hand side), and for the treatment group before and after the health shock (right-hand side). It shows that more individuals in the control group declare higher physical health than in the treatment group. Individuals facing health shocks within the treatment group have lower physical health before as compared to after.

Figure I.2.7 – DISTRIBUTION OF THE PS BEFORE AND AFTER THE MATCHING AMONG GROUPS



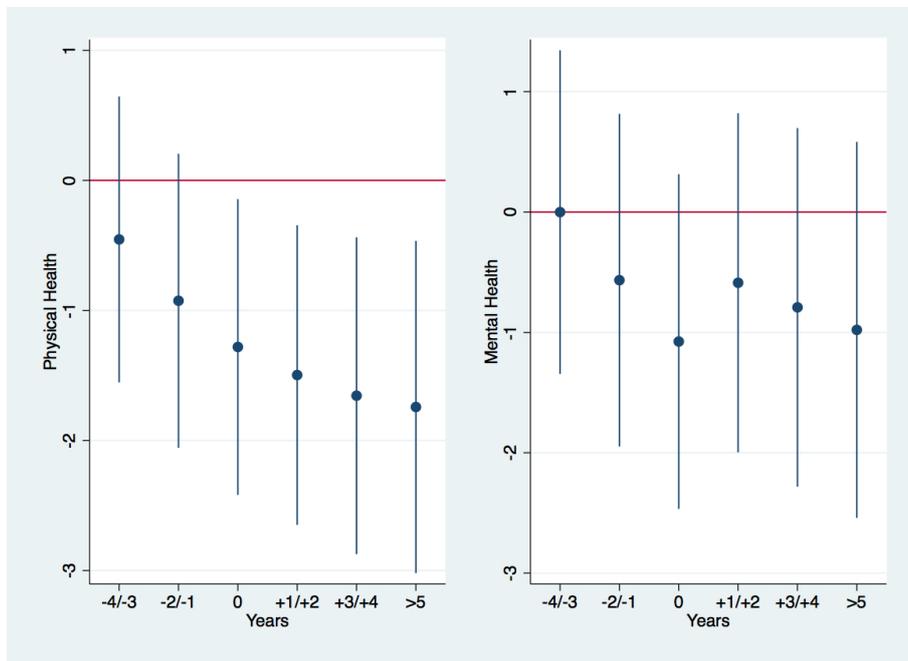
Note: This shows the distribution of the PS among the treated and the control group. It illustrates that before matching there are some differences between these two groups. After matching, however, the two groups seem to be more comparable.

Figure I.2.8 – DISTRIBUTION OF THE PS AMONG GROUPS



Note: This figure illustrates that most of the treated individuals are matched with a control individual who has a propensity score close to their own.

Figure I.2.9 – DISTRIBUTION OF MENTAL HEALTH BY GROUP AND WITHIN THE TREATMENT GROUP



Note: This figure displays the distribution of mental health for both the control and the treatment group (left-hand side), and for the treatment group before and after a health shock (right-hand side). It shows that more individuals in the control group declare higher mental health than those in the treatment group. Individuals facing health shocks within the treatment group have lower levels of mental health before the shock as compared to after.

Table I.2.6 – IMPACT OF A CHILD’S HEALTH SHOCK ON THE MOTHER’S GENERAL HEALTH

Full Table

	(1)	(2)	(3)	(4)
Child’s health shock	-0.348*** (0.064)	-0.318*** (0.072)	-0.348*** (0.073)	-0.318*** (0.078)
Year dummies (ref=2005)				
Year=2006	0.218*** (0.035)	0.203*** (0.043)	0.445*** (0.095)	0.459*** (0.104)
Year=2007	0.305*** (0.038)	0.285*** (0.047)	0.678*** (0.147)	0.703*** (0.159)
Year=2008	-0.115*** (0.040)	-0.177*** (0.053)	0.207 (0.156)	0.226 (0.171)
Year=2009	0.206*** (0.047)	0.140** (0.058)	0.744*** (0.226)	0.768*** (0.244)
Year=2010	-0.309*** (0.048)	-0.443*** (0.061)	0.321 (0.294)	0.341 (0.319)
Year=2011	-0.143*** (0.052)	-0.247*** (0.072)	0.858* (0.439)	0.952** (0.475)
Year=2012	-0.140** (0.056)	-0.236*** (0.082)	1.315** (0.628)	1.492** (0.678)
Education (ref=no qualification)				
Vocational qualification		0.092 (0.368)		0.103 (0.397)
Degree or equivalent		0.250 (0.407)		0.274 (0.438)
Standard grade		0.119 (0.401)		0.155 (0.433)
Higher grade		-0.153 (0.437)		-0.122 (0.470)
Observations	37721	37721	37721	37721

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table I.2.6 - IMPACT OF A CHILD'S HEALTH SHOCK ON THE MOTHER'S GENERAL HEALTH (CONTINUED)

Full Table

	(1)	(2)	(3)	(4)
Age category (ref= 16-24)				
25-34		-0.012 (0.093)		-0.020 (0.101)
35-44		0.142 (0.117)		0.147 (0.127)
45 and older		0.115 (0.160)		0.140 (0.172)
Income		0.015 (0.011)		0.014 (0.012)
Couple		-0.024 (0.069)		-0.014 (0.074)
Rural vs. Urban		-0.109 (0.084)		-0.130 (0.090)
Working Status		0.037 (0.055)		0.043 (0.059)
Child's age			-0.166** (0.070)	-0.196*** (0.076)
Observations	37721	37721	37721	37721

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: This table displays the full list of coefficients from Table I.2.2, including control variables. Age is a categorical variable coded as follows: 1 for being 16 to 24-years-old; 2 for 25-34; 3 for 35-44; and 4 for 45+. Education attainment is categorical variable coded as follow: 1 for no qualifications; 2 for vocational qualifications; 3 for degree or equivalent; 4 for standard grade; and 5 for higher grade. Income designates the quintile equalized total net household annual income. Marital status is a dummy variable equal to 1 if the mother is in couple, 0 otherwise. Place of residence is a dummy variable equal to 1 if the mother lives in a rural area, 0 otherwise. Child age goes from 9 months to 11-years-old, with an average of 4 years. Mother's health status designates self-reported health status, with 5 categories. We report coefficients from a fixed effect ordered logit model.

Table I.2.7 – IMPACT OF THE CHILD’S HEALTH SHOCK ON THE MOTHER’S PHYSICAL AND MENTAL HEALTH

	(1)	(2)	(3)	(4)	(5)	(6)
	Physical health	Physical health	Physical health	Mental health	Mental health	Mental health
Child health shock	-0.830*** (0.156)	-0.727** (0.284)	-0.673** (0.286)	-0.426 (0.202)	-0.284 (0.347)	-0.404 (0.350)
Education (ref=no qualification)						
Vocational qualification	1.762*** (0.270)	-0.613 (1.230)	-0.603 (1.230)	1.798*** (0.355)	-0.385 (1.504)	-0.404 (1.504)
Degree or equivalent	2.226*** (0.291)	-0.253 (1.338)	-0.256 (1.338)	1.531*** (0.383)	-1.149 (1.636)	-1.183 (1.636)
Standard grade	1.438*** (0.294)	0.157 (1.349)	0.129 (1.350)	1.685*** (0.388)	-1.357 (1.650)	-1.318 (1.650)
Higher grade	1.712*** (0.352)	-1.703 (1.433)	-1.681 (1.434)	2.038*** (0.464)	-0.162 (1.753)	-0.149 (1.753)
Age category (ref= 16-24)						
25-34	-0.417** (0.198)	-0.249 (0.300)	-0.171 (0.304)	-0.185 (0.251)	-0.222 (0.367)	-0.367 (0.371)
35-44	-0.525** (0.225)	-0.084 (0.390)	0.028 (0.398)	-0.030 (0.289)	0.044 (0.478)	-0.195 (0.486)
45 and older	-1.172*** (0.339)	-0.514 (0.551)	-0.464 (0.555)	0.648 (0.432)	0.848 (0.674)	0.651 (0.679)
Income	0.235*** (0.026)	0.010 (0.038)	0.018 (0.039)	0.316*** (0.033)	0.083* (0.047)	0.074 (0.047)
Couple	0.234 (0.164)	0.579** (0.238)	0.597** (0.238)	-2.258*** (0.209)	-1.788*** (0.291)	-1.818*** (0.291)
Rural vs. Urban	0.090 (0.148)	0.032 (0.274)	0.023 (0.274)	0.603*** (0.193)	-0.213 (0.336)	-0.202 (0.336)
Working Status	1.161*** (0.192)	0.735*** (0.237)	0.881*** (0.251)	0.563** (0.241)	0.632** (0.290)	0.437 (0.307)
Child’s age	-0.018 (0.022)	-0.059** (0.028)	0.007 (0.275)	-0.027 (0.027)	-0.029 (0.034)	-0.271 (0.336)
Year dummies (ref=2005)						
Year=2007			-0.293 (0.561)			0.543 (0.686)
Year=2009			-0.393 (0.870)			1.151 (1.064)
Year=2012			-0.565 (2.448)			2.158 (2.993)
Constant	49.310*** (0.483)	43.779*** (8.411)	43.369*** (8.430)	48.271*** (0.623)	48.319*** (10.287)	49.478*** (10.309)
Observations	37721	37721	37721	37721	37721	37721

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: This table displays the full list of coefficients from Table I.2.3, including control variables. Age is a categorical variable coded as follows: 1 for being 16 to 24-years-old; 2 for 25-34; 3 for 35-44; and 4 for 45+. Education attainment is a categorical variable coded as follows: 1 for no qualifications; 2 for vocational qualifications; 3 for degree or equivalent; 4 for standard grade; and 5 for higher grade. Income designates the quintile equalized total net household annual income. Marital status is a dummy variable equal to 1 if the mother is in a couple, 0 otherwise. Place of residence is a dummy variable equal to 1 if the mother lives in a rural area, 0 otherwise. Child age goes from 9 months to 11-years-old, with an average of 4 years. Mother’s health status designates SF-12 physical or mental indices. We report coefficients from a fixed effect linear model.

Table I.2.8 – HETEROGENEITY IN THE IMPACT OF A CHILD'S HEALTH SHOCK ON THE MOTHER'S SELF-REPORTED GENERAL HEALTH STATUS

Full Table

	(1)	(2)
Child health shock	-0.094 (0.152)	-0.399*** (0.176)
Education (ref=no qualification)		
Vocational qualification	0.301 (0.601)	0.331 (0.707)
Degree or equivalent	0.940 (0.691)	-0.258 (0.896)
Standard grade	0.215 (0.701)	1.011 (0.858)
Higher grade	0.682 (0.847)	-0.041 (0.965)
Age category (ref= 16-24)		
25-34	0.004 (0.181)	-0.070 (0.301)
35-44	0.132 (0.243)	-0.026 (0.403)
45 and older	0.090 (0.340)	0.246 (0.673)
Income	0.052** (0.022)	0.039 (0.044)
Observations	9537	3189
Standard Errors in parentheses		
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$		

Note: The table displays the full list of coefficients from Table I.2.3, including control variables. Age is a categorical variable coded as follows: 1 for being 16 to 24-years-old; 2 for 25-34; 3 for 35-44; and 4 for 45+. Education attainment is a categorical variable coded as follows: 1 for no qualifications; 2 for vocational qualifications; 3 for degree or equivalent; 4 for standard grade; and 5 for higher grade. Income designates the quintile equalized total net household annual income. Marital status is a dummy variable equal to 1 if the mother is in a couple, 0 otherwise. Place of residence is a dummy variable equal to 1 if the mother lives in a rural area, 0 otherwise. Child age goes from 9 months to 11-years-old, with an average of 4 years. Mother's health status designates self-reported general health status in categories. We report coefficients from a fixed effect ordered logit model.

TABLE I.2.8: HETEROGENEITY IN THE IMPACT OF A CHILD'S HEALTH SHOCK ON THE MOTHER'S SELF-REPORTED GENERAL HEALTH STATUS (CONTINUED)

Full Table		
	(1)	(2)
Couple	-0.144 (0.141)	0.083 (0.189)
Rural vs. Urban	-0.191 (0.177)	0.159 (0.352)
Child's age	-0.173 (0.155)	-0.218 (0.276)
Year dummies (ref=2005)		
Year=2006	0.433** (0.205)	0.499 (0.361)
Year=2007	0.677** (0.322)	0.672 (0.580)
Year=2008	0.148 (0.344)	0.540 (0.629)
Year=2009	0.681 (0.498)	0.905 (0.878)
Year=2010	0.461 (0.654)	0.543 (1.183)
Year=2011	1.053 (0.974)	1.378 (1.766)
Year=2012	1.413 (1.377)	1.974 (2.512)
Observations	9537	3189
Standard Errors in parentheses		
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$		

Note: The table displays the full list of coefficients from Table I.2.3, including control variables. Age is a categorical variable coded as follows: 1 for being 16 to 24-years-old; 2 for 25-34; 3 for 35-44; and 4 for 45+. Education attainment is a categorical variable coded as follows: 1 for no qualifications; 2 for vocational qualifications; 3 for degree or equivalent; 4 for standard grade; and 5 for higher grade. Income designates the quintile equalized total net household annual income. Marital status is a dummy variable equal to 1 if the mother is in a couple, 0 otherwise. Place of residence is a dummy variable equal to 1 if the mother lives in a rural area, 0 otherwise. Child age goes from 9 months to 11-years-old, with an average of 4 years. Mother's health status designates self-reported general health status in categories. We report coefficients from a fixed effect ordered logit model.

Part II

FIRMS' DECISIONS TO ALLOCATE R&D TO RARE DISEASES

Part I was dedicated to diagnostic services and its impact on health: not solely on the health of patients but also on their social support structure. Access to diagnostic is an essential step forward in order to benefit from appropriate health care and treatment. Accordingly, improving access to diagnostic services simultaneously impacts disease market R&D attractiveness by increasing market size. Part II introduces the second key actor in a patient's diagnostic and therapeutic "odyssey": pharmaceutical firms whose R&D investment decisions ultimately impact treatment opportunities and the health of patients with rare diseases. Incentives aiming to increase profitability of rare disease markets have been introduced to encourage pharmaceutical innovation. Chapter 3 investigates the impact of the Orphan Drug legislation implemented in 2000 in Europe, while Chapter 4 analyzes the distribution of R&D among rare diseases.

Introductory Section

This introductory section to Chapters 3 and 4 presents the challenges encountered and the solutions found in setting up an original database used in both chapters, which are devoted to innovation in rare disease areas.

Challenges in Setting up an Original Dataset

This section provides a detailed description of the original dataset constructed for Chapters 3 and 4, which focus on R&D investment allocated to rare diseases. It comprises yearly disease-level data on rare disease biomedical research. While data on clinical trial activities for rare diseases were readily accessible, academic publications were not registered in the existing databases. Still, pharmaceutical advances are conditioned upon the constitution of knowledge on the diagnostic of diseases, their etiology, and natural history. This prerequisite can be proxied by the stock of academic publications on rare diseases. Biomedical innovation is also a valuable source of information for R&D on rare diseases, which compliments pharmaceutical innovation.

MEDLINE is the largest database of academic references on life sciences and biomedical topics. This database is maintained by the United States NLM at the NIH. To search content on the MEDLINE database, one can use PubMed, which is a free search engine. Simple searches on PubMed can be carried out by entering keywords into PubMed's search window presented in Figure II.0.1.

When computing the number of academic publications per rare disease, we cannot simply use the names of rare diseases as keywords for a number of reasons. First, because there are between 5,000 and 8,000 distinct rare diseases, a separate manual research was not an option here. Second, rare diseases have complicated names and a large number of synonyms. For example, the disease "Glycogen storage disease due to glucose-6-phosphatase deficiency type Ib" has 16 synonyms. Moreover, even if most scientific publications are available in English, an exhaustive search would require covering several other languages and publications in a large number of countries. Finally, we cannot assume that a publication that mentions a rare disease's name qualifies as biomedical research on that rare disease. We thus used Orphanet codes for rare diseases to count their occurrence in biomedical literature.

Orphanet is the reference portal for information on rare diseases and orphan drugs in Europe. It was established in 1997 by the French Ministry of Health and the French National Institute for Health and Medical Research (INSERM). The database and website is maintained by the European Commission. Orphanet attributes a unique identifier to

Figure II.0.1 – PUBMED’S SEARCH WINDOW



Source: <https://www.ncbi.nlm.nih.gov/pubmed>

each disease and transmits information on expert services in its 37 partner countries worldwide with the input of national partner teams. The database includes information on orphan drugs, expert centers, research projects, diagnostic tests, registries, bio-banks, and patient organizations (Rodwell and Aymé, 2015).

MedGen is also a free search engine to access specialized information on genetic disorders. One can search MedGen using Orphanet codes to find information on genetic disorders. Figure II.0.2 displays the MedGen webpage in relation to the rare disease, “Alexander disease” with Orphanet code “58.”

The format of the URL https://www.ncbi.nlm.nih.gov/medgen/?term=orphanet_58. Using a list of all possible Orphanet codes, we systematically replaced the % in https://www.ncbi.nlm.nih.gov/medgen/?term=orphanet_% by the code belonging to the list provided by Orphanet. The source code of the webpage allowed us to retrieve the precise MedGen UID within its html tag (see Figure II.0.3 for the html tag identification). For that purpose, we used the Python library BeautifulSoup4.

Once we had the MedGen UID for all Orphanet codes in a database (we display in Figure II.0.3 the output in Excel), we searched all the publications identified at the MedGen UID level.

When searching PubMed using MedGen UID, the URL of the result webpage for “Alexander Disease” is: https://www.ncbi.nlm.nih.gov/pubmed?LinkName=medgen_pubmed&from_uid=78724. We apply the same methodology as described above to replace % in https://www.ncbi.nlm.nih.gov/pubmed?LinkName=medgen_pubmed&from_uid=% by all the MedGen UID collected in the Excel output. The difficulty here is that PubMed displays only 20 results per page. To webscrape all the citation contents corresponding to one MedGen UID, we had to scroll through all of the pages one after the other and retrieve their textual content. The Selenium library and Chrome Driver in Python were used to automate the sending of these requests. Figure II.0.5 displays the Excel output,

Figure II.0.2 – MEDGEN’S RESULT WINDOW FOR “ALEXANDER DISEASE,” ORPHANET CODE “58”

NCBI Resources How To

MedGen MedGen orphanet_58

Full Report ▾ Send to: ▾

Alexander disease (ALXDRD)
 MedGen UID: 78724 Concept ID: C0270726 • Disease or Syndrome

Synonyms: Alexander's disease; Alexanders leukodystrophy; ALXDRD; Megalencephaly in infancy accompanied by progressive spasticity and dementia

Modes of inheritance: Autosomal dominant inheritance (HPO, OMIM, Orphanet)

SNOMED CT: Alexander disease (81854007); Alexander's disease (81854007); Fibrinoid leukodystrophy (81854007)

Gene (location): GFAP (17q21.31)

OMIM®: 203450

Orphanet: ORPHA58

⬆ **Disease characteristics** Go to: ⌵ ⌶

Excerpted from the GeneReview: Alexander Disease

Alexander disease is a progressive disorder of cerebral white matter that predominantly affects infants and children and has variable life expectancy. The later-onset forms present with a slower clinical course. The infantile form comprises about 42% of affected individuals, the juvenile form about 22%, and the adult form about 33%. A neonatal form is also recognized. The neonatal form leads to severe disability or death within two years. Characteristics include seizures, hydrocephalus, severe motor and intellectual disability, and elevated CSF protein concentration. MRI shows severe white matter abnormalities with involvement of the basal ganglia and cerebellum. The infantile form presents in the first two years of life, typically with progressive psychomotor retardation with loss of developmental milestones, megalencephaly, frontal bossing, and seizures. Other findings include hyperreflexia and pyramidal signs, ataxia, and occasional hydrocephalus secondary to aqueductal stenosis. Affected children survive weeks to several years. The juvenile form usually presents between ages four and ten years, occasionally in the mid-teens. Findings can include bulbar/pseudobulbar signs, ataxia, gradual loss of intellectual function, seizures, normocephaly or megalencephaly, and breathing problems. Survival ranges from the early teens to the 20s-30s. The adult form is the most variable. [from GeneReviews]

Full text of GeneReview (by section):
[Summary](#) | [Diagnosis](#) | [Clinical Characteristics](#) | [Genetically Related \(Allelic\) Disorders](#) | [Differential Diagnosis](#) | [Management](#) | [Genetic Counseling](#) | [Resources](#) | [Molecular Genetics](#) | [References](#) | [Chapter Notes](#)

Authors:
 Siddharth Srivastava | Sakkubai Naidu [view full author information](#)

Source: https://www.ncbi.nlm.nih.gov/medgen/?term=orphanet_58

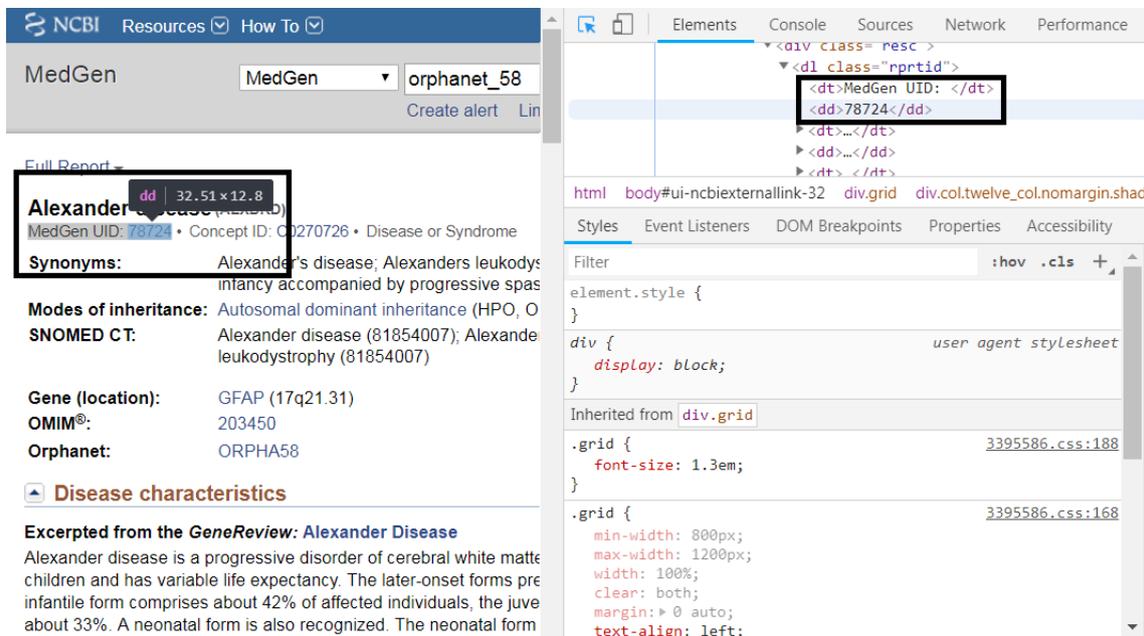
along with the citation content. The 20 different citations are displayed in columns C through V (20 columns in total), except for the final page that may have contained less results.

Using this output, we then had to retrieve all the dates inside the citation. We explored the citation content to find regularities in date reporting and obtained a list of publication dates (see Figure II.0.6). Finally, using Stata, we counted the yearly number of publications at the rare disease level.

We faced various complications during the data collection. For example when one citation contained multiple numbers, we had to identify the correct publication date. There were also sudden changes in date reporting methods from Pubmed. Python codes to reproduce the webscraping is available in the final Appendix.

We searched MEDLINE in July 2017 for all dates from its inception to present day using the MEDGEN unique identifier of the 8,755 diseases classified as rare diseases. We then generated the number of scientific publications for each rare disease (See Figure II.0.7 for final results in Stata).

Figure II.0.3 – MEDGEN’s RESULT WINDOW FOR “ALEXANDER DISEASE,” ORPHANET CODE “58”



Source: https://www.ncbi.nlm.nih.gov/medgen/?term=orphanet_58

Figure II.0.4 – EXCEL OUTPUT CONTAINING THE MEDGEN UID FOR “ALEXANDER DISEASE,” ORPHANET CODE “58” — SOURCE CODE

	A	B
1	medgen	orpha
2	78724	58
3	83402	1063
4	891703	2661
5	337988	2772
6	78604	48471
7	96582	1040
8	357030	79477
9	137977	2066
10	328427	140503
11	339210	88918
12	325510	3180
13	90939	98957

Source: Python data scraping output using the library BeautifulSoup4.

Figure II.0.5 – EXCEL OUTPUT CONTAINING THE CITATION CONTENT FOR “ALEXANDER DISEASE,” MEDGEN UID 78724

	A	B	C
1	medgen	numberofpag	citation
2	78724	1	<p class="details">Clin Immunol. 2000 Nov
3	78724	2	<p class="details">BMC Infect Dis. 2016 Jun 10
4	78724	3	<p class="details">BMC Pediatr. 2014 Oct 15
5	78724	4	<p class="details">J Clin Immunol. 2014 Jan
6	78724	5	<p class="details"><span class="jrnl" title="Journal of investigational allergology &
7	78724	6	<p class="details">Mol Immunol. 2009 Jun
8	78724	7	<p class="details">Curr Gene Ther. 2007 Aug
9	78724	8	<p class="details">Arch Pedia
10	78724	9	<p class="details">FEMS Immunol Med Microbiol
11	78724	10	<p class="details">J Clin Immunol. 2002 Jul
12	78724	11	<p class="details">Front Biosci. 2000 Dec 1
13	78724	12	<p class="details">J Virol. 1999 Feb
14	78724	13	<p class="details">Hum Mutat. 1997
15	78724	14	<p class="details">Hum Mol Genet. 1993 Feb
16	78724	15	<p class="details">Immunol Rev. 1994 Apr
17	78724	16	<p class="details">Am J Hum Genet. 1994 Jan
18	78724	17	<p class="details">Tohoku J Exp Med. 1981 Dec
19	78724	18	<p class="details">Clin Genet. 1987 Feb
20	78724	19	<p class="details">J Pediatr. 1991 Sep
21	78724	20	<p class="details">Am J Dis Child. 1977 Jun
22	78724	21	<p class="details">Vet Med Nauki. 1978

Source: Webscraping data output using the Selenium library and Chrome Driver in Python.

Figure II.0.6 – EXCEL OUTPUT CONTAINING THE CITATION CONTENT FOR “ALEXANDER DISEASE,” MEDGEN UID 78724

	A	B	C	D	E	F
1	medgen	date1	date2	date3	date4	date5
2	78724	2016	2017	2017	2017	2017
3						
4						

Source: Webscraping data output containing only publication dates, finally.

Figure II.0.7 – DATABASE EXTRACTION FOR “ALEXANDER DISEASE,” MEDGEN UID 78724

	code_maladie	date	academic_r-h
3008	78724	1996	4
13154	78724	1997	4
17142	78724	1998	6
25041	78724	1999	13
33525	78724	2000	5
44759	78724	2001	11
50821	78724	2002	12
57397	78724	2003	14
64649	78724	2004	9
71246	78724	2005	9
84598	78724	2006	23
87863	78724	2007	10
96651	78724	2008	14
103995	78724	2009	17
112916	78724	2010	14
125700	78724	2011	12
126910	78724	2012	25
136914	78724	2013	29
143814	78724	2014	13
155974	78724	2015	13
161496	78724	2016	71
168065	78724	2017	94

Source: Author’s database containing the yearly number of publication on “Alexander Disease,” Orphanet code “58,” MedGen UID 78724.

Chapter 3

European Initiatives to Foster R&D in Rare Disease Areas: The Orphan Drug Legislation after 18 Years

1 Introduction

With 36 million people affected by a rare disease in the EU with few treatment options as highlighted in the General Introduction, the allocation of pharmaceutical R&D resources in rare diseases is crucial as R&D investments determine treatment and care opportunities for patients with rare diseases.

Patients with rare diseases are likely to be in poor health related to unaccountable genetic inheritance as well as multiple obstacles in accessing appropriate tests and treatments for their conditions (Schieppati et al., 2008).

Rare diseases remain largely under-served by drug development as the production of drugs targeting rare diseases is not as profitable as other drugs because of both higher R&D costs (Buckley, 2008) and insufficient market size for fixed costs recovery. This has prompted policy makers to introduce supply-side incentives to encourage pharmaceutical firms to increase their R&D activities in rare disease areas.

As a result, the US, EU, Japan, and Australia have enacted a new legislation incentivizing firms' R&D investments in rare disease areas. The ODA was enacted in 1983 in the US and offered to all drugs targeting diseases with a prevalence¹ of less than 75/100,000 the following advantages: a 50% tax credit, fee waivers from the FDA, grants programs, scientific advice, protocol assistance, pre-licensing access, free pricing, and a 95% reimbursement under Medicare.

In Europe, incentives for pharmaceutical firms to invest in rare disease areas was enacted in 2000 with the European Union OD legislation (Conformité Européenne (CE) number 141 2000) that supports orphan drug development. Despite the expected impact of the OD policy adoption on pharmaceutical firms' R&D investment decisions, little empirical work has been done to evaluate how this innovate policy might have affected private innovation, especially in Europe. Previous studies conducted on the US Orphan Drug Act estimated a significant private R&D response to incentives created by the ODA (Lichtenberg and Waldfogel, 2003; Yin, 2008).

Yin (2008) finds a significant increase by 69% in the flow of new clinical trials for drugs treating rare diseases in the US from 1981 to 1994, following the change in regulation in 1983. Lichtenberg and Waldfogel (2003) find that by 1998, there were more than five times as many orphan drugs as there had been in 1979.

However, to the best of our knowledge, no research has investigated firms' R&D responsiveness to the implementation of the OD in Europe. More importantly, the OD policy incentivizes R&D in rare disease areas for which the target population is under the threshold of 50/100,000 people. The target population refers to the groups of patients targeted by a particular health technology, rather than the disease prevalence. It can differ from the disease prevalence, depending of the firms' R&D portfolio decisions.

¹Prevalence designates the mean number of patients affected by a disease for a given period of time.

As a result, the OD policy may have spurred research in subsets of the patient population experiencing diseases traditionally classified as non-rare. The increasing trend in precision medicine—defined as drugs relying on genetic, epigenetic, and protein bio-markers—has led to specific disease sub-type refinements. This may have, to some extent, been encouraged by the introduction of the OD policy (Chandra et al., 2017).

In the EU, from the inception of the OD regulation through 2015, 133 orphan drugs were granted MA (Giannuzzi et al., 2017b). The OD policy is often described as having led to unprecedented investments by manufacturers in R&D targeting rare diseases. However, neither the overall impact on R&D investments of the OD policy, nor the indirect impact on diseases that are not defined as rare have ever been studied.

In this chapter, we address the ability of supply-side market incentives to foster pharmaceutical innovation in rare diseases and measure the causal impact of the OD legislation on R&D activity in rare diseases, using a DiD design. More specifically, we examine if the OD regulation has led to an increase in the level of R&D investments as proxied by clinical trial activities and academic publications, for both rare diseases and rare targeted populations. We examine the magnitude and the long run effects of these causal impacts.

The paper is organized as follows: Section 2 introduces the context of the study; Section 3 presents the data and the empirical strategy including a set of robustness checks; Section 4 presents our main results, which are then discussed in Section 5.

2 Context

2.1 Overview of the R&D Process for Pharmaceuticals

The drug development process in Europe, from basic science to marketing, is considerably long and faces a number of hurdles. The R&D process for pharmaceuticals is described as a sequential process, each step entailing inherent risks. Figure II.3.1 summarizes each step described in the section.

The first step of the drug development process is defined as the *discovery stage* or referred to as *non-clinical development*. It designates the synthesis of drug candidates by chemists and biologists in order to develop concepts for new compounds. The main objective of non-clinical development is to evaluate the pharmaco-dynamic toxicity to predict potential safety problems in the subsequent *clinical development stage*. Pre-clinical research is carried out on animal subjects, and if the results are deemed promising, is followed by studies on humans.

Clinical development testing typically comprises four distinct phases (I to IV), each of which involves different types of tests regarding safety and efficacy. The main objective of the clinical development phases is to evaluate a dose-response relationship and the clinical efficacy along with the drug's safety in a given indication.

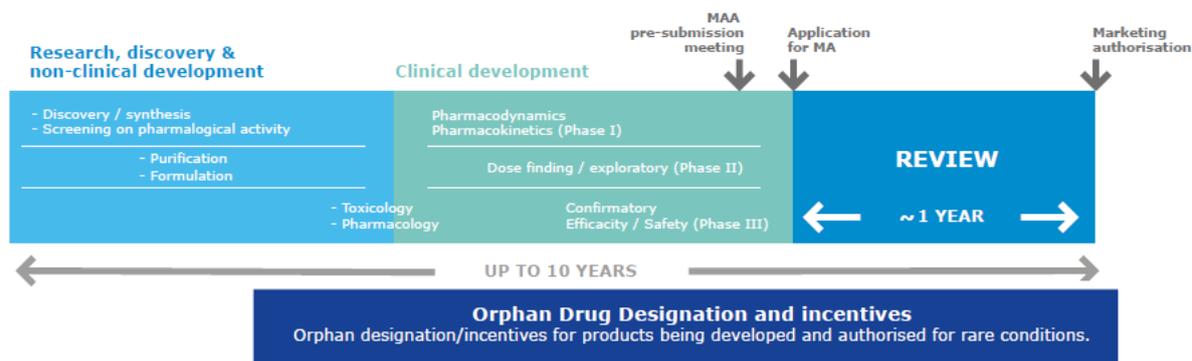


Figure II.3.1 – OVERVIEW OF MEDICINAL PRODUCT DEVELOPMENT, SOURCE: EUROPEAN MEDICINES AGENCY

Phase I comprises human pharmacology studies and is performed on a small number of healthy human subjects to obtain data on safe dosage ranges and potential toxicity. Phase II comprises therapeutic exploratory studies and is performed on a larger number of humans who are patients of the corresponding drug indication. The goal of Phase III is to confirm preliminary evidence from the exploratory stages by testing the drug in large-scale trials, usually relying on evidence from randomized controlled trials.

If supported by phase III clinical testing results, the drug sponsor can apply for registration as an approved drug. Finally, a marketed drug is subject to post-marketing surveillance in phase IV, following marketing authorization. The objective of Phase IV is to collect data about the health technology benefits, risks, and optimal use in the patient population corresponding to the marketing authorization. The average duration of drug development is ten years².

2.2 R&D Success Rates and Costs in Rare Disease Markets

To what extent are rare disease development processes comparable to those of non-rare diseases in (1) the R&D success rates, and (2) the R&D cost levels?

Overall success rates from Phase I to market approval for all existing drugs that have gone into clinical development have recently been estimated at 13.8% (Wong et al., 2019) using data for the period 2000-2005. Comparatively, orphan drug development's success rates are significantly lower, with only 6.2% of drug development projects reaching the market.

If we compare success rates phase by phase, we observe that the probability of success in Phase I increases from 66.4% for non-orphan to 75.9% for orphan drugs; Phase II and III success rates fall from 58.3% to 48.8% (non-orphan versus orphan drugs); and

²Source: European Medicines Agency website accessible on: <https://www.ema.europa.eu/en/human-medicines-regulatory-information>

from 59.0% to 46.7% (non-orphan versus orphan), leading to a decline in the overall probability of success for orphan drugs (Wong et al., 2019).

Finally, if we compare the probability of the success of trials using bio-markers (defined as those likely to qualify for the OD policy rewards on the basis of a rare target population), we see that they exhibit almost twice the overall success rates as those trials without bio-markers (10.3% vs. 5.5%) (Wong et al., 2019).

The existing evidence on total costs of developing an innovative health technology is mixed. The most widely cited papers on the theme, (DiMasi et al., 2003, 2016), suggest that average out-of-pocket cost per approved new compound is \$1,395 million (2013 USD), showing an increase at an annual rate of 8.5% above general price inflation³.

However, a recent study using publicly available data found the out-of-pocket clinical costs per approved orphan drug to be \$166 million and \$291 million (2013 USD) per non-orphan drug⁴ (Jayasundara et al., 2019).

This result suggests that average orphan drug development costs could be lower than conventional drugs while most of the literature acknowledges the contrary.

On one hand, recruitment of patients for conducting clinical trial activities may raise R&D costs, which are also driven by the fact that patients are likely to be spread over multiple locations. On the other hand, we observe that while double-blind, placebo-controlled trials with demonstrated statistically significant benefits are required in Phase III for conventional drugs, it is less often the case for orphan drugs. Moreover, the number of enrolled patients in orphan drug clinical trials is lower than in conventional trials (Logviss et al., 2018) so that the overall R&D costs could be lower in orphan drug trials.

Rare diseases indeed qualify for fast-track clinical testing procedures and marketing authorization application procedures as they are life-threatening and as it is very challenging to recruit patients for conducting large-scale trials due to the very nature of rare diseases. In particular, orphan drug candidates do not systematically go through phase III testing and directly apply to marketing authorization if the drug's Phase II results show clinical efficacy, which may explain why R&D costs are estimated to be lower for orphan drugs.

2.3 The Orphan Drug Policy in Europe

This section reviews the legal framework of the Orphan Drug policy in Europe that was enacted on the 16 December 1999 based on the Official Journal of the European Communities published in 2000 under the title "Regulation (EC) No 141/2000" and entered into force the day of its publication.

³Estimates include the costs R&D projects abandoned during testing that were linked to the costs of the drug that obtained marketing approval.

⁴Authors only looked at clinical costs per approved drug and do not include abandoned linked compound, contrary to (DiMasi et al., 2003, 2016).

The Act motivates the need for implementing the Orphan Drug policy by stating that “patients suffering from rare conditions should be entitled to the same quality of treatment as other patients,” and highlighting the limited coordinated actions taken so far at the European level to address the lack of R&D investments allocated to rare diseases.

One important feature of the OD legislation is that it considers a medicinal product as an orphan drug if “it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating *condition* affecting not more than five in 10 thousand persons in the Community when the application is made.” Neither prevalence nor disease appear in the text, and the use of the term “condition” creates ambiguity as to whether or not the condition must be defined as rare *stricto sensu* to qualify for the OD incentives. Later in the text, the Act designates the need for the sponsor to disclose the proposed so-called “therapeutic indication.”

Once complying with the unique requirement validated by the Committee for Orphan Medicinal Product, the Act details the incentives offered by the OD policy. In order to encourage R&D on orphan medicinal products, the Orphan Regulation incorporates five incentives:

(1) *Protocol assistance*: The OD policy offers the possibility for the drug sponsor to request regulatory assistance from the European Medicines Agency on the conduct of tests to demonstrate the quality, safety, and efficacy of the orphan drug, as well as assistance with the marketing authorization application process. The incentive consists of a 100% fee reduction for protocol assistance.

(2) *Direct access to the centralized procedure* for the application for Marketing Authorization.

(3) *10-year market exclusivity*: The European Medicine Agency guarantees the automatic refusal of “another application for a marketing authorization, or grant a marketing authorization, or accept an application to extend an existing marketing authorization, for the same therapeutic indication, in respect of a similar medicinal product” for a period of 10 years, or 12 years for pediatric drugs.

(4) *Fee reductions for centralized applications and grants* within the framework of EU-funded research: 50% reduction and direct application for Marketing Authorization in the centralized procedure of the European Medicines Agency and 100% fee reduction for pre-authorization inspections. In 2007, the funds made available by the EU for fee exemptions for orphan medicinal products amounted to 6,000,000.⁵

(5) *Priority access to EU research programs* “to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium-sized undertakings provided for in framework programs for research and technological development.”

⁵Source: European Medicine Agency.

The OD policy creates incentives for drug development as it increases the profitability of rare disease markets. As academic publications are an indicator of the stock of knowledge, they are related to research expenditures, which in turn is influencing both the supply of (scientific opportunities) and the demand for innovation (disease burden) (Lichtenberg, 2018a). We argue that the policy has direct impact on clinical trial activities while the effect is diluted when considering academic research.

Still, each clinical activity will result in academic publications for clinical research protocols and the resulting publications differed in time as compared to clinical trial counts. Before the introduction of the policy, we assume that the disease burden was already appraised as high and scientific opportunities existed but costs of conducting research were too high. By lowering the cost of conducting research on rare disease markets, the policy could have stimulated the stock of scientific knowledge and drug development on rare diseases.

3 Data and Empirical Strategy

We aim to measure the impact of the OD legislation enacted in 2000 in Europe on pharmaceutical investment decisions. We use the European definition of rare disease, namely all conditions affecting less than 5/10,000 patients and uncommon disease markets, i.e. between 5/10,000 and 20/10,000 patients. Our empirical investigation is based on a DiD specification, using uncommon but non-rare diseases as a control group.

3.1 Data

Pharmaceutical investment decisions in rare disease are available in the Orphanet dataset. Orphanet is an information portal for rare diseases and orphan drugs granted by the European Commission; it provides disease-specific clinical trial activities in Europe from 1997 to 2015. Orphanet was established in France by the INSERM in 1997. This initiative then became European from 2000 and gradually grew to a consortium of 40 countries within Europe and across the globe. The Orphanet dataset comprises nearly all rare diseases, granting them a unique Orphanet identification number to facilitate sharing information on each disease.

Our measure of pharmaceutical investment decisions is the number of new clinical trials in a given year at the disease-level. This has an advantage in that it reflects current firm investment decisions more accurately than the yearly stock of clinical trial activities. As clinical trials may span more than 17 years (DiMasi et al. (2003)), using the number of new clinical trials avoids capturing past investment decisions in the analysis (Yin (2008)).

Our second proxy measure of R&D investment is the number of academic publications per disease. Academic publications were retrieved using Pubmed, which is a search engine accessing MEDLINE, the largest database of academic references on life sciences and biomedical topics. We developed an algorithm coded in Python to automatize searches. Using the MEDGEN unique identifier for each rare disease, we searched MEDLINE from

its inception date to present and created a database providing us with the yearly number of scientific publications for each rare disease.

In our setting, we observe the treatment group and a comparison group before and after the introduction of the OD policy. Our treatment group is all rare diseases as defined by the EU and our control group comprises uncommon diseases: both treatment and control are similar prior to the introduction of the OD policy in terms of drug development trends.

The treatment group is segmented into two sub-groups, which are both targeted by the Orphan Drug policy: rare diseases that do respect the European prevalence threshold of 50/100000 and rare diseases with a therapeutic indication (i.e., non-rare diseases segmented in sub-populations with common epigenetic or biological characteristics). Rare therapeutic indications are also targeted by the Orphan Drug legislation, even if the prevalence of the disease exceeds the European threshold. The OD legislation may also have had an impact on non-rare disease drug markets since clinical trials that tailor a subset of patients within traditionally non-rare disease populations might fall within the scope of the OD legislation. Thus, after the adoption of the policy, firms may have increased the number of OD-qualifying clinical trials to benefit from supply-side incentives. This differentiation between rare diseases and rare therapeutic indications allows us to investigate and compare the effect of the Orphan Drug policy across those two groups.

The control group comprises uncommon but non-rare diseases identified in the Global Disease Burden 2015 survey (Institute for Health Metrics and Evaluation), which is the most comprehensive worldwide observational epidemiological study to date. It includes prevalence at the disease level. We identify 94 diseases with respective prevalence ranging between 5/10,000 and 20/10,000 patients; we consider them as uncommon but non-rare diseases. To retrieve the pharmaceutical investment decisions in uncommon but non-rare diseases, we retrieve the number of new clinical trials per disease between 1997 and 2015 in Europe on ClinicalTrials.gov, which is provided by the US National Library of Medicine. Academic publications are retrieved on Pubmed using major Medical Subject Headings (MeSH) terms. MeSH terms are thesaurus terms indexing articles for Pubmed. In order to account for the increasing trend in precision medicine pharmaceutical developments, we remove from the control group five uncommon but non-rare diseases that fell within the scope of the OD legislation and thus would not strictly fit our identification assumptions.

3.2 Empirical Strategy

Average marginal effects

We estimate the average impact of OD legislation on pharmaceutical investment decisions and R&D efforts using the following DiD specification per disease-year observation for the two R&D proxies (clinical trials and academic publications):

$$CT_{it} = f(\alpha_0 + \beta_1 Post_t + \beta_2(Post \times Rare)_{it} + \psi_i + \lambda_t + \epsilon_{it}) \quad (3.1)$$

$$Publ_{it} = f(\alpha_0 + \beta_1 Post_t + \beta_2(Post \times Rare)_{it} + \psi_i + \lambda_t + \epsilon_{it}) \quad (3.2)$$

CT_{it} represents the count number of clinical trials for condition i in year t .

$Publ_{it}$ represents the count number of publications for condition i in year t .

$Post_t$ indicates whether the policy was in application in year t .

$(Post \times Rare)_{it}$ is the interaction term denoting an observation of a treated disease after the policy adoption.

ψ_i denotes the disease fixed-effect and λ_t is the time fixed effect.

ϵ_i is a random error term for condition i in time t .

The function f represents the functional relationship between the explanatory variables and the count number of clinical trials.

As the outcome variable is a count variable and is heavily skewed to the right, with a large proportion of zero values, we use a conditional fixed-effects Poisson model. Linear models would have produced inefficient estimates in this context. The conditional fixed-effects Poisson model also allows us to account for unobservable heterogeneity between diseases that is constant over time. The Poisson model is estimated with robust standard errors to account for heteroscedasticity of unknown form and correlation within each disease with time. Standard errors are clustered by diseases. As the Poisson model is a nonlinear model, the relationship between the explained and the explanatory variables is a function of the model being estimated. As such, the interpretation of the interaction term is not straightforward, as the coefficient is not the same as the marginal effect [Ai and Norton \(2003\)](#) (i.e., the derivative of the conditional expectation with respect to time for both the treatment group and the control group). Relying on [Mustillo et al. \(2012\)](#), we compute the average marginal effects to interpret our results.

Impact on under-researched rare diseases

We complement this analysis by investigating how the Orphan Drug policy affected the probability of at least one clinical trial, to explore whether or not the OD policy allows for the achievement of better equality in R&D between rare diseases. We investigate the extensive margins through two fixed effect logit models:

$$CT_{it}^* = f(\alpha_0 + \beta_1 Post_t + \beta_2(Post \times Rare)_{it} + \psi_i + \lambda_t + \epsilon_{it})$$

$$CT_{it}^* = 1 \text{ if } Clinical_Trials_{it} > 0, 0 \text{ otherwise} \quad (3.3)$$

Average marginal effects (i.e. for the latent variable model, the difference in the expected probabilities of success for both the treatment group and the control group) are displayed to interpret the results.

Time variation of the impact of the OD policy

We finally investigate the variation of the impact of the OD policy over time. To do so, we follow [Finkelstein \(2004\)](#) and include indicators for the time period (lags) after the adoption of the OD policy, using the following specification:

$$CT_{it} = f(\alpha_0 + \beta_1 Post_{1-3,t} + \beta_2 Post_{4-6,t} + \beta_3 Post_{7-10,t}$$

$$+ \beta_4 Post_{>11,t} + \beta_1(Post_{1-3} \times Rare)_{it} + \beta_2(Post_{4-6} \times Rare)_{it}$$

$$+ \beta_3(Post_{7-10} \times Rare)_{it} + \beta_4(Post_{>11} \times Rare)_{it} + \psi_i + \lambda_t + \epsilon_{it}) \quad (3.4)$$

$$Publ_{it} = f(\alpha_0 + \beta_1 Post_{1-3,t} + \beta_2 Post_{4-6,t} + \beta_3 Post_{7-10,t}$$

$$+ \beta_4 Post_{>11,t} + \beta_1(Post_{1-3} \times Rare)_{it} + \beta_2(Post_{4-6} \times Rare)_{it}$$

$$+ \beta_3(Post_{7-10} \times Rare)_{it} + \beta_4(Post_{>11} \times Rare)_{it} + \psi_i + \lambda_t + \epsilon_{it}) \quad (3.5)$$

This method allows us to investigate whether the impact of the policy was immediate or delayed and whether it varied in magnitude over time.

4 Results

4.1 Descriptive statistics

Table II.3.1 displays the distribution of the clinical trials for both treatment and control groups. We observe that, before the OD regulation, the mean number of clinical trials is around 0 for the treatment group and equal to 0.44 for the control group. Low investment in rare and uncommon diseases is consistent with the low expected returns of drug development for diseases with small patient populations (Drummond et al. (2007)). After the policy adoption, we observe that the mean number of clinical trials was multiplied by 67 in the treatment group, and by 12 in the control group. The mean number of clinical trials is significantly larger (the difference in means between the treatment group and the control group is -5.21, $p < 0.001$) in the control group, which is consistent with higher R&D investments for diseases with larger patient populations.

Table II.3.2 displays the distribution of academic publications in both treatment and control groups. Before the policy introduction in 2000, the mean number of academic publications is 11 in the treatment, versus 87.18 in the control group, the difference in means being significant ($p < 0.001$). After the policy introduction, the mean number of publications is multiplied by 2.17 in the treatment group, versus 1.74 in the control group.

4.2 Impact of OD legislation on clinical trials

Table II.3.3 displays coefficients for the DiD estimates using a conditional fixed effects Poisson model. Model (1) shows coefficients for all diseases targeted by the OD policy. As explained above, these diseases are a combination of rare diseases and Orphan Drug qualifying disease subdivision (rare therapeutic indications). Of the 820 diseases with at least one observation with a non-zero outcome, 167 are non-rare diseases, which represents 21%. In model (2), we restrict our sample to rare diseases only, as defined by the European cut-off on prevalence (all conditions affecting less than 5/10.000 patients).

The DiD coefficient is positive and significant in both models, indicating a positive impact of the OD legislation on the number of clinical trials at disease-level. Table II.3.4 displays the average DiD effects for model (1) and model (2). The OD policy significantly and positively affected the number of clinical trials and showed an increase of 51.67 ($p < 0.001$) in the number of clinical trials in the treatment group. Coefficients and marginal effects differ slightly according to the treatment group specification. The effect is larger when considering rare diseases only: the average marginal effect shows an increase of 69.01 ($p < 0.001$) in the number of clinical trials in the treatment group. Results suggest that: (1) the policy had a causal effect on the number of clinical trials in the treatment group; (2) the average treatment effect is larger among rare diseases (as compared to rare therapeutic indications).

We now turn to the fixed effect logit model. As displayed in Table II.3.5, the DiD coefficient is positive and non-significant in both models. Table II.3.6 displays the average DiD effects for model (1) and model (2) and results suggest that the policy had no impact on

the probability of rare diseases to be targeted by a clinical trial when they were formerly set aside from drug development.

The results in Table II.3.7 suggest that the positive effect of the OD policy was delayed four years after its introduction, as the coefficient of the interaction term for the period 2000-2003 is not significant. The effect of the policy on the treatment group is then significant and increases over the 2003 to 2010 period. It then decreased from 2010 to 2015. This result still holds when adopting a more restrictive definition of the treatment group, removing the OD-qualifying non-rare diseases.

4.3 Impact of the OD Legislation on Academic Publications

Table II.3.8 displays coefficients for the DiD estimates using a conditional fixed effects Poisson model on the number of academic publications. Model (1) shows coefficients for all diseases targeted by the OD policy. In model (2), we restrict our sample to only rare diseases as defined by the European cut-off on prevalence (all conditions affecting less than 5/10.000 patients). The DiD coefficient is positive and significant in both models, indicating a positive impact of the OD legislation on the number of academic publications at disease-level.

Table II.3.9 displays the average DiD effects for model (1) and model (2). The OD policy significantly and positively affected the number of publications and showed a significant but rather low increase of 0.25 ($p < 0.001$) in the mean number of academic publications. The effect is comparable when considering rare diseases. Results suggest that: (1) the policy had a causal effect on the number of publications in the treatment group; (2) the average treatment effect is equivalent among rare diseases or rare therapeutic indications.

The results in Table II.3.10 suggest that the positive effect of the OD policy was immediate after its introduction. This result still holds when adopting a more restrictive definition of treatment group, removing the OD-qualifying non-rare diseases.

4.4 Robustness checks

The DiD research design estimates the average treatment effect on the treated of the OD legislation as long as the clinical trial trends and the academic publication trends are uncorrelated with policy adoption. In order to validate the DiD estimator, it is necessary that the outcome variable trends are the same in the untreated and treated diseases in the absence of treatment (Angrist and Pischke (2008)). This subsection explores the plausibility of this key identifying assumption. As it is not possible to test this assumption in the absence of a counterfactual outcome, we can test the validity of the DiD estimator by comparing the pre-treatment trends across groups. If the trends are comparable, we can reasonably expect that they would have continued to be so in the absence of the OD policy adoption.

Figure II.3.2 illustrates the pre-trend variation in the number of clinical trials from 1997 to 2000, which seems to support the choice of the difference-in-differences research design. The same observation can be made when considering academic publications in Figure II.3.3.

We also evaluate pre-treatment trends by estimating the DiD design containing anticipatory effects (lead) denoted $\beta_{-\tau}(Post \times Rare)_{it-\tau}$, following Angrist and Pischke (2008) and Autor (2003). Since the policy was adopted in 2000, and we have data from 1997, we can compute two different anticipatory effects. Thus we will estimate the following dynamic specifications:

$$\begin{aligned} Clinical_Trials_{it} = & f(\alpha_0 + \beta_1 Post_t + \beta_2(Post \times Rare)_{it} \\ & + \sum_{\tau=1}^2 \beta_{-\tau}(Post \times Rare)_{i,t-\tau} + \psi_i + \lambda_t + \epsilon_{it}) \quad (3.6) \end{aligned}$$

$$\begin{aligned} Publications_{it} = & f(\alpha_0 + \beta_1 Post_t + \beta_2(Post \times Rare)_{it} \\ & + \sum_{\tau=1}^2 \beta_{-\tau}(Post \times Rare)_{i,t-\tau} + \psi_i + \lambda_t + \epsilon_{it}) \quad (3.7) \end{aligned}$$

Results are displayed in Table II.3.11 for clinical trials and in Table II.3.12 for publications, and suggest that there were no anticipatory effects as $\beta_{-\tau}$ are insignificant. The results are the same when adopting the two definitions of the treatment group: all treated diseases (rare diseases and rare therapeutic indications) or rare diseases only.

Finally, to take account of the fact that the treatment group is 17 times larger than the control group, we randomly select 100 rare diseases in the treatment group and replicate

the empirical analysis. Results are displayed in Table [II.3.13](#).

Model (1) shows marginal effects from the estimation of the Poisson fixed effect model to measure the impact of the OD policy on clinical trial activities. While in magnitude the coefficient is still large and somewhat comparable to previous estimates (43.41 compared to 52.67 in the whole sample), the marginal effect loses significance.

Model (2) shows marginal effects from the estimation of the logit fixed effect model to measure the impact of the OD policy on clinical trial activities' extensive margin. Results suggest an absence of impact on the probability of a disease being targeted by clinical trial activities; the marginal effect being insignificant and around 0, similar to the full sample analysis.

Finally, Model (3) shows marginal effects from the estimation of the Poisson fixed effect model to measure the impact of the OD policy on academic publications. Results are very similar to the full sample analysis: the marginal effect is significant and of magnitude 0.18 versus 0.25 in the full sample analysis.

5 Discussion

This paper studies how innovation policies impact private pharmaceutical R&D decisions. More specifically, we examined the OD legislation policy, which created supply-side incentives for pharmaceutical firms in order to foster R&D in rare disease areas.

Regarding academic publications, we observe a significant but rather low increase after policy adoption, with an increase of 0.25 academic publications per disease. The effect of the policy on academic publication was immediate, persistent during the whole period of observation, and increasing in magnitude (from 0.07 during the period 2000-2003, to 0.54 in the period 2012-2015).

Considering the clinical trials at rare disease-level, the coefficient on our DiD interaction term was found to be positive and significant, indicating a positive impact of the policy on the number of clinical trials undertaken at disease-level. The OD policy thus affected positively the number of clinical trials and increased by 52 the count of clinical trials per disease in the treatment group. Before the implementation of the policy, the cumulative number of clinical trials was 25. Therefore a jump from 25 to 52 is quite substantial, given

the overall costs of drug development. If the clinical trials in the treatment group would have progressed at the same rate as the control group on the period (i.e., in absence of the OD regulation), the clinical trials would have progressed from 25 to 557 (an increase of roughly 21%), while the cumulative number of clinical trials in the treatment group reaches 6,521 in 2015 (an increase of roughly 259%) in post-treatment period.

This is consistent with evidence from [Yin \(2008\)](#), that shows a significant increase of 69% of clinical trials for drugs treating rare diseases in the US from 1981 to 1994 after the ODA adoption in the US. Still, when investigating the impact of the policy on clinical trials' extensive margins, we observe that rare diseases or rare therapeutic indications that were not previously targeted by drug development do not experience an increase in the probability of being targeted by drug development; this tends to tone down the success of the policy given that the primary objective is to increase treatment opportunities for patients with high levels of unmet needs.

Increases in medical expertise and improved understanding of how genetics and environment interact with patients' drug response has led to segmentation of existing diseases to create niche target indications that meet the requirements of the OD policy ([Garrison Jr and Austin, 2006](#)).

Precision medicine has thus greatly developed, and the extent to which the OD has spurred R&D investments towards rare target indications versus rare diseases is an important issue given that the first objective of the OD policy is to create treatment opportunities for patients with rare diseases. Previous studies showed that biomarker trials, using diagnostic companion tests, help the pharmaceutical industry tailor the subset of patients, who experience maximum responsiveness to the drug, and thus show higher success rates to market approval than other drugs: in particular, higher success rates than orphan drugs ([Wong et al., 2019](#)). Our results show that in fact the effect of the policy was larger for the rare disease group as compared to the rare therapeutic indication group by increasing by 69 per disease (as compared to 52 in the total sample) the count of clinical trials in the rare disease group only. However the policy still spurred R&D in OD qualifying rare therapeutic indications.

Looking at the long term effects of the policy on clinical trials activities, our results suggest that the policy was effective after four years, which is arguably due to the lengthy process of clinical trial site identifications, patient recruitment, creation of the research

team, and elaboration of clinical research protocols.

We also observe that the treatment effect subsequently declined after 2010. Figure II.3.4 in the [Appendix](#) displays the number of diseases targeted each year in the treatment group, showing a large increase from 2004. We further explore the magnitude of this decrease by investigating graphically the trend in the number of clinical trials by group.

Figure II.3.2 in the [Appendix](#) illustrates the variation in the number of clinical trials between groups. We observe a large decrease from 2010 in the treatment group, not impacting the control group.

Several hypotheses may explain the large decrease in the number of clinical trials for the treatment group. First, it could be that the increasing trend in precision medicine drug development impacted the pharmaceutical investment decisions and displaced research from rare disease towards research in OD-qualifying subdivisions. However, when we take the number of clinical trials of the treatment group containing OD-qualifying (non-rare) diseases in Figure II.3.2 and II.3.3 in the chapter's [Appendix](#), we continue to observe a large decrease in the number of clinical trials.

Another explanation might be that the development of economic evaluation in response to increases in drug prices results in lower R&D investments in rare diseases, as manufacturers no longer expect to recoup R&D expenditures from relatively small target patient populations if there is uncertainty in accessing the market. Finally, it is likely that developing drugs targeting rare diseases is increasingly challenging and costly, and that the large decline of 2010 illustrates the decrease in productivity of the pharmaceutical sector, which has been shown by many research studies ([Cockburn, 2007](#); [Pammolli et al., 2011](#)).

While we cannot establish in our dataset whether these arguments play a role in the decrease in the number of clinical trials targeting rare diseases from 2010, this paper acknowledges the positive response of manufacturers to supply-side incentives fostering R&D in rare diseases areas.

Existing literature in economics has investigated the power of Orphan Drug legislation in the US to foster R&D investments in rare diseases. They discuss the potential signal that represents the existence of a special status for orphan drugs and its subsequent

impact on market valuation in the context of Initial Public Offering (IPO) in the US stock markets. They interpret the potential signal given by the orphan drug legislation and highlight how crucial it is for the pharmaceutical industry, which depends heavily on external investments in the drug development process. As discussed in the introduction, this means the process is particularly lengthy, expensive, and risky (Gorry and Useche, 2018).

Yet it remains very challenging to isolate the effects of any one specific incentive (fee waivers, market exclusivity, etc.) in the broad range of incentives offered by the Orphan Drug Act or the OD policy, given that they were all jointly implemented. Still Gorry and Useche (2018) argue that the signaling effect may play a larger role than the post-market approval market exclusivity as they observe that OD designations appear to be more important for IPO investors than patent portfolios. Still, separation of the effects of the policy would be a valuable input for policy makers to fully understand how policy mechanisms affect private decision opportunities for drug development in under-served research areas.

Regarding data limitations, it is very likely that the clinical trial registry used in this chapter is not exhaustive. Clinical trial registries were available in 1997 but at that time the registration was provided on a voluntary basis. The compulsory registration of clinical trials started from the FDA Amendment Act of 2007. The database is not exhaustive before 2007. Still, we argue that (1) a study conducted in 2012 reveals that 22% complied with the mandatory reporting (Prayle et al., 2012); (2) even if the dataset is not exhaustive, as our methodology relies on evaluation of trends between the control and the treatment group, changes in absolute numbers have no implications on the results; (3) graphically we do not observe jumps following the year 2007 (see Figure II.3.2).

We used the American clinical trial registry as it is the largest clinical trial registry available to date. Moreover, the European clinical trial registry was implemented in 2004, which is after the policy change.

It would have also been interesting to distinguish between private and public research. Orphanet does not include information on drug sponsors, and only displays the principal investigator of the clinical trials, the variable being poorly documented. Similarly, we did not collect any information on drug sponsors for the control group dataset.

Finally, while we wanted to investigate the impact of the OD policy on R&D investments allocated to rare diseases, we were unable to distinguish European publications from others as using the academic affiliations of authors is likely to be misleading.

While this work provided evidence of the large impact of innovation policy on R&D private decisions, studies using R&D costs and investigating how the OD modified firms' R&D portfolio would be valuable. Moreover, further work could investigate drug characteristics such as drug efficacy and its subsequent impact on the quality of life for patients with rare diseases in relation to the cost burden at the European level of fostering drug development.

6 Appendix

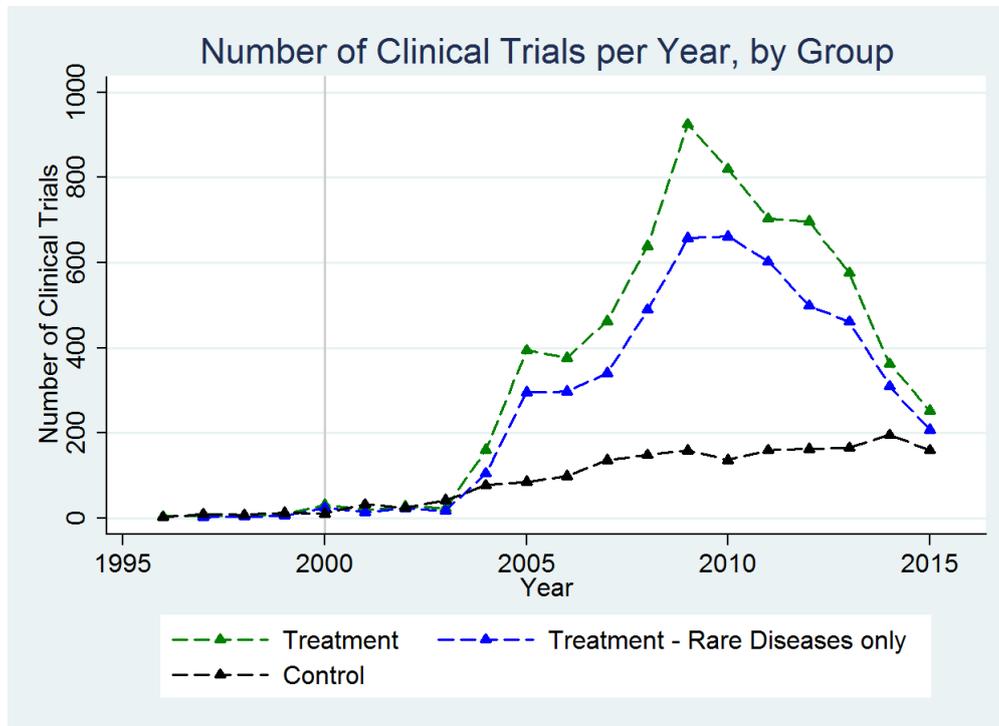


Figure II.3.2 – NUMBER OF CLINICAL TRIALS PER YEAR, 1997-2015

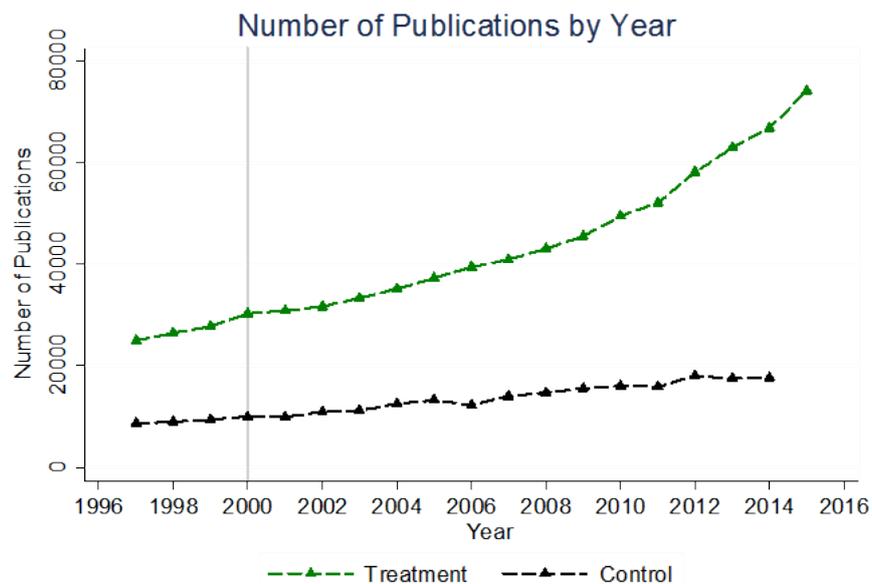


Figure II.3.3 – NUMBER OF ACADEMIC PUBLICATIONS PER YEAR, 1997-2015

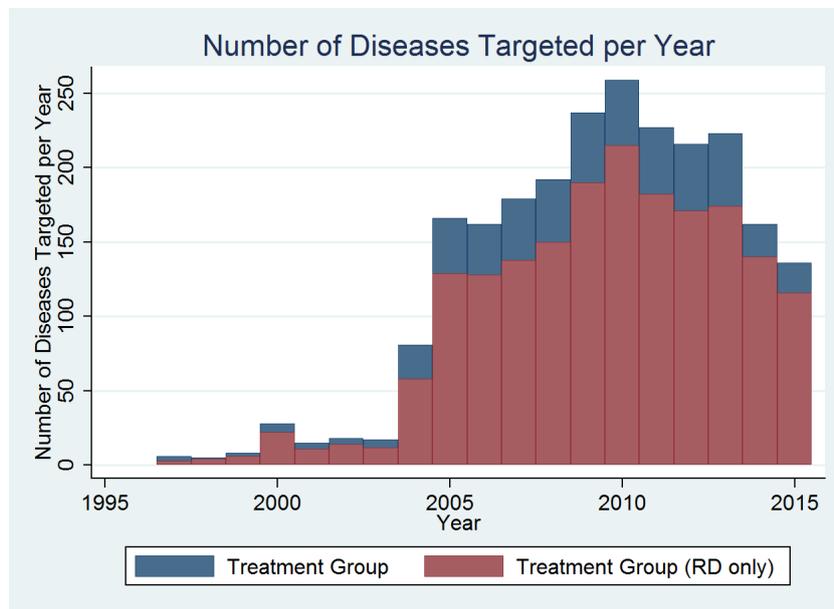


Figure II.3.4 – NUMBER OF DISEASES TARGETED BY CLINICAL TRIAL ACTIVITIES, 1997-2015

Table II.3.1 – DISTRIBUTION OF CLINICAL COUNTS, BY SUB-GROUP

Group	Mean	SD	Min	Max	Diff
<i>Before Policy Adoption</i>					
Treatment group (N=9323)	0.0006	0.03	0	2	-0.44***
Control group (N=89)	0.4400	1.28	0	10	
<i>After Policy Adoption</i>					
Treatment group (N=9323)	0.0400	0.52	0	46	-5.21***
Control group (N=89)	5.2500	9.46	0	78	

Source: Author's data.

Table legend: Statistics displayed are: (1) Mean ; (2) Standard deviation; (3) Minimum; (4) Maximum ; (5) Diff refers to the mean differences between treatment and control groups. *** $p < 0.001$ for the t-test of equality of means

Table II.3.2 – DISTRIBUTION OF ACADEMIC PUBLICATION COUNTS, BY SUB-GROUP

Group	Mean	SD	Min	Max	Diff
<i>Before Policy Adoption</i>					
Treatment group (N=7812)	11.03	64.82	0	1963	-76.15***
Control group (N=89)	87.18	400.64	0	4481	
<i>After Policy Adoption</i>					
Treatment group (N=7812)	23.95	207.86	0	51882	-127.40***
Control group (N=89)	151.35	619.57	0	6847	

Source: Author's data.

Table legend: Statistics displayed are: (1) Mean ; (2) Standard deviation; (3) Minimum; (4) Maximum ; (5) Diff refers to the mean differences between treatment and control groups. *** $p < 0.001$ for the t-test of equality of means

Table II.3.3 – MODEL (1) DISPLAYS COEFFICIENTS FOR A CONDITIONAL FIXED EFFECT POISSON MODEL FOR THE FULL TREATMENT GROUP AND MODEL (2) DISPLAYS COEFFICIENTS FOR A CONDITIONAL FIXED EFFECT POISSON MODEL FOR TREATMENT GROUP = RARE DISEASES, ONLY

	(Model 1)	(Model 2)
Policy	2.22*** (7.15)	2.36*** (12.45)
Treated#Policy	1.72*** (5.05)	1.89*** (5.44)
Time FE	YES	YES
Disease FE	YES	YES
Observations	16074	12901

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.4 – AVERAGE DID EFFECT FOR POISSON MODELS

	(Mar. Eff.)	(SE)	(Unadjusted 95% Conf. Interval)
MODEL (1)	51.67***	20.52	[11.46; 91.88]
MODEL (2)	69.01***	30.82	[8.59; 129.44]

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.5 – MODEL (1) DISPLAYS COEFFICIENTS FOR A FIXED EFFECT LOGIT MODEL FOR THE FULL TREATMENT GROUP AND MODEL (2) DISPLAYS COEFFICIENTS FOR A CONDITIONAL FIXED EFFECT LOGIT MODEL FOR TREATMENT GROUP = RARE DISEASES, ONLY

	(Model 1)	(Model 2)
Policy	36.75*** (7.96)	48.39*** (7.97)
Treated#Policy	1.63 (1.15)	1.86 (1.36)
Time FE	YES	YES
Disease FE	YES	YES
Observations	16074	12901

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.6 – AVERAGE DiD EFFECT FOR LOGIT MODELS

	(Mar. Eff.)	(SE)	(Unadjusted 95% Conf. Interval)
MODEL (1)	0.03	0.02	[−0.01; 0.06]
MODEL (2)	0.02	0.02	[−0.02; 0.07]

t statistics in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.7 – MODEL (3) DISPLAYS COEFFICIENTS FOR A CONDITIONAL FIXED EFFECT POISSON MODEL WITH TIME VARYING EFFECTS OF POLICY ADOPTION

	(Model 1)	(Model 2)
Policy (from 2000 to 2003)	1.27*** (3.84)	1.35*** (3.95)
Policy (from 2004 to 2007)	2.62*** (9.20)	2.67*** (8.70)
Policy (from 2008 to 2010)	2.68*** (8.86)	2.82*** (8.68)
Policy (from 2011)	2.42*** (7.54)	2.54*** (7.42)
treated#policy (from 2000 to 2003)	.36 (1.00)	.54 (1.36)
treated#policy (from 2004 to 2007)	1.69 (5.12)	1.82 (5.01)
treated#policy (from 2008 to 2010)	2.06 (6.04)	2.25 (5.99)
treated#policy (from 2011)	1.45 (4.06)	1.64 (4.21)
Time FE	Yes	Yes
Disease FE	Yes	Yes
Observations	16074	12901

t statistics in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.8 – MODEL (1) DISPLAYS COEFFICIENTS FOR A FIXED EFFECT POISSON MODEL FOR THE FULL TREATMENT GROUP AND MODEL (2) DISPLAYS COEFFICIENTS FOR A CONDITIONAL FIXED EFFECT LOGIT MODEL FOR TREATMENT GROUP = RARE DISEASES, ONLY

	(Model 1)	(Model 2)
Policy	1.07*** (7.29)	1.13*** (7.97)
Treated#Policy	0.25*** (4.47)	0.28*** (4.52)
Time FE	YES	YES
Disease FE	YES	YES
Observations	129428	106039

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.9 – AVERAGE DiD EFFECT FOR THE POISSON MODELS

	(Mar. Eff.)	(SE)	(Unadjusted 95% Conf. Interval)
MODEL (1)	0.25	0.06	[0.14; 0.37]
MODEL (2)	0.29	0.06	[0.16; 0.41]

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.10 – MODEL (3) DISPLAYS COEFFICIENTS FOR A CONDITIONAL FIXED EFFECT POISSON MODEL WITH TIME VARYING EFFECTS OF POLICY ADOPTION

	(Model 1)	(Model 2)
Policy (from 2000 to 2003)	0.27*** (11.86)	0.26*** (12.13)
Policy (from 2004 to 2007)	0.45*** (12.90)	0.44*** (13.34)
Policy (from 2008 to 2010)	0.62*** (9.57)	0.61*** (9.63)
Policy (from 2011)	0.88*** (5.92)	0.85*** (6.67)
treated#policy (from 2000 to 2003)	0.07*** (3.03)	0.06*** (2.77)
treated#policy (from 2004 to 2007)	0.13*** (3.57)	0.11*** (3.34)
treated#policy (from 2008 to 2010)	0.22*** (3.26)	0.20*** (3.03)
treated#policy (from 2011)	0.54*** (4.59)	0.49*** (4.78)
Time FE	Yes	Yes
Disease FE	Yes	Yes
Observations	129428	106039

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.11 – DISPLAYS COEFFICIENTS FOR A CONDITIONAL FIXED EFFECT POISSON MODEL FOR YEARS BEFORE AND AFTER THE POLICY ADOPTION. OUTCOME = CLINICAL TRIALS

	(Model 1)	(Model 2)
Policy	2.42*** (6.44)	2.46*** (6.54)
treated#policy (after policy adoption)	1.76*** (3.39)	1.90*** (3.45)
treated#policy (one year before)	0.10 (0.14)	-0.08 (-0.10)
treated#policy (two year before)	0.04 (0.05)	0.51 (0.57)
Time FE	Yes	Yes
Disease FE	Yes	Yes
Observations	122 043	99 993

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.12 – DISPLAYS COEFFICIENTS FOR A CONDITIONAL FIXED EFFECT POISSON MODEL FOR YEARS BEFORE AND AFTER THE POLICY ADOPTION. OUTCOME = ACADEMIC PUBLICATIONS

	(Model 1)	(Model 2)
Policy	0.57*** (6.30)	.46*** (6.54)
treated#policy (after policy adoption)	0.16*** (3.39)	0.18*** (4.51)
treated#policy (one year before)	0.05 (0.14)	0.06 (1.64)
treated#policy (two year before)	0.02 (0.56)	0.02 (0.66)
Time FE	Yes	Yes
Disease FE	Yes	Yes
Observations	13855	11118

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table II.3.13 – AVERAGE DiD EFFECT ON SUB-SAMPLES

	(Mar. Eff.)	(SE)	($P > z $)
MODEL (1)	43.41	26.40	0.21
MODEL (2)	0.04	0.06	0.55
MODEL (3)	0.18***	0.13	0.01

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: Models (1), (2), and (3) display the marginal effects along with their standard error (SE) and p-value ($P > |z|$) of estimations on a sample composed of the full control group and a random selection of 100 rare diseases. Model (1) shows marginal effects from the estimation of the Poisson fixed effect model to measure the impact of the OD policy on clinical trial activities. Model (2) shows marginal effects from the estimation of the logit fixed effect model to measure the impact of the OD policy on clinical trial activities extensive margin. Model (3) shows marginal effects from the estimation of the Poisson fixed effect model to measure the impact of the OD policy on academic publications.

Chapter 4

(In)equality in the Allocation of R&D Resources for Rare Diseases

1 Introduction

A disease is characterized as rare if it affects fewer than 1 in 2,000 citizens, which in the European Union represents 250,000 or fewer patients (Drummond and Towse, 2014). There are over 7,000 recognized rare diseases —80% of which are genetic —with a total of 350 million people affected worldwide, therefore patients with rare diseases are not actually very rare when considered collectively (Giannuzzi et al., 2017a). Yet the diagnosis of rare diseases may be very challenging, and often the causes and features of rare diseases remain elusive. The course of the disease is often unpredictable, and most of the recognised rare diseases are debilitating and/or life threatening (Field and Boat, 2010).

Rare diseases can affect anyone, at any age, and are associated with significant health needs (Schieppati et al., 2008). Patients with rare diseases generally face poor health statuses not only because of the disease itself, but also because their health care pathway to accessing appropriate diagnosis and treatment for their condition can be lengthy and complicated. The costs of drug development to target rare diseases are particularly high as industries have difficulties in recruiting patients in clinical trials (Gericke et al., 2005). Pharmaceutical industries consider R&D investments in rare diseases too costly and risky given the low expected returns due to the small population involved. Consequently, patients with rare diseases are underserved by drug development.

The pharmaceutical sector is a highly regulated sector, from the very first step of translational research to the market authorization of the drug and marketing (Scott Morton and Kyle, 2011). While pharmaceutical firms naturally pursue a revenue maximization exercise, the regulator is in a position to endorse ethical considerations and impact the allocation of R&D investment by increasing firms' profitability in underserved research areas. Despite governmental initiatives providing incentives for pharmaceutical firms to invest in rare diseases, such as the the European Union Orphan Drug regulation enacted in 2000,¹ it is estimated by the National Center for Advancing Translational Sciences² that in 2018 95% of rare diseases still did not have treatment options.

Given that disparities in investment decisions are likely to determine patients' access to treatments, the allocation of R&D resources can be a determinant of inequalities in access

¹Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p.1), last amended by Regulation (EC) No 596/2009 (OJ L 188, 18.07.2009, p. 14)

²See: <https://ncats.nih.gov/>

to care in the whole population ([Williams and Cookson, 2000](#)). The regulation schemes in pharmaceutical markets directly impact the distribution of R&D investments across diseases in need of appropriate treatment, and indirectly impact treatment and care opportunities, which ultimately affect the health status of patients with rare diseases. Several studies conducted on the relationship between pharmaceutical innovations and mortality suggest that the launching of a new drug decreases mortality in various contexts and therapeutic areas ([Cookson and Dolan, 2000](#); [Hughes et al., 2005b](#); [?](#); [Temkin, 2003](#)). The regulation schemes in pharmaceutical markets directly impact a fairer distribution of R&D investments across diseases in need of appropriate treatment, and indirectly impact treatment and care opportunities —and ultimately the health status of patients with rare diseases. Moreover, several studies that were conducted on the relationship between pharmaceutical innovations and mortality suggest that the launch of new drugs decreases mortality in various contexts and therapeutic areas ([Lichtenberg and Virabhak, 2002](#); [Lichtenberg and Waldfogel, 2003](#); [Lichtenberg, 2014b,a, 2018a](#)).

There have been considerable discussions in the philosophical and political economy literature regarding the role of the welfare state in promoting efficiency and equity in the provision of certain goods and services ([Cookson and Dolan, 2000](#); [Hughes et al., 2005a](#); [?](#); [Temkin, 2003](#)). Most decisions about the reimbursement of health care interventions are based on their comparative cost-effectiveness, in which the benefits from a treatment are valued along with its costs ([Anell, 2004](#)). Since drugs for rare diseases are often expensive, only benefit a small number of patients, and therefore are unlikely to be found to be cost-effective, the question of how many resources should be invested in R&D, especially for rare diseases, is a moral dilemma for policy makers ([McCabe et al., 2005](#); [Paulden et al., 2014](#)).

In this context, the social justice literature can offer a pertinent framework to discuss the objectives and the equity principles in the allocation of resources within health care systems. Since the allocation of pharmaceutical R&D resources is a major concern for policy makers, social justice theory will be relevant when policy makers formulate preferences and choices when promoting the health of patients with rare diseases. However in this paper we do not have access to data on the health care access or health status of patients with rare diseases, so we therefore consider diseases as being the observations of importance and use data on R&D investments for rare diseases. Policy makers explicitly endorse specific considerations with a safeguarding of the R&D of orphan drugs via, for example, the European Union Orphan Drug regulation in 2000.

However, the characteristics of the rare diseases that are prioritised by R&D are not disclosed. Here, we therefore aim to uncover which of the disease characteristics appear to encourage R&D within rare diseases. We assess whether there are disparities in the distributions of R&D investments within rare diseases, categorizing them according to several characteristics. We firstly consider them individually, and then in combination with the population size to benefit.

The objectives are twofold. First, to investigate whether the distributions are equal within the allocation of R&D resources in rare diseases using cumulative distribution functions and stochastic dominance tests. Second, to identify the characteristics of rare diseases that appear to lead R&D investments. R&D investments are successively measured using five alternative proxies: the number of clinical trials per rare disease, the number of research projects per rare disease, the number of approved drugs with marketing authorization at the European level, the number of orphan drug designations, and the number of published articles per rare disease on bibliographic databases. We appraise rare disease characteristics with the Orphanet data using condition-specific mean age at death, mean age at first onset, disease prevalence, along with two constructed binary characteristics, which inform the uncertainty on the disease evolution and the likelihood of an immediate danger of death.

Our results suggest that R&D investments underserve rare diseases that occur in infancy and that affect a smaller number of patients; this is observed for most of our R&D proxies. R&D investments are concentrated in more profitable markets in rare diseases in which there is a higher chance of finding patients able to join a clinical trial, thereby lowering the R&D costs. The other characteristics that appear to lead R&D resource allocation for rare diseases include an older mean age at symptom appearance, a larger market size, a lower level of uncertainty regarding the disease presentation and progression, and a non-immediate danger of death.

The paper is structured as follows: Section 1 presents the conceptual framework, Section 2 introduces the data, and Section 3 the method. Section 4 presents the empirical application on rare diseases. Discussion and concluding remarks are provided in Section 5.

2 A Conceptual Framework to Study the Distribution of R&D Investments for Rare Diseases

2.1 The Appraisal of Health Care Treatments: From a Reference Case ...

Cost-effectiveness plays a key role in reimbursement decisions for new innovative therapies in most countries because resources are scarce and choices must be made. Economic evaluation is used to guide choices by assessing the cost and the health benefits, which are usually measured as QALY.

QALY is a generic outcome summarizing both quality of life and survival. Quality of life is built based on an assessment of multiple dimensions of a health state and with utility weights assigned to each possible health state; these utility weights represent the value given by society to one health state relative to another. The use of a QALY allows evaluating not only whether the treatment extends survival but also the quality of life associated with those life years gained, which will be particularly relevant for treatments that extend life at the expense of negative side effects.

Many countries claim to use a cost-effectiveness criterion in their decision-making process expressed as a cost-per-QALY threshold below which a new treatment is considered to be cost-effective and above which it is not considered to be cost-effective ([Stafinski et al., 2011](#)). In other words, treatments costing less than this explicit threshold per unit of QALY gained are considered to be a cost-effective use of a limited health care budget, while treatments costing more than the threshold are found to be too expensive for the expected health gain. Decision-makers make health care decisions across a broad set of treatments for various health conditions, and their ability to measure health gains using the same unique output that are QALYs ensures fair and comparable decision-making. This means that a QALY is a QALY and there is anonymity towards who gets an extra QALY. As such, QALY is egalitarian. QALYs are considered equal regardless of the patient or contextual factors concerned; this includes age, baseline health, socioeconomic status, activity status, disability or severity of disease.

Health care decisions are guided by a maximization principle ([Bentham, 2004](#)) according to which policy makers should aim at maximizing the total sum of health within the population. Hence, particular attention should be given to the capacity to benefit from

public resources. No extra weight is given to any particular patient group, whatever the level of their health needs and the severity of the disease.

2.2 The Appraisal of Health Care Treatments: ... to a Special Case

While in theory egalitarian principles guide decision-making, policy makers sometimes distance themselves from the reference framework of health care technology assessments and can mitigate or soften the use of the threshold, especially when it concerns rare diseases. For example, decision-makers may consider disease characteristics, such as the burden of illness and the severity of the condition, as well as the population size to benefit from the treatment, within their reimbursement decisions in health care (Thébaud and Wittwer, 2017; Lichtenberg, 2001a). Recent amendments at the National Institute for Clinical Excellence in the UK adopted a threshold ten times higher than the normal limit when appraising treatments for very rare diseases suggesting that the greater the QALY gain, the more generous the threshold used when appraising such treatments³ (Paulden, 2017).

Granting a special status to rare diseases, and especially orphan drugs, is supported by the WHO which recommends prioritising “those with the greatest need,” even in settings in which resources are substantially constrained. Similarly, the consideration of patients with needs for highly specialized treatments is emphasised in the European Commission (EC), which explicitly mentions the right of patients with a rare disease to be entitled to the same quality of treatment as any other patient. Such views on fairness are relevant to prioritarian principles (Michael, 2013; Temkin, 2003), which give emphasis to health needs; these principles stipulate that the most severely ill categories of patients should receive priority according to the “Rule of Rescue” (McKie and Richardson, 2003) and regardless of their capacity to benefit from public funding.

While those principles are likely to guide decision-makers, they shall be considered in conjunction with the trade-offs decision-makers inevitably have to make between the advantages and disadvantages of each health care decision. The use of public resources needs to be justified to the general public and taxpayers while including equitable considerations. A higher cost-effectiveness threshold for some health care treatments on the rationale of burden of illness and wider societal impact violates “a key principle of

³See <https://www.nice.org.uk/news/feature/changes-to-nice-drug-appraisals-what-you-need-to-know>.

procedural justice by not giving these patients the same ‘voice’ in (the) decision-making processes as that afforded to the identifiable beneficiaries of new technologies,” as (Paulden, 2017) underlines.

This relates to the consideration that the health gain of one individual with a rare disease could be valued differently than the health gain of an individual with a common disease. There are a number of elements to support such a statement of valuing the health gains differently because of specific individual characteristics. For example, interviews conducted on the general population regarding priority setting in the allocation of public resources suggest that society expresses preferences for the distribution of public resources in favour of deprived categories of patients. This is true regardless of the opportunity cost in health care provision and the fact that priority setting may divert resources away from other categories of patients (Brazier et al., 2013; Rogge and Kittel, 2016).

In particular, it appears that people mostly agree that priority should be given to the young over the old, as suggested in the ethical arguments defended by fair innings considerations (Williams, 1997a,b). According to the fair innings argument, a patient’s age could be an accepted criterion for priority setting under the assumptions that every individual is entitled to live for a reasonable length of life. With that in mind, health care resources should be distributed to ensure that each individual has the opportunity to live a reasonable number of life years. The fair innings argument could also be interpreted as an efficiency argument since a treatment targeting younger people is likely to provide a longer benefit duration as younger patients comparatively have more years to live than older patients (Mossialos and King, 1999). Similarly, Aghion et al. (2010) argued that gains in life expectancy at a young age and during active life (i.e., before the age of 40) matter more for economic growth than gains in life expectancy at an older age because better health at a young age has long-term consequences in terms of worker productivity.

2.3 Which Criteria Guide the Distribution of R&D Investments for Rare Diseases?

As was mentioned earlier, in this paper we do not focus on patients with rare diseases but we consider diseases as being the observations of importance. We can, however, transpose the fair innings argument and the priority given to “younger patients” to the distribution of R&D investment for rare diseases if we assume that the level of R&D is likely to impact future health attainments. It would consist of favoring R&D investments

in rare diseases with an average age of symptom onsets and/or an average at death within infancy, childhood, or young adulthood.

Despite policy makers appearing to explicitly endorse ethical considerations in the decision-making process and institutions like the WHO or the European Commission expressing recommendations as to which patients to prioritize, neither organization discloses *ex ante* where the investments for orphan drugs should be encouraged. However, we can analyze the distribution of R&D investments across rare diseases *ex post* and investigate whether R&D investments for rare diseases that are related to the younger population dominate other patient populations.

We propose here to analyze the distribution of R&D investment across rare diseases. We study whether there is equality in R&D investment within rare disease areas according to specific characteristics of rare diseases. We do not argue that our empirical investigation will provide estimates of the magnitude of inequalities in R&D investments for patients with rare diseases, nor provide a comprehensive set of the determinants of inter-individual differences in R&D investment across rare diseases. Our analysis is meant to identify the subgroups of rare diseases, which appear to be underserved by R&D and which could be targeted by policy makers in search of more equitable distribution of R&D investments across rare diseases introducing, for example, a principle of compensation from a disadvantaged natural lottery.

3 Data

We investigate the inequity in the allocation of R&D resources using data from Orphanet, which is the reference portal providing information about orphan drugs and rare diseases. Orphanet was established in France by the INSERM in 1997. This initiative then became European in 2000, and gradually grew to a consortium of 40 countries within Europe and across the globe⁴. The Orphanet dataset comprises data of all rare diseases, granting them a unique Orphanet identification number to facilitate sharing information on each disease.

3.1 R&D Resource Outcome Measures

Orphanet provides us with four different outcome variables that can be used to proxy the R&D resources allocated to each of the rare diseases at the European level. We first use

⁴See: <https://www.orpha.net/consor/cgi-bin/index.php>.

an inventory of clinical trial activities targeting rare diseases. Clinical activities include interventional studies treating or preventing a rare disease using drugs, or a combination of drugs and biological products. Second, we use the list of research projects targeting each rare disease. Research projects are projects that have been selected through a competitive process established by a scientific committee, or issued from a national research funding. Clinical trial activities and research projects include both single-center and national and international multicenter research projects at the European level. Third, Orphanet provides us with the number of orphan drug designations that qualify for the financial incentives provided by the EU Orphan Drug legislation. Finally, we consider the number of drugs with marketing authorization at the European level per rare disease (we refer to them as orphan drugs).

The four outcome proxies for R&D investments are completed with an outcome of published research on rare diseases, which is measured by the number of scientific publications per disease. We accessed MEDLINE using the PubMed search engine in July 2017 from its inception date to present using the MEDGEN unique identifier of the 8,755 diseases classified as rare diseases. We then counted the number of scientific publications for each rare diseases. MEDLINE is the largest database of academic references on life sciences and biomedical topics, and our search was based on an algorithm coded in Python.

Table II.4.1 displays the descriptive statistics of the R&D resource outcome measures. There is a total of 9,220 rare diseases, and most of them attract almost no R&D resources. The mean number of research projects, clinical trials, orphan designation, and orphan drugs appears to be very low, ranging from 0.12 and 0.72, the median being 0 for each of the outcomes. The third quartile is equal to zero for research projects, clinical trials, orphan designation and orphan drugs, suggesting the absence of any investment for the vast majority of rare diseases. The number of academic publications captures the knowledge currently built on each rare disease; this includes, for example, the natural history of the disease, information on diagnostic criteria and the impact of the disease on quality of life and health status. The mean number of academic publications per rare disease is approximately 578 (median = 85), while the maximum reached for one of the rare diseases is 177,430 articles.

We present in Table II.4.2 the linear correlation coefficient between all the R&D resource outcome measures. Correlations range from 0.16 to 0.69; this suggests that R&D resource outcome measures capture different aspects of R&D but are positively correlated. In

particular, some R&D resources represent investments corresponding to different phases of drug development, which are related. For example, the number of clinical trials is correlated with the number of orphan drugs with a linear correlation coefficient equal to 0.63. This is explained by clinical trial activities being a prerequisite for market approval.

3.2 Rare Disease Characteristics

Rare disease characteristics were provided by the Orphanet dataset and include the following variables: the average age at first symptom appearance, the average age at death, and the prevalence of the disease in the population.

The average age at symptom appearance for each disease was not provided as a single age but as a category among a choice of four: *Infancy*, *Childhood*, *Adults & Elderly*, and *All ages*. The prevalence of each rare disease in the population was sometimes provided as a value (25%) but most of the time provided as an interval (75%); the latter mainly happens because of the uncertainty surrounding the number of patients with the condition is high. We homogenized the values and intervals using interval overlaps and the mid-point of each interval to construct a discrete variable of prevalence in four categories: < 1 over 1,000,000; 1–9 over 1,000,000; 1–9 over 100,000; 1–9 over 10,000. We then created two binary variables using the same data. First, we created a dummy variable representing an *immediate danger of death* equal to one when the age of first symptom appearance equals the average age of death category. Second, we constructed a dummy variable measuring the *uncertainty on disease evolution* equal to one if the age of symptom appearance and/or the mean age at death is classified as unpredictable.

Table II.4.3 presents the distribution of the average *age at symptom onset* in categories. While one-third of the diseases have an average age in Childhood and another third in the Adults & Elderly age range, one in four diseases have an average age at symptoms onset in Infancy or in All ages. Therefore, rare diseases may appear at any point in life. On the contrary, the average age at death shows great discrepancies in distribution across the age groups as displayed in Table II.4.4. Almost half of the rare diseases are characterised with an average age at death that is unpredictable (All ages), and only 22% of the rare diseases are given a normal life expectancy.

Figure II.4.1 displays the frequency distribution for the prevalence variable and suggests that rare disease prevalence is highly skewed towards 0. For 77% of rare diseases in the

sample, the prevalence is under one case for 1,000,000 individuals. This suggests that rare diseases are mainly ultra-rare (Table II.4.5).

We investigate the relationships between all the rare disease characteristics using the Cramer's V^5 statistic. The age of symptom onset is by construction related to the mean age at death in the sense that the patient cannot be at risk of death before symptom onset, and so the Cramer's V is 0.46. The relationships are weaker between the other variables: the association between the mean age at death and the prevalence is 0.19, while it is 0.24 for the prevalence and the age at symptom onset.

All disease characteristics were not always available for each rare disease in the Orphanet dataset. We studied more specifically the attrition in the dataset. The shared missing pattern for all variables is visually described in Figure II.4.2. All the R&D investment variables (research projects, clinical trials, orphan designation, and orphan drugs) for the 9,220 rare diseases are non-missing since they are directly provided in Orphanet, and the count is equal to zero in the absence of R&D investments.

The search for academic publications provided us with 95% of correspondence between the Orphanet identification number and the MEDGEN unique identifier. These 5% missing values are shared with all the rare disease characteristics. Regarding the rare diseases characteristics, the average age at symptom appearance and average age of death share most of their missing values, while prevalence is the rare disease characteristic with the lowest level of missing values. We further investigated missing values by comparing the average number of our R&D resources outcome measures for missing values versus non-missing values. Results are reported in Table II.4.6 and suggest that when some diseases characteristics have missing values, the distribution of the R&D proxy outcomes among the missing data usually have a significantly lower average. Most of the rare disease characteristics share the same missing values.

⁵The Cramer's V statistic indicates how strongly two categorical variables are associated with one another (Sheskin, 2003). The statistic ranges from 0 and 1, the maximum value indicating a perfect relationship.

4 Methods

We are especially interested in the share of R&D investment devoted to rare diseases and how it is distributed across rare diseases.

We detect inequalities when comparing Cumulative Distribution Functions (CDF) of the R&D investments devoted to rare diseases conditioned on a set of variables representing disease characteristics. Our approach loosely follows [Lefranc et al. \(2009a\)](#) and [Lefranc and Trannoy \(2016\)](#), and the disease characteristics are similar to so-called “circumstances” according to [Roemer \(1998\)](#).

Let us consider two distributions A and B with respective cumulative distribution functions $F_A(y)$ and $F_B(y)$. A dominates at first order B, written $A \leq_{FSD} B$ if and only if $F_A(y_j) \leq_{FSD} F_B(y_j)$, where y_i represents one of the five proxies of R&D investment provided as a discrete outcome such as $y_j = \{y_1, y_2, \dots, y_k\}$.

It means that R&D investments are higher in distribution A than in distribution B, and this is true at all points in the distribution. Graphically, the cumulative distribution function of R&D investment of the subgroup of rare diseases in B is always above that of rare diseases in A, at any point in the distribution.

For example, let us consider the CDF of the number of academic publications on rare diseases with an average age of symptom onset classified in *Adult & Elderly*. If, on the one hand, this CDF is clearly different from the CDF of the number of academic publications in rare diseases with an average age of symptom onset classified in *Infancy* and if, on the other hand, the difference is such that a rare disease has a higher chance of being researched when the average age at symptom onset is classified in *Adult & Elderly*, we can conclude that there is an inequality in R&D investments. Rare diseases with an older average age at symptom onset are favored in comparison with rare diseases with an average age at symptom onset classified in *Infancy*.

We compare the cumulative distribution functions of each of the five proxies for R&D investments. The five proxy variables are: (1) the number of research projects, (2) the number of academic publications, (3) the number of clinical trials, (4) the number of orphan designations, and (5) the number of orphan drugs with marketing authorization across age classes of the disease symptoms. These variables are inherently discrete.

Empirically, the inference procedure relies on tests of stochastic dominance at first order, such as unilateral Kolmogorov-Smirnov (KS) tests of equality of distribution, which are appropriate with discrete variables. For each characteristic, we test the null hypothesis of equality of the distributions in pairs. Then, we test the null hypothesis of first-order stochastic dominance of the distribution of A over B, and the distribution B over A. If the test accepts dominance of one distribution over the other but not the other way round ((e.g., $F_A(y_i) \leq_{FSD} F_B(y_i)$, and $F_B(y_i) \not\leq_{FSD} F_A(y_i)$)), we consider that the equality of the distributions is violated.

The same approach can be proposed when comparing subgroups of rare diseases according to any characteristic such as the average age of symptom appearance, average age at death, prevalence, and two binary characteristics on uncertainty of disease evolution and immediate danger of death.

It is important to emphasize that this approach remains relevant even when all disease characteristics are not observed or cannot be combined. According to [Lefranc et al. \(2009a\)](#) and [Lefranc et al. \(2009b\)](#), equality of distributions conditional on “circumstances” (here, disease characteristics), is a necessary condition even if disease characteristics are not fully described. As a result, if the KS test shows significant differences between CDFs, then we can say that the equality of distributions is violated if we had the opportunity to perfectly measure all the disease characteristics. This provides a rationale for first performing the nonparametric test separately on the CDF conditional on each disease characteristic individually, which is helpful because of the relatively small size of the sample.

We then considered combining several rare disease characteristics together in order to generate a set of disease characteristics; however, this was only possible with the prevalence level. We weighted the rare diseases according to their frequency in the population of patients with rare diseases along with each of the other disease characteristics. To do so, we used frequency weights based on the prevalence point estimates, when available and prevalence in class, so that we maximised accuracy. When prevalence was available in class, we used the mean prevalence of the class. The weight was based on a normalized prevalence variable $prev_i$ scaled between 0 and 1 using the ratio $\frac{prev_i - prev_{min}}{prev_{max} - prev_{min}}$.

5 Results

5.1 Non-Parametric Tests on Each Disease Characteristic

We compare the distributions of R&D investments as measured by five alternative proxies according to different rare disease characteristics and use the significance level of the differences between distributions using Kolmogorov–Smirnov (KS) tests to verify the existence of stochastic dominance.

Average age at symptoms appearance

Results comparing the distribution of the five different proxies of R&D investments for rare diseases according to the four categories of age at symptoms appearance are presented in Table II.4.7. They suggest that the distribution of all proxies of R&D investment targeting rare diseases occurring during *Infancy* is dominated by the distribution of any R&D investment of rare diseases with an average age of symptom onset classified in *All Ages* and in *Adult & Elderly*. All five proxies of R&D investment appear to favor rare diseases in older age groups. When rare diseases in *Infancy* are compared with rare diseases in *Childhood*, the distributions of the number of research projects, clinical trials, and academic publications all favor rare diseases in *Childhood* (p values 0.006, 0.012, 0.061, respectively); however, we cannot conclude on dominance when comparing the distribution of the number of orphan designations and the distribution of number of orphan drugs with marketing authorization (p values 0.234, 0.701, respectively).

The distribution of most of the R&D proxies for rare diseases in *Childhood* and *Infancy* is dominated by the distributions for rare diseases in *Adult & Elderly* and *All ages*, except for the distribution of the number of research projects with *All ages* where the Kolmogorov–Smirnov test is inconclusive (p value = 0.696). When considering *Adult & Elderly* versus *All ages*, we find that for the distribution of two of the R&D outcomes (the number of research projects and academic publications) in *Adult & Elderly* dominate the distribution in *All ages*, and the distribution of clinical trials in *All ages* dominates the one in category *Adult & Elderly*. The KS tests remain inconclusive for the number of orphan designations and of orphan drugs (p value 0.771 and 0.990, respectively).

Average age at death

Results for the paired KS tests comparing the distribution of R&D investments for rare diseases over the five categories of the average age at death are presented in Table II.4.8. They suggest that the distributions of R&D investments targeting dis-

eases with an average age at death in *Infancy* are dominated by the distributions of R&D investments for higher categories of average age at death (*Adult & Elderly*, *All ages*, *Normal Life Expectancy*). This result holds for all R&D proxies, except for the distribution of the number of orphan drugs (p values 0.272, 0.417, 0.184, respectively).

When rare diseases in *Infancy* are compared to rare diseases in *Childhood*, the distribution of the number of academic publications is in favor of diseases with mean age at death in *Childhood* (p value = 0.036). The dominance tests are inconclusive when we compare the distributions of the number of research projects, clinical trials, orphan designation,s and orphan drugs with marketing authorization (p values 0.136, 0.742, 0.832, 1.000, respectively). When considering rare diseases with an average age at death in *Childhood* versus rare diseases in *Adult & Elderly* or in *Normal Life Expectancy*, the distributions of all R&D investments, except the number of orphan drugs for the category *Adult & Elderly* (p value = 0.156), favor diseases in categories *Adult & Elderly* and *Normal Life Expectancy*. When considering rare diseases with an average age at death in *Childhood* versus *All Ages*, the distribution of academic research favors the category *All Ages* (p value = 0.065). We cannot conclude on dominance for the distribution of the number of research projects, clinical trials, orphan designations, and orphan drugs.

When considering rare diseases with an average age at death in *Adults & Elderly* versus those in *All Ages*, results suggest that the distributions of most proxies of R&D for the category *Adults & Elderly* dominate the distributions of R&D for rare diseases with an unpredictable mean age of death. However, the test cannot make any conclusions regarding dominance between *Adults & Elderly* versus *All Ages* in the distribution of the number of orphan drugs (p = 0.136).

When considering rare diseases with an average age at death in *Adults & Elderly* versus those with *Normal Life Expectancy*, results suggest that the distributions of clinical trials for the category *Adults & Elderly* dominate the distributions of R&D for rare diseases with *Normal Life Expectancy*.

When considering rare diseases with an average age at death in *All Ages* versus those with *Normal Life Expectancy*, results suggest that the distributions of all proxies for R&D for rare diseases with *Normal Life Expectancy* dominate the distributions of R&D for diseases in the category *All Ages*.

Prevalence in the population

Results for the two-tailed KS tests comparing the distribution of R&D investments for rare diseases over the four prevalence categories are presented in Table II.4.9. They suggest that the distributions of most proxies of R&D targeting diseases in higher prevalence categories dominate the distributions of R&D investments of diseases in lower prevalence categories. When considering rare diseases with a prevalence $< 1,000,000$ versus rare diseases in higher prevalence categories, all distributions of R&D investments favor diseases in higher prevalence categories (p value = 0.000 in all cases).

When considering rare diseases with a prevalence 1–9 over 1,000,000 versus rare diseases in higher prevalence categories, the distributions of academic research and clinical trial activities favor diseases in higher prevalence categories. When considering rare diseases with a prevalence 1–9 over 1,000,000 versus rare diseases in 1–9 over 10,000, the distributions of orphan designations favor diseases in 1–9 over 10,000. We cannot make conclusions on dominance when we compare the distributions of the number of research projects, orphan designations, and orphan drugs (research projects and orphan designations, respectively) for rare diseases with a prevalence 1–9 over 1,000,000 versus 1–9 over 100,000 (respectively, 1–9 over 10,000).

When considering rare diseases with a prevalence 1–9 over 10,000 versus rare diseases with a prevalence of 1–9 over 100,000, the distributions of academic research, clinical trials, and orphan designations favor diseases in the higher prevalence category. The KS tests remain inconclusive for the number of research projects and of orphan drugs (p value 0.296 and 0.263, respectively).

Immediate danger of death

We now partition rare diseases between those with an immediate danger of death versus the other rare diseases by combining the average age at symptom onset and the mean age at death. We compare the distribution of the five proxies of R&D investment for those two groups of rare diseases.

Results are presented in Table II.4.10. They suggest that the distributions of R&D investment targeting diseases with an immediate danger of death are dominated by the distributions of R&D investment of diseases with non-immediate danger of death across most proxies of R&D investment, except for the distribution of the number of research projects and orphan drugs where the test is inconclusive (p value 0.886, 0.121, respectively).

Uncertainty on Disease Evolution

We now compare rare diseases according to whether there is uncertainty surrounding their evolution. We consider diseases for which both the average age at symptom onset and the average age at death are classified in the *All Ages* category in the dataset to be uncertain. The binary comparisons presented in Table II.4.11 show that the distributions of two proxies of R&D investment (academic research and orphan designations) of diseases with uncertainty on disease evolution are dominated by the distributions of the R&D investment of diseases with lower uncertainty (p values 0.006 and 0.001, respectively). The KS tests remain inconclusive for the distribution of the number of research projects, clinical trials, and orphan drugs.

5.2 Non-Parametric Tests on Characteristics of Each Disease Weighted by Disease Prevalence

We performed the same analysis accounting for the prevalence category of the rare diseases using weights. Most of the results still hold in the weighted analysis.

Average age at symptoms appearance

Results displayed in Table II.4.12 suggest that the distribution of most of R&D investments targeting diseases with a lower category of average age at symptom onset (*Infancy and Childhood*) are dominated by the distributions of R&D investment for all other categories of average age at symptom onset (*Adults & Elderly* and *All ages*).

The distribution of most of the R&D proxies for rare diseases in *Infancy* is dominated by the distributions for rare diseases in *Adult & Elderly* and *All ages*, except for the distribution of the number of research projects with *Adult & Elderly* in which the KS test is inconclusive (p value = 0.191).

When rare diseases in *Childhood* are compared with rare diseases in *All ages*, the distribution of all R&D outcomes both favor rare diseases in *All ages*; however, we cannot make conclusions on dominance when considering the number of research projects. When rare diseases in *Childhood* are compared with rare diseases in *Adult & Elderly*, the distribution of the number of academic publications and the distribution of the number of orphan designations are both in favor of diseases occurring in *Adult & Elderly* (p

value 0.000 and 0.011, respectively). However, we cannot make conclusions on dominance when considering the number of research projects, clinical trials, and orphan drugs.

When considering *Adult & Elderly* versus *All ages*, we find that the distribution of three of the R&D outcomes (clinical trials, orphan designation, and orphan drugs) over five for rare diseases in category *Adult & Elderly* are dominated by rare diseases in *All ages* (p value 0.001, 0.001, 0.044, respectively). The KS tests remain inconclusive for the number of research projects and academic publications.

Average age at death

Results for the paired KS tests comparing the distribution of R&D investment for rare diseases over the five categories of the average age at death are presented in Table II.4.13. They suggest that the distributions of R&D investments targeting diseases with an average age at death in *Infancy* are dominated by the distributions of R&D investments for higher categories of average age at death (*Adult & Elderly*, *All ages*, *Normal Life Expectancy*). This result holds for the five R&D proxies, except for the distribution of the number of orphan drugs when considering the categories *All ages* and *Normal Life Expectancy* (p value 0.366 and 0.184, respectively).

When rare diseases in *Infancy* are compared to rare diseases in *Childhood*, the distributions of the number of research projects and clinical trials are in favor of diseases occurring in *Childhood* (p values 0.000 and 0.000, respectively). However, the distribution of the number of academic research, orphan designations, and orphan drugs are in favor of diseases with mean age at death in *Infancy* (p values 0.000, 0.000, and 0.032, respectively).

The distribution of most of the R&D proxies for rare diseases with mean age at death in *Childhood* is dominated by the distributions for rare diseases with mean age at death in *Adult & Elderly*, *All ages*, and *Normal Life Expectancy*.

When considering rare diseases with an average age at death in *Adults & Elderly* versus those in *All ages*, results suggest that the distributions of all proxies of R&D for the category *Adults & Elderly* dominates the distributions of R&D for disease with an unpredictable mean age of death. When considering rare diseases with an average age at death in *Adults & Elderly* versus those with *Normal Life Expectancy*, results suggest that the distributions of all proxies of R&D for the category *Adults & Elderly* dominate the distributions of R&D for disease with an average age at death in *Adults & Elderly*.

Immediate danger of death

When combined with disease prevalence, results suggest that the distribution of all R&D investment targeting diseases with an immediate danger of death is dominated by the distributions of R&D investment in diseases without immediate danger of death. Results are displayed in Table [II.4.14](#).

Uncertainty on disease evolution

Results in Table [II.4.15](#) compare rare diseases according to whether there is uncertainty surrounding their evolution. The results differ from that computed in the absence of weights. More specifically, they suggest that the distributions of R&D investment targeting diseases with lower uncertainty are dominated by the distributions of R&D investment in diseases with higher uncertainty, when considering the following proxies: research projects, clinical trials, and orphan designations (p values 0.000, 0.041 and 0.007, respectively). The KS tests are inconclusive for all the number of academic publications and orphan drugs (p values 0.971 and 0.396, respectively).

6 Discussion and Conclusion

We investigated the distribution of R&D investment across rare diseases as measured by the number of research projects, academic publications, clinical trials, orphan designations, and orphan drugs with marketing authorization. When comparing the distribution of these five proxies of R&D investment across rare diseases with different average age of symptom onset, it appeared that the life stages at which the disease occurs are associated with different levels of R&D investment.

Results suggest that diseases with symptoms appearing during *Infancy* and *Childhood* are dominated, in terms of R&D investment, by rare diseases with symptoms appearing among the *Adult & Elderly*. When considering the average age at death of rare diseases, the same age groups of *Adult & Elderly* are favoured. Results suggest that diseases with an average age at death in *Infancy*, and in *Childhood* are dominated, in terms of R&D investment, by diseases with an older average age at death. This result is robust to the inclusion of frequency weights accounting for the prevalence levels in our sample.

While it is known that rare diseases are generally underserved by drug development in comparison with other diseases, our study shows that within rare diseases there

are subgroups of rare diseases that are worse off regarding R&D. Rare diseases that affect younger patients are the most deprived in terms of drug development among rare diseases. This shows that the guiding principle for R&D investment for rare diseases is not a fair innings argument, but a market size argument. There is little money for pharmaceutical firms to make in rare diseases, so R&D investments are concentrated in more profitable areas.

Epidemiology studies conducted on rare diseases show that up to 75% of rare diseases are pediatrics (Bavisetty et al., 2013). However, R&D investment in infancy are underdeveloped. One reason may be that developing therapies for children is more challenging. Children are a very heterogeneous group with different physiological, developmental, psychological, and pharmacological characteristics (Joseph et al., 2015). The consideration of growth and puberty are also crucial issues, and therapies must anticipate the impact they may have on the reproductive system (Lathyris et al., 2014). The metabolization of drugs is heterogeneous across age groups within childhood, which makes it difficult to evaluate the optimal dosage while preventing toxicity.

Overall, the development of therapies for children is more costly and thus less attractive to pharmaceutical firms. Furthermore, R&D in therapies for children raise important ethical concerns, as parents must provide consent in place of their child and may be reluctant to expose their child to the likelihood of adverse effects and newly developed treatments (Joseph et al., 2015).

Our results also confirm that market share is a driver of R&D activities, which is in line with previous evidence (Dubois et al., 2015) that rare diseases in high prevalence categories are favored by R&D investment. As drug development entails large fixed costs that are decreasing with market size, since recruitment in clinical trials is far more costly for ultra-rare diseases, a larger market size gives pharmaceutical firms the opportunity to recover their fixed costs.

We also compared the distribution of R&D activities when rare diseases are associated with an immediate danger of death after the first onset of symptoms, and when rare diseases show a high level of uncertainty in terms of the rate of progression or disease presentation. Our results suggest that rare diseases with an immediate danger of death and rare diseases that embody a high level of uncertainty are more deprived of drug development than other rare diseases. In the analysis with frequency weights based on

prevalence levels, diseases with high level of uncertainty are favored, but the risk of death surrounding rare diseases still does not foster further R&D investment.

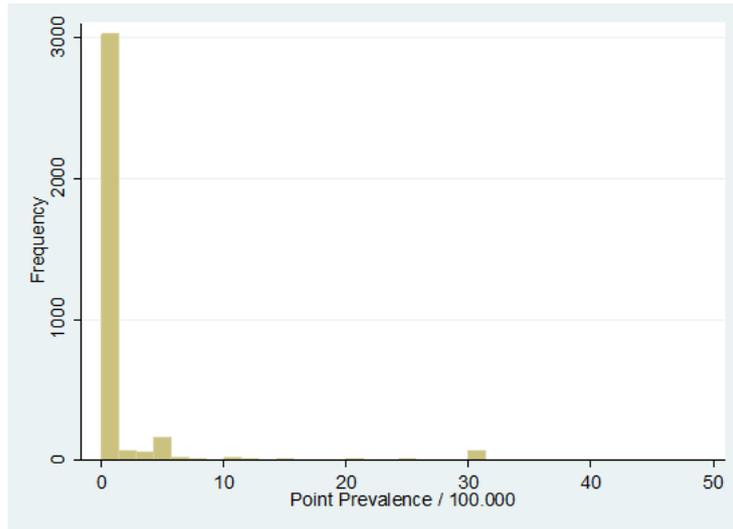
This study presents limitations, especially regarding the dataset we used. All the disease characteristics were not available for all the rare diseases in the sample. This limited data availability prevented us from aggregating rare diseases characteristics in the analysis. It would have been interesting to aggregate these disease characteristics to generate a “type,” in the sense of [Roemer \(1998\)](#). We faced dramatic reductions in sample size due to missing data when building a complete balanced data. Still, we studied the missing data patterns and found that the difference in the mean number of R&D resources of missing values compared to the non-missing values is negative and quite low. Another limitation important to emphasize is that R&D investments are likely to increase the availability of some disease characteristics, and vice versa, if some disease characteristics are available R&D is likely to be stimulated (see [Figure II.4.3](#)).

We summarized the average value for each of the proxies of R&D investment in [Figure II.4.4](#). The hierarchy in disease characteristics is rather stable across the proxies of R&D investment. The most deprived category over all R&D investment is the group of rare diseases with an average age at first symptom during *Infancy* and *Childhood*. The second most deprived characteristic is uncertainty about rare disease evolution, followed by the group of diseases with an immediate danger of death.

While the difference in average R&D investment is very low, it is somewhat dependent on disease characteristics. While it would have been interesting to actually consider other disease characteristics, such as patients’ socioeconomic status or ethnic origin ([Lichtenberg, 2005](#)), to the best of our knowledge no dataset is currently available to explore these questions. This points out the existence of inequalities in the distribution of R&D across rare diseases that are not currently addressed at the European level. The health promotion of the most deprived subgroups of rare disease could be a desirable form of compensation to prevent long term discrepancies in health technology availability and ultimately discrepancies in patients’ opportunities to access care and treatment.

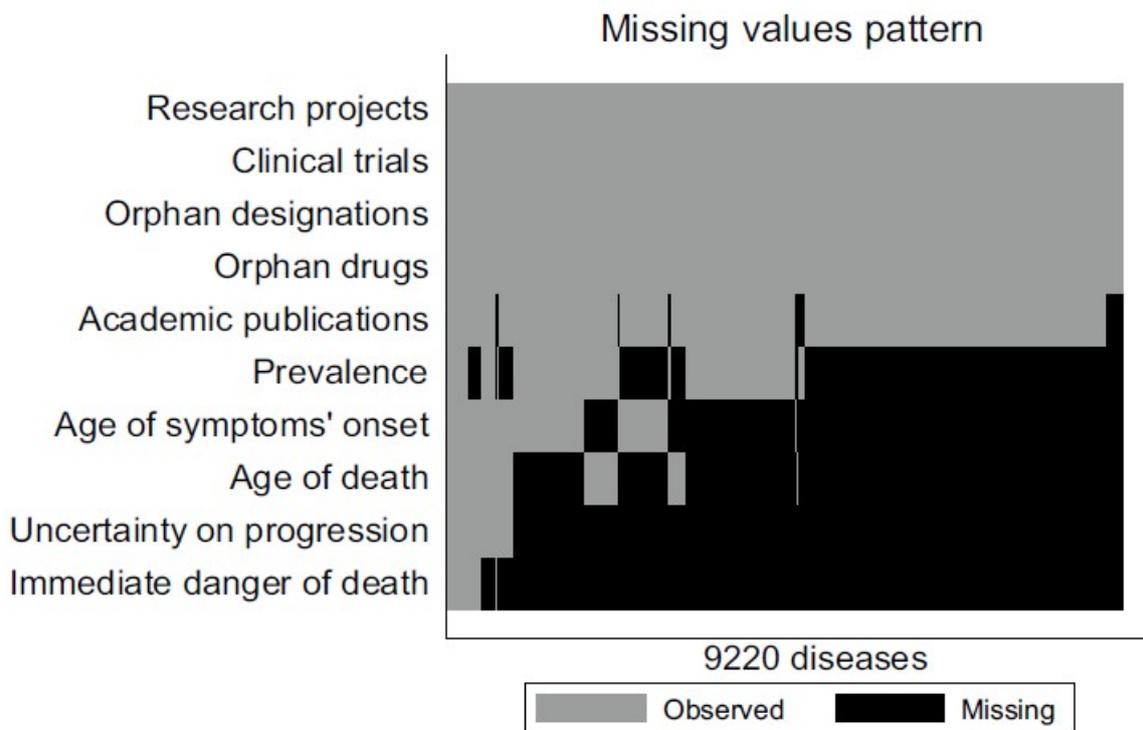
7 Appendix

Figure II.4.1 – FREQUENCY DISTRIBUTION OF RARE DISEASE PREVALENCE



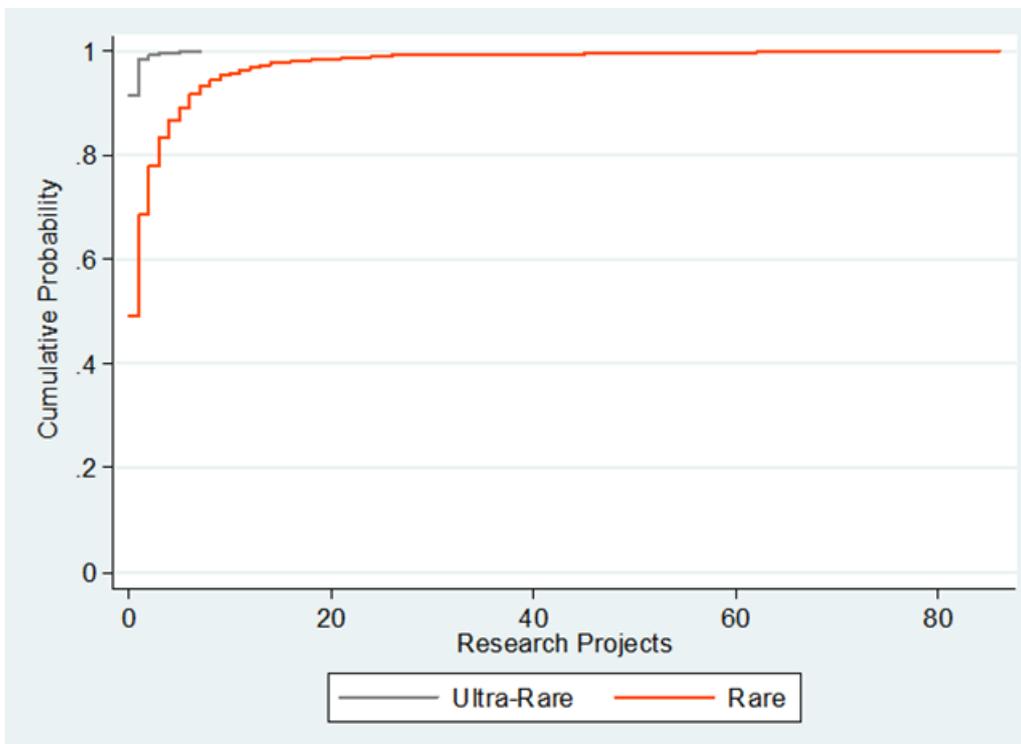
Source: Orphanet

Figure II.4.2 – MISSING VALUE PATTERNS



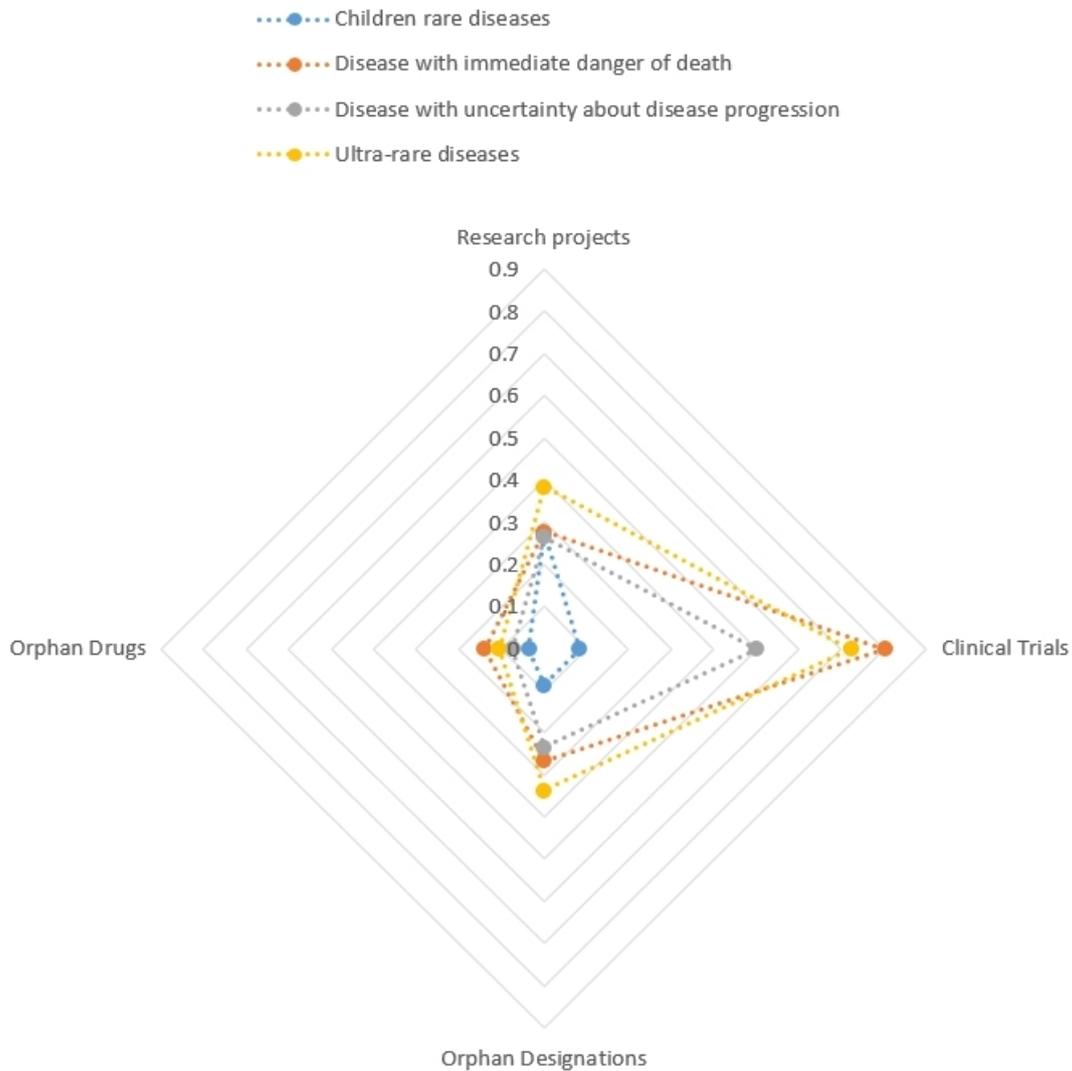
Note: Missing value patterns in terms of all variables of interest. This graph provides a visual investigation of shared missing values between all variables considered in the analysis. Variables are displayed on the y-axis depending on the number of missing values in increasing order.

Figure II.4.3 – CUMULATIVE DISTRIBUTION OF RESEARCH PROJECTS OF ULTRA-RARE VERSUS NON ULTRA-RARE DISEASES



Source: Orphanet

Figure II.4.4 – MEAN R&D LEVELS DIFFERENTIATED ACROSS CIRCUMSTANCES



Note: Mean R&D levels differentiated across disease characteristics. Yellow line indicates the mean number for each of the R&D outcomes (Research Projects, Clinical Trials, Orphan Designations, and Orphan Drugs, respectively) for the ultra-rare diseases. Academic Publications do not appear on the graph because of scale compatibility. Yet, the hierarchy between means for Academic Publications across disease types is comparable to the one observed for Research Projects.

Table II.4.1 – DESCRIPTIVE STATISTICS OF R&D VARIABLES

R&D characteristics	Mean	SD	P25	P50	P75	Minimum	Maximum
Research Projects (n=9220)	0.38	2.08	0	0	0	0	86
Academic Research (n=8755)	577.77	3632.40	9	85	500	0	177430
Clinical Trials (n=9220)	0.72	5.51	0	0	0	0	202
Orphan designations (n=9220)	0.33	2.49	0	0	0	0	92
Orphan Drugs (9220)	0.10	0.76	0	0	0	0	28

Note: Statistics displayed are: SD: Standard deviation; P25: First quartile; P50: Median; P75: Third quartile.
Source: Orphanet and authors' dataset containing MEDLINE disease-specific number of publications.

Table II.4.2 – LINEAR CORRELATION COEFFICIENT BETWEEN ALL R&D OUTCOME VARIABLES

Linear correlation coefficient	Research Projects	Academic Research	Clinical Trials	Orphan designations
Academic Research	0.23			
Clinical Trials	0.38	0.19		
Orphan designations	0.50	0.26	0.69	
Orphan Drugs	0.24	0.16	0.63	0.59

Source: Authors' dataset containing MEDLINE disease-specific number of publications.

ALLOCATION OF R&D RESOURCES FOR RARE DISEASES

Table II.4.3 – DISTRIBUTION OF THE MEAN AGE AT SYMPTOM APPEARANCE FOR RARE DISEASES

Mean age at symptoms' onset	Freq.	Percent.	Cumulative freq.
<i>Infancy</i>	536	20.36	20.36
<i>Childhood</i>	748	28.42	48.78
<i>Adult & Elderly</i>	743	28.23	77.01
<i>All ages</i>	605	22.99	100
Total	2632	100	

Source: Orphanet dataset.

Table II.4.4 – DISTRIBUTION OF THE MEAN AGE AT DEATH FOR RARE DISEASES

Mean age at death	Freq.	Percent.	Cumulative freq.
<i>Infancy</i>	98	6.03	6.03
<i>Childhood</i>	149	9.17	15.20
<i>Adult & Elderly</i>	244	15.02	30.22
<i>All ages</i>	780	48.00	78.22
<i>Normal Life Expectancy</i>	354	21.78	100
Total	1625	100	

Source: Orphanet dataset.

Table II.4.5 – DISTRIBUTION OF THE PREVALENCE FOR RARE DISEASES

Prevalence in class	Freq.	Percent.	Cumulative freq.
< 1/1,000,000	2739	76.79	76.79
1–9/1,000,000	229	6.42	83.21
1–9/100,000	387	10.85	94.06
1–9/10,000	212	5.94	100
Total	3567	100	

Source: Orphanet dataset.

Table II.4.6 – MEAN DIFFERENCE IN R&D PROXIES BETWEEN MISSING VALUES AND NON-MISSING VALUES FOR DISEASE CHARACTERISTICS

Characteristics 'c'	R&D proxies 'r'														
	Research projects			Academic research			Clinical trials			Orphan designations			Orphan drugs		
	Mean <i>r</i> if <i>c</i> non- missing	Mean <i>r</i> if <i>c</i> missing	Diff	Mean <i>r</i> if <i>c</i> non- missing	Mean <i>r</i> if <i>c</i> missing	Diff	Mean <i>r</i> if <i>c</i> non- missing	Mean <i>r</i> if <i>c</i> missing	Diff	Mean <i>r</i> if <i>c</i> non- missing	Mean <i>r</i> if <i>c</i> missing	Diff	Mean <i>r</i> if <i>c</i> non- missing	Mean <i>r</i> if <i>c</i> missing	Diff
Mean age of death	0.92	0.27	-0.65***	905.6	508.3	-397.3***	1.34	0.59	-0.75***	0.69	0.26	-0.43***	0.20	0.08	-0.11***
Mean age of symptoms onset	0.69	0.27	-0.41***	889.5	452.3	-437.1***	1.67	0.34	-1.3***	0.72	0.18	-0.53***	0.22	0.06	-0.17***
Uncertainty of disease progression	0.92	0.32	-0.59***	1061	523.6	-537.8***	1.99	0.58	-1.4***	0.90	0.27	-0.63***	0.28	0.08	-0.19***
Immediate danger of death	0.93	0.35	-0.57***	689.3	571.3	-118.0	1.61	0.67	-0.94*	0.64	0.32	-0.33***	0.18	0.10	-0.08***
Prevalence	0.62	0.24	-0.38***	789.4	443.0	-346.3***	1.14	0.46	-0.67***	0.62	0.15	-0.47***	0.17	0.06	-0.10***

Note: This table displays the difference in the mean number of each of the R&D proxies (research projects, academic publications, clinical trials, orphan designations, and orphan drugs, respectively) when each of the disease characteristics is either non-missing or missing. Diff is calculated using t-tests with unequal variances, $Diff = mean\ r(if\ c\ missing) - mean\ r(if\ c\ nonmissing)$

Source: Orphanet and authors' dataset containing MEDLINE disease-specific number of publications.

Ha: $diff < 0$; we display p values as follows: *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$.

Table II.4.7 (continued)

Mean age at symptom onset Column Versus Row	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>					<i>All ages</i>					
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	
AR		1.000					1.000										0.963				
CT			1.000					1.000										FSD 0.031			
OD				1.000					1.000										?		
MA					1.000					1.000										?	
<i>All ages</i>																					
RP	1.000					0.872					FSD 0.003										
AR		0.974					0.935					FSD 0.005									
CT			1.000					1.000					0.994								
OD				1.000					1.000					?							
MA					1.000					1.000					?						
																0.895					

Note: The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.8 – FIRST-ORDER STOCHASTIC DOMINANCE WITH MEAN AGE AT DEATH (REPORTED *p* VALUES)

Mean age at death Column versus row	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>Infancy</i>															
RP						?					FSD				
						0.136					0.000				
AR							FSD					FSD			
							0.036					0.000			
CT								?					FSD		
								0.742					0.000		
OD									?					FSD	
									0.832					0.013	
MA										?					?
										1.000					0.272
<i>Childhood</i>															
RP	?										FSD				
	0.999										0.009				
AR		.										FSD			
		0.998										0.000			
CT			?										FSD		
			1.000										0.000		
OD				?										FSD	
				0.872										0.031	
MA					?										?
					0.998										0.156
<i>Adult & Elderly</i>															
RP															
	1.000														
AR															
		1.000													

Note: The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance. RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.8 (continued)

Mean age at death	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>				
Column versus row	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
CT			1.000					1.000							
OD				1.000					1.000						
MA					? 1.000					? 1.000					
Mean age at death	<i>All ages</i>					<i>Normal Life Expectancy</i>									
Column versus row	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA					
<i>Infancy</i>															
RP	FSD 0.002					FSD 0.000									
AR		FSD 0.000					FSD 0.000								
CT			FSD 0.000					FSD 0.001							
OD				FSD 0.071					FSD 0.005						
MA					? 0.417					? 0.184					
<i>Childhood</i>															
RP	? 0.420					FSD 0.010									
AR		FSD 0.065					FSD 0.000								

Note: The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table 4.8 (continued)

Mean age at death Column versus row	<i>All ages</i>					<i>Normal Life Expectancy</i>				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
CT			?					FSD		
			0.264					0.004		
OD				?					FSD	
				0.590					0.012	
MA					?					FSD
					0.833					0.084
<i>Adult & Elderly</i>										
RP	.					?				
	1.000					1.000				
AR		.					?			
		0.997					0.633			
CT			.					.		
			1.000					0.979		
OD				.					?	
				1.000					0.981	
MA					?					?
					1.000					0.940
<i>All ages</i>										
RP						FSD				
						0.019				
AR							FSD			
							0.003			
CT								FSD		
								0.020		
OD									FSD	
									0.002	

Note: The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.8 (continued)

Mean age at death	<i>All ages</i>					<i>Normal Life Expectancy</i>									
Column versus row	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA					
MA										FSD 0.039					
<i>Normal Life Expectancy</i>															
RP	1.000														
AR		0.992													
CT			1.000												
OD				1.000											
MA					1.000										
Mean age at death	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>				
Column versus row	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>All ages</i>															
RP	1.000					?					FSD 0.024				
AR		1.000					0.998					FSD 0.003			
CT			1.000					?					FSD 0.000		
OD				1.000					?					FSD 0.016	

Note: The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance. RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.8 (continued)

Mean age at death Column versus row	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
MA					?					?					?
					1.000					1.000					0.136
<i>Normal Life Expectancy</i>															
RP	1.000					1.000					0.754				
AR		1.000					0.998					0.219			
CT			1.000					1.000					0.880		
OD				1.000					1.000					0.595	
MA					?					?					0.912
					1.000					1.000					

Note: The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.9 – FIRST-ORDER STOCHASTIC DOMINANCE USING PREVALENCE IN CLASS (REPORTED *p* VALUES)

Prevalence in class	< 1/10,000,001					1-9/1,000,000					1-9/100,000					1-9/10,000				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>< 1/10,000,001</i>																				
RP						FSD 0.000					FSD 0.000				FSD 0.000					
AR							FSD 0.000					FSD 0.000				FSD 0.000				
CT								FSD 0.000					FSD 0.000						FSD 0.000	
OD									FSD 0.000					FSD 0.000						FSD 0.000
MA										FSD 0.000					FSD 0.000					FSD 0.000
<i>1-9/1,000,000</i>																				
RP	.										?				?					
	1.000										0.738				0.247					
AR		.										FSD 0.002				FSD 0.000				
		0.998																		
CT			.										FSD 0.038			FSD 0.000				
			1.000																	
OD				.										?						FSD 0.000
				1.000										0.330						
MA					.										?					?
					1.000										0.824					0.151
<i>1-9/100,000</i>																				
RP	.					?									?					
	1.000					1.000									0.296					
AR		.															FSD 0.005			
		0.999																		

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.9 (continued)

Prevalence in class	< 1/10,000,001					1-9/1,000,000					1-9/100,000					1-9/10,000						
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA		
CT			.					.													FSD	
			1.000					1.000														0.042
OD				.					?													FSD
				1.000					1.000													0.000
MA					.					?												?
					1.000					0.962												0.263
<i>1-9/10,000</i>																						
RP	.					?					?											
	1.000					1.000					0.982											
AR		.					.					.										
		1.000					0.924					0.982										
CT			.					.					.									
			1.000					1.000					0.996									
OD				.					.				.									
				1.000					1.000				0.993									
MA					.					?				?								
					1.000					1.000				1.000								

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov-Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance. RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.10 – FIRST-ORDER STOCHASTIC DOMINANCE TESTS WITH IMMEDIATE DANGER OF DEATH (REPORTED p VALUES)

Immediate danger of death Column versus row	Yes					No				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>Yes</i>										
RP						?				
						0.886				
AR							FSD			
							0.011			
CT								FSD		
								0.000		
OD									FSD	
									0.089	
MA										?
										0.121
<i>No</i>										
RP	?									
	1.000									
AR		.								
		0.999								
CT			.							
			1.000							
OD				.						
				1.000						
MA					.					
					?					
					1.000					

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials, OD orphan designations; MA orphan drugs with market approvals.

Table II.4.11 – FIRST-ORDER STOCHASTIC DOMINANCE TESTS WITH A HIGH LEVEL OF UNCERTAINTY ON DISEASE EVOLUTION (REPORTED *p* VALUES)

Uncertainty about disease evolution Column versus row	Yes					No				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>Yes</i>										
RP						?				
						0.791				
AR							FSD			
							0.006			
CT								?		
								0.850		
OD									FSD	
									0.001	
MA										?
										0.311
<i>No</i>										
RP	?									
	1.000									
AR		.								
		1.000								
CT			?							
			0.932							
OD				.						
				1.000						
MA					?					
					1.000					

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance. RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approval.

Table II.4.12 – FIRST-ORDER STOCHASTIC DOMINANCE TESTS USING MEAN AGE AT SYMPTOM ONSET, OBSERVATIONS WEIGHTED BY PREVALENCE (REPORTED p VALUES)

Mean age at symptoms onset Column versus row	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>					<i>All ages</i>				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>Infancy</i>																				
RP						FSD 0.006					?					FSD 0.001				
AR							.				0.151					FSD 0.000				FSD 0.000
CT																FSD 0.000				FSD 0.000
OD																FSD 0.000				FSD 0.000
MA																				FSD 0.002
<i>Childhood</i>																				
RP																?				?
AR																0.088				0.011
CT																				FSD 0.000
OD																				FSD 0.001
MA																				FSD 0.001
<i>Adult & Elderly</i>																				
RP																				?
AR																				0.148
																				?
																				0.963

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.12 (continued)

Mean age at symptoms onset Column versus row	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>					<i>All ages</i>						
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA		
CT			1.000					0.144													FSD 0.001	
OD				1.000					0.934													FSD 0.001
MA					1.000					?												FSD 0.044
<i>All ages</i>																						
RP		0.929				?				0.039					?							
AR			?							1.000					?							
CT				1.000																		
OD					1.000										1.000							
MA						1.000										1.000						

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.13 – FIRST-ORDER STOCHASTIC DOMINANCE TESTS WITH MEAN AGE AT DEATH, OBSERVATIONS WEIGHTED BY PREVALENCE (REPORTED *p* VALUES)

Mean age at death Column versus row	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>Infancy</i>															
RP						FSD 0.000					FSD 0.000				
AR							1.000)					FSD 0.000			
CT								FSD 0.000)					FSD 0.000		
OD									0.997					FSD 0.000	
MA										1.000					FSD 0.000
<i>Childhood</i>															
RP	1.000										FSD 0.000				
AR		FSD 0.000										FSD 0.000			
CT			1.000										FSD 0.000		
OD				FSD 0.000										FSD 0.000	
MA					FSD 0.032										FSD 0.000
<i>Adult & Elderly</i>															
RP	1.000					1.000									
AR		1.000					1.000								

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.13 (continued)

Mean age at death Column versus row	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
CT			1.000					0.800							
OD				1.000					1.000						
MA					1.000					1.000					
Mean age at death Column versus row	<i>All ages</i>					<i>Normal Life Expectancy</i>									
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA					
<i>Infancy</i>															
RP	FSD 0.000					FSD 0.000									
AR		FSD 0.0001					FSD 0.000								
CT			FSD 0.000					FSD 0.000							
OD				FSD 0.007					FSD 0.000						
MA					?					?					
					0.366					0.184					
<i>Childhood</i>															
RP	FSD 0.000					FSD 0.000									
AR		FSD 0.000					FSD 0.000								

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance. RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.13 (continued)

Mean age at death Column versus row	<i>All ages</i>					<i>Normal Life Expectancy</i>				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
CT			FSD 0.000					FSD 0.000		
OD				FSD 0.001					FSD 0.000	
MA					FSD 0.095					FSD 0.007
<i>Adult & Elderly</i>										
RP	.					1.000				
AR	0.992	.					0.304			
CT		0.182	.					0.794		
OD			1.000	.					0.853	
MA				0.992	.					0.911
<i>All ages</i>										
RP						FSD 0.000				
AR							FSD 0.002			
CT								FSD 0.006		
OD									FSD 0.087	

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.13 (continued)

Mean age at death	<i>All ages</i>					<i>Normal Life Expectancy</i>											
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA							
MA																FSD	0.216
<i>Normal Life Expectancy</i>																	
RP	0.982																
AR		0.580															
CT			1.000														
OD				0.988													
MA					0.908												
Mean age at death	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>						
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA		
<i>All ages</i>																	
RP	1.000					0.110										FSD	0.000
AR		1.000					0.446									FSD	0.000
CT			1.000					0.912								FSD	0.000
OD				1.000					0.260							FSD	0.000

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance. RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.13 (continued)

Mean age at death Column versus row	<i>Infancy</i>					<i>Childhood</i>					<i>Adult & Elderly</i>				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
MA					?										FSD
					0.438					1.000					0.000
<i>Normal Life Expectancy</i>															
RP											FSD				
	1.000					1.000					0.084				
AR												FSD			
		1.000					0.835					0.000			
CT													FSD		
			1.000					1.000					0.000		
OD														FSD	
				1.000					0.554					0.000	
MA															FSD
					?					1.000					0.043

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance. RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.14 – FIRST-ORDER STOCHASTIC DOMINANCE TESTS WITH IMMEDIATE DANGER OF DEATH, OBSERVATIONS WEIGHTED BY PREVALENCE (REPORTED *p* VALUES)

Immediate danger of death	Yes					No				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>Yes</i>										
RP						FSD 0.017				
AR							FSD 0.000			
CT								FSD 0.004		
OD									FSD 0.000	
MA										FSD 0.001
<i>No</i>										
RP	.									
AR	0.593	.								
CT		0.994	.							
OD			1.000	.						
MA				1.000	.					
					1.000					

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov– Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represents being dominated at first-order dominance, and ? represents when we cannot conclude on dominance. RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Table II.4.15 – FIRST-ORDER STOCHASTIC DOMINANCE TESTS WITH A HIGH LEVEL OF UNCERTAINTY ON DISEASE EVOLUTION, OBSERVATIONS WEIGHTED BY PREVALENCE (REPORTED p VALUES)

Uncertainty about disease evolution	Yes					No				
	RP	AR	CT	OD	MA	RP	AR	CT	OD	MA
<i>Yes</i>										
RP						?				
AR						0.971	?			
CT							0.019			
OD								0.477		
MA									0.191	?
										0.396
<i>No</i>										
RP		FSD 0.000								
AR			?							
CT			0.081							
OD				FSD 0.041						
MA					FSD 0.007					
						?				
						0.391				

The results are highlighted when FSD dominance is assessed. FSD represents stochastic dominance at first order at 10% related to the results of the Kolmogorov–Smirnov tests: if the test accepts dominance of one distribution over the other but not the other way round, we consider that equality of opportunity is violated. Dots represent being dominated at first-order dominance, and ? represents when we cannot conclude on dominance.

RP research projects; AR academic research; CT clinical trials; OD orphan designations; MA orphan drugs with market approvals.

Part III

REGULATORS' CHALLENGES IN DEFINING THE CONDITIONS OF ACCESS TO INNOVATIVE DRUGS

Part II was dedicated to firms' decisions to invest in research on rare diseases. The key issue of disease refinement into indications to qualify for the OD legislation incentive highlights the links between diagnostic criteria and drug development as one driver of firms' decisions to allocate R&D to rare diseases. Part III is devoted to regulators and their challenges in measuring clinical benefits of orphan drugs in order to define the socially acceptable conditions of access to innovation for patients with rare diseases. Chapter 5 examines the causal impact of pharmaceutical innovation on longevity, and Chapter 6 provides a critical discussion of the economic evaluation of health technologies.

Chapter 5

Orphan Drugs and Longevity in the US, Revisited (1999-2015)

1 Introduction

In the United States, rare diseases are defined as diseases affecting fewer than 200,000 people at any given time. About 25-30 million Americans are affected by a rare condition (Griggs et al., 2009). Since 1983, emphasis has been placed on the health status of patients with rare diseases since the implementation of the Orphan Drug Act (ODA)—see Chapter 3 for a presentation of the ODA policy (Lichtenberg and Waldfogel, 2003; Lichtenberg, 2013; Yin, 2008).

In total, 575 drugs and biological products were launched for rare diseases between 1983 and 2017 (Luzzatto et al., 2018). Commentaries on ODA policy generally rest on these stylized facts to conclude that this intervention was game changing for patients with rare diseases.

While these incentives have been introduced to foster R&D investments in rare disease areas, the actual objective of the policy was to increase therapeutic opportunities for patients with rare diseases to ultimately positively impact their health.

The clinical benefits of approved pharmaceutical products are documented by clinical studies, generally based on Randomized Control Trials (RCT). They rely on data collected from a predefined number of patients, which is particularly limited for rare diseases, although clinical trial requirements tend to be more flexible to obtain market authorization (Logviss et al., 2018).

Sub-groups of patients may benefit more or less from pharmaceutical innovation. In this chapter, we use a large longitudinal administrative database including death certificates in order to explore the aggregate benefit from pharmaceutical innovation and the external validity of clinical trial results. We specifically address health benefits from pharmaceutical innovation for patients with rare diseases.

The costs of new approved drugs for rare diseases is a major concern for health policy makers worldwide. In recent years, high prices have been granted for rare disease drugs. One example is the treatment of Gaucher's disease, costing on average US\$200,000 per patient per year (Luzzatto et al., 2018). These facts confirm the need for evaluating long-term impacts of innovation on the health outcomes of patients with rare diseases.

Two previous studies investigated this research question. First, [Lichtenberg \(2013\)](#) studied the impact of new orphan drugs on premature mortality as measured by YPLL from 1999-2007 on US and French data. YPLL is a widely used measure of premature mortality and computes the disease specific sum of years lost, up to some reference age (usually 65 and 75 years). This represents the loss of opportunity for patients measured in years to 65 and 75 years old, respectively ([Jang et al., 2014](#)). The results suggested that a reduction in the US growth rate of YPLL65 attributable to the lagged number of drug approvals was 4.2% for the US, and 1.1% in France. Second, [Lichtenberg \(2001b\)](#) found that mortality from rare diseases grew at a slower rate than mortality from other diseases after the introduction of the ODA in 1983. The author's estimates showed that one additional orphan drug approval in year t prevented 211 deaths in year $t + 1$ and ultimately prevented 499 deaths.

We propose here to update and extend the analysis conducted by [Lichtenberg \(2001b\)](#) and [Lichtenberg \(2013\)](#) by investigating variations of diagnostic efficiency across rare diseases. The probability of getting a correct diagnosis for a rare condition is affected by both the development of clinical expertise on each pathology and by the diagnostic tools being made available to detect a particular condition. From 2000 onwards, development on diagnostics has led to scale diagnostic efficiency from 10% to 30–50%, which represents considerable improvements ([Dawkins et al., 2018](#); [Baynam et al., 2016](#)).

Rationalization of healthcare pathways or developments of DNA-sequencing diagnostic methods is likely to impact the cause of death coding, hence spuriously increasing premature mortality. Failure to control for variation in diagnostic ability may lead to an underestimate of the impact of pharmaceutical innovation on premature mortality from rare diseases.

Using all US death certificates from 1999 to 2015, we compute the YPLL to age 65, 70, 75, 80, and 85 to assess premature deaths. We match these death certificates to data on pharmaceutical innovation and, more interestingly, the cumulative number of expert centers and diagnostics tests at the international level.

We then measure the causal impact of pharmaceutical innovation and academic publications in rare disease areas using a two-way fixed effect model. We then investigate the time variation of the impact of pharmaceutical innovation on longevity.

The chapter is organized as follows: Section 2 introduces the data and the empirical strategy, Section 3 presents our main results and robustness checks, which we discuss at greater length in Section 4.

2 Data and Empirical Strategy

2.1 Data

Longevity of patients with rare diseases

We assess longevity using Multiple Cause of Death mortality data from the National Vital Statistics System of the National Center for Health Statistics. They provide mortality data by multiple causes of death for all deaths that occurred within the United States during the period 1999-2015. Causes of death are coded according to the International Classification of Diseases (ICD), tenth revision (ICD-10 codes) owned by the WHO. ICD-10 codes are used to classify death certificates according to the underlying cause of death.

To retrieve all ICD-10 codes corresponding to a rare disease, we use data from Orphanet. Orphanet is an information portal for rare diseases and orphan drugs granted by the European Commission that provides the list of the ICD-10 codes identifying rare diseases. We compute disease-specific years of potential life lost (YPLL) using all death certificates for which rare diseases are major causes of death. YPLL is a measure of premature mortality traditionally used in epidemiology and health economics and obtained by subtracting each patient's age at death from the reference age and summing this difference for each ICD-10 codes. We exclude records of individuals who died at or after the disease reference age. We calculate YPLL65 using 65-years-old as a reference age, and YPLL70, YPLL75, YPLL80, YPLL85 using 70-, 75-, 80-, and 85-years-old as reference ages, respectively.

Pharmaceutical innovation

Our measure of pharmaceutical innovation is the cumulative number of approved drugs in a given year identified at rare-disease level. Orphanet provides the date of US market approvals for each drug targeting a rare disease.

Academic Publications

Our measure of academic research intensity is the cumulative number of publications in a given year identified at rare-disease level. Data collection is presented in the chapter's preamble.

Variation in diagnostic ability

Physicians' ability to appropriately diagnose a rare pathology interacts with the diagnostic technology available at the time of the diagnostic. For example, the development of DNA-sequencing and diagnostic testing is likely to have affected the probability of obtaining the correct diagnosis for a subset of rare diseases when made available. Diagnostic technology is therefore likely to impact mortality rates. To control for disease-specific variation in diagnostic ability, we use international data on the number of diagnostic tests per disease and the number of expert centers per disease for each year, provided by Orphanet. Expert centers designate structures or networks dedicated to the medical management and/or genetic counseling for rare diseases.

Age-adjusted mortality rates

We compute age-adjusted mortality rates using our Multiple Cause of Death mortality data and the US Census Bureau population estimates from 2000 to 2015. We use the US 2000 population as a standard age composition. We compute both age-adjusted mortality rates for rare diseases and non-rare diseases. Adjusted mortality rates for non-rare diseases exclude external causes of death such as injury or poisoning.

2.2 Empirical Strategy

Fixed Effect Model Specification

We estimate the average impact of pharmaceutical innovation and academic publications on Years of Potential Life Lost (YPLL) per disease-year observation during the period 1999-2015 using a fixed effect specification, whilst conditioning on observed characteristics and time invariant unobserved heterogeneity at the disease level:

$$YPLL(RA)_{dt} = \alpha_0 + \beta_1 DrugLaunches_{dt-k} + \beta_2 ExpertCenters_{dt} + \beta_3 DiagnosticTests_{dt} + \psi_d + \lambda_t + \epsilon_{dt} \quad (5.1)$$

$$YPLL(RA)_{dt} = \alpha_0 + \beta_1 AcademicPublications_{dt-k} + \beta_2 ExpertCenters_{dt} + \beta_3 DiagnosticTests_{dt} + \psi_d + \lambda_t + \epsilon_{dt} \quad (5.2)$$

$YPLL_{dt}$ represents the count number of YPLL for disease d in year t using 65, 70, 75, 80, and 85 as Reference Ages (RA).

$DrugLaunches_{dt}$ is the cumulative number of drug launches for disease d in year t .

$AcademicPublications_{dt}$ is the cumulative number of academic publications for disease d in year t .

$ExpertCenters_{dt}$ represents the cumulative number of expert centers opened for disease d in year t .

$DiagnosticTests_{dt}$ denotes the cumulative number of diagnostic tests launched for disease d in year t .

ψ_d denotes the disease fixed effect that allow us to control for average differences across rare diseases in any time invariant observables and unobservables.

λ_t is the time fixed effect, that allows us to control for aggregate trends in our outcomes variables.

ϵ_{dt} is a random error term for condition i in time t .

Time variation in the impact of pharmaceutical innovation

In order to investigate the time variation in the impact of pharmaceutical innovation and academic publications on premature longevity, we include indicators for time period (lead and lag) after each drug approval using the following specification:

$$\begin{aligned}
 YPLL(RA)_{dt} = & \alpha_0 + \beta_1 Lag_{-4;-6,dt} + \beta_2 Lag_{-2;-4,dt} + \beta_3 Lag_{0;-2,dt} \\
 & + \beta_4 Lead_{0;2,dt} + \beta_5 Lead_{2;4,dt} + \beta_6 Lead_{4;6,dt} + \beta_7 Lead_{6;8,dt} + \beta_8 Lead_{8;10,dt} \\
 & + \beta_9 Lead_{10;12,dt} + \beta_{10} Lead_{12;15,dt} + \beta_{11} ExpertCenters_{dt} + \beta_{12} DiagnosticTests_{dt} + \psi_d + \lambda_t + \epsilon_{dt}
 \end{aligned}
 \tag{5.3}$$

$Lag_{-4;-6,dt}$ designates a dummy variable equal to one between -4 and -6 years before the introduction of the pharmaceutical innovation in year t for disease d . Other leads and lags are constructed the same way.

3 Results

3.1 Descriptive Statistics

Age-adjusted mortality rates for both rare diseases and other diseases are computed in Figure III.5.1. The latter excludes external causes of death such as poisoning or injuries. Mortality rates for other diseases are larger than the those for rare diseases, as expected, however we observe that the trends over time are very similar (see Figure III.5.2).

Finally, we compare annual age-adjusted mortality rates for rare diseases with therapeutic options to rare diseases without any approved therapy in Figure III.5.3. Results show that age-adjusted mortality rates are decreasing in the rare disease without treatment group, while stable in the other group.

Our sample includes 1,173 ICD-10 codes identifying rare diseases, among which only 5% (96 diseases) have an approved treatment. We refer to those 96 diseases as our treatment group (the treatment being the drug approval), while the other 1,077 diseases are in the control group.

Table III.5.1 displays the descriptive statistics. The treatment group exhibits a larger mean number of deaths, and a larger YPLL for any reference age as compared to the control group. As larger market sizes are observed among diseases targeted by R&D activities, the larger mean observed in the treatment group could reflect larger prevalence rates. Regarding academic publications, we observe similar patterns between the treatment and the control group: the treatment group shows a higher number of academic publications (353 versus 108 in the control), the difference being significant ($p < 0.005$).

We now present the proportion of diseases with at least one diagnostic test or one expert center. The treatment group shows a higher proportion of diagnostic tests being available (50% versus 13% in the control), and the difference is significant ($p < 0.005$). A similar comment applies to expert centers. The treatment group also shows a significantly larger proportion of expert centers (44% versus 17% in the control, $p < 0.005$).

The within variation of the treatment group before and after one drug approval reveals an increasing mean number of deaths (71% increase of the mean number of deaths) and YPLL (37% increase). We similarly observe an increase in the proportion of diseases with at least one diagnostic test (50% versus 10% before drug approval, the difference being significant $p < 0.005$) and at least one expert center (44% versus 12% before drug approval, the difference being significant $p < 0.005$).

Academic publications increase after drug approval (172 academic publications versus 353 before drug approval, the difference being significant $p < 0.005$).

In the treatment group, 174 approved drugs for rare diseases are represented among 96 diseases. Table III.5.2 displays the yearly number of approved drugs for rare diseases as well as the mean number of drugs per rare disease. The yearly number of approved drugs per disease is low, but increases slightly from 1 in 1999 to 1.2 in 2015. Note that not all orphan drugs are represented in the dataset¹. Indeed, when an ICD code is not available for a rare disease that has an approved drug, we were not able to include the drug in the analysis. Moreover, to ensure consistency in the analysis, we did not make the hypothesis that the mortality rate was null for the considered year if we did not find any records for a particular ICD-10 code. Consequently, our panel data is not balanced.

¹All drug approvals by year and ICD-10 codes are provided as additional descriptive statistics in Table III.5.16.

3.2 Empirical Results

Table III.5.3 displays the impact of lagged pharmaceutical innovation on Years of Potential Life Lost. Results suggest that the lagged stock of drug is significantly reducing the number of Years of Potential Life Lost (-455, $p < 0.05$) when using 65-years-old as the reference age to compute the YPLL. When using 70-, 75-, 80- or 85-years-old as the reference age, the lagged stock of drug turns out to be insignificantly related to the current number of YPLL. In Table III.5.4, we add as covariates the cumulative number of expert centers and diagnostic tests. Results show that the lagged stock of drugs significantly reduces YPLL (-455, $p < 0.05$) when using 65-years-old as the reference age. The coefficient on the cumulative number of expert centers is positive but insignificant. The cumulative number of diagnostic tests significantly reduces the number of Years of Potential Life Lost (-269, $p < 0.001$). This result holds for all reference ages.

We now investigate the time variation in the impact of pharmaceutical innovation on YPLL by including time lags and leads. Results displayed in Table III.5.5 show that between one and six years prior to drug approval, mortality rates do not significantly decrease in the treatment group. Between two and four years after the introduction of the pharmaceutical innovation, we observe a significant decline in the number of YPLL65 and YPLL70 (-665, $p < 0.05$; -701, $p < 0.05$, respectively). This result does not hold for YPLL75, YPLL80, and YPLL85. As in previous results, the cumulative number of diagnostic tests significantly increases YPLL for all reference ages. Figures III.5.4, III.5.5, III.5.6, III.5.7, and III.5.8 present graphic representations of the time variation in the impact of pharmaceutical innovation on YPLL65, YPLL70, YPLL75, YPLL80, and YPLL85, respectively.

Table III.5.6 displays the impact of lagged cumulative number of academic publications on Years of Potential Years Lost. Results suggest that the lagged stock of drug is insignificantly related to the number of Years of Potential Life Lost for all 70, 75, 80 or 85 years old as the reference age. In Table III.5.7, we add as covariates the cumulative number of expert centers and diagnostic tests.

3.3 Robustness Checks

Redefinition of the Sample — ICD-10 scope

ICD-10 codes do not uniquely identify rare diseases. In some cases, Orphanet has assigned the same ICD-10 code to several rare diseases. They usually correspond to disease subtypes, however ICD-10 may also aggregate different rare diseases and/or non-rare diseases.

We investigate whether the estimated impact is diluted because we use too broad a disease classification, and thus fail to precisely identify disease subgroups. We suggest two other ways to account for this issue:

- (1) We count the number of different rare diseases by ICD-codes and include in the sample ICD-10 codes matching one unique Orphanet rare disease identifier.
- (2) We select ICD-10 codes depending on the average annual number of deaths, following [Lichtenberg \(2013\)](#). For each ICD-10 code in our sample, we compute the annual average number of deaths. By comparing conditional mortality rates for the US in 2007 for non-rare cancers and rare cancers, [Lichtenberg \(2013\)](#) shows that mortality rates from rare cancers are over three times as high as those for non-rare cancers. The maximum annual number of deaths if the average mortality rate from rare diseases is twice (3 times or 4 times, respectively) the average US mortality rate—given that the maximum prevalence for rare diseases is 1/1500 individuals in the US—is 3,200 deaths annually (4,800 or 6,400 deaths annually, respectively).

To select ICD-10 codes that are unlikely to include non-rare diseases, we consider in the sample ICD-10 codes for which the annual average number of deaths is below the threshold of 3,200 deaths (4,800 and 6,400 deaths per year, respectively). Results are displayed in [Tables III.5.8, III.5.9, and III.5.10](#). Time variation in the impact is very similar that described in the result section: we observe a decrease in the number of Years of Potential Years Lost for all reference ages, and the decrease is significant between two and four years after the drug launch. The decrease in the mean number of YPLL per rare disease is much larger than what we previously observed with the entire sample. This is due to the drastic reduction in the number of ICD-10 considered in the analysis; from 1,173 to 559 ICD-10 codes when we use the very restrictive threshold of 3,200 deaths on average per year.

Resampling

One specificity of our analysis is that we observe many rare diseases in the control group than in the treatment group. It reflects the fact that only 5% (96 diseases) have an approved treatment. Our control is thus 17 times larger than the treatment group. We provide in Table III.5.11 the results of the empirical analysis using 100 randomly selected diseases in the control group. The results are comparable, showing that the impact of pharmaceutical innovation is larger in the sub-sample analysis. Pharmaceutical innovation occasions a decline in the number of YPLL65 and YPLL70 (-640, $p < 0.1$; -747, $p < 0.1$, respectively). This result does not hold for YPLL75, YPLL80, and YPLL85. As in previous results, the cumulative number of diagnostic tests significantly increases YPLL for all reference ages.

Main hypothesis testing

Our main assumption here is the common trend assumption: in the absence of treatment, the evolution of YPLL in the treatment and the control groups would have been the same. In other words, drug development must not depend on trends of YPLL before drug approvals. As discussed in the introduction of this chapter, drug development is related to market size but not directly related to premature mortality, as it reduces market size. Hence, drug development is unlikely to be a response to variation in premature mortality.

Similarity of trends under the counterfactual is not directly testable. However, we can test to see whether the distribution of the YPLL follows a specific trend before drug launches. If the common trend assumption holds, YPLL for rare diseases prior to drug launch should not follow a different trend than the one we observe in rare diseases in the control group. As the treatment is time varying, we are able to test whether we fail to reject pre-treatment common trends. Results in Table III.5.5 show that up to eight years prior to a drug launch, the treatment group does not exhibit significant specific trend in YPLL for all age groups. If the trends across groups before treatment are comparable, we can reasonably expect that they would have continued to be so in the absence of drug launches. This supports our empirical strategy.

4 Discussion and Conclusion

In this chapter, we estimated the impact of pharmaceutical innovation on longevity of patients with rare diseases. We make use of large administrative databases registering causes of deaths to appraise premature mortality on a period of time of 17 years.

We contribute to existing literature by controlling for variation in rare disease diagnostic ability. One main feature of rare diseases is that their diagnosis is extremely challenging, as was underlined in the General Introduction. Every innovation that will impact the probability of receiving a correct diagnosis for a rare condition, from rationalization of healthcare pathways, to developments of DNA-sequencing diagnostic methods, is likely to impact the cause of death coding and hence spuriously increase premature mortality.

Failure to control for variations in diagnostic workup ability may cause us to underestimate the impact of pharmaceutical innovation on premature mortality from rare diseases.

Our results suggest that pharmaceutical innovation as measured by the cumulative number of approved drugs significantly reduces the number of YPLL65 by an average of -455 ($p < 0.05$) per disease. Previous estimates by [Lichtenberg \(2013\)](#) find a 4.2% decrease in YPLL65. However, existing literature is based on a different functional form, that was not supported in our specific context²

The investigation of time variation in the impact of drug approval on premature mortality suggests that drug approval significantly decreases the number of YPLL65 and YPLL70 between two and four years after approval. We believe that the delay between drug approval and its consequences on premature mortality is due to a progressive drug utilization in rare patient populations. Four years after market approval, no significant differences in trends are observed between the treated and control groups. As compared to previous studies, delay before the impact of pharmaceutical innovation is significant for YPLL65, and tends to be lower than for cancer drugs (between 2-4 years compared

²The choice of the functional form in this chapter was led by the large number of observations with null value for YPLL and we did not want to transform null values into some arbitrary low value for the log to be defined. The log transformation would be required if the relationship between the dependent and the independent variable was not linear (and possibly exhibited an exponential relationship), but our specific context did not depict a situation in which an increase in the number of drugs caused the number of YPLL to decrease at an increasing rate. Still, we provide estimates of models using $\ln(\text{YPLL})$ in Tables [III.5.12](#), [III.5.13](#), [III.5.14](#) and [III.5.15](#). Note that the investigation of the time trend provided in [Figure III.5.9](#) does not support the use of a fixed effect model specification as placebo tests show that the number of YPLL is decreasing prior to the introduction of the drug, which is the sign that our identification assumption is violated.

5-9 years in [Lichtenberg \(2018a\)](#)). Results on diagnostic tests reveal that variations in diagnostic ability are a strong predictor of an increase in YPLL for all age references considered.

Regarding academic research, previous results suggest that our analysis should differentiate between private versus public research ([Lichtenberg, 2017](#)). Moreover, existing literature suggests that we should include more lags in order to capture the long term effect of academic publications on premature mortality. [Lichtenberg \(2018b\)](#) shows that the number of years of potential life lost from cancer before ages 80 and 70 is inversely related to the novelty of ideas in articles published 12–24 years earlier. We leave these two questions for further research.

While we put emphasis on premature mortality, all drugs brought to the market do not impact longevity but improve the quality of life of patients with rare diseases. We cannot measure the impact on quality of life with the data we use. To the best to our knowledge, there are no datasets with QALYs and/or Disability-Adjusted Life Year (DALY)s (with some exceptions for certain types of rare cancers) that are presently available.

Moreover, it is very challenging to measure the treatment’s added-value. Amélioration du Service Médical Rendu (ASMR), evaluated by the Commission of Transparency³ in France is measuring the level of improvement in medical benefits of drugs. We tried to use that information but we faced two difficulties: (1) cost-effectiveness evaluations in France were implemented from 2011, which would therefore reduce our period of observation; (2) ASMR is not provided for every drug, but for a limited number having particular characteristics (budget impact, innovation), meaning that the coverage was very limited in our dataset.

Only five percent of patients with rare diseases have approved therapies for their condition. Still, it is likely that a number of these patients are taking off-label prescriptions. Few papers have explored the proportion of off-label prescribing among patients with rare diseases and no data on off-label utilization of drugs in the context of rare diseases

³ The Transparency Commission is a scientific body made up of doctors, pharmacists, and specialists in methodology and epidemiology. It assesses the medicines that have obtained their MA when the laboratory that markets them wishes to obtain their registration on the list of reimbursable medicines in France (Articles L.162-17 of the Social Security Code and L.5123 -2 of the public health code). Source: The French National Authority for Health, https://www.has-sante.fr/portail/jcms/c_412210/fr/commission-de-la-transparence, accessed the 08/06/2019.

is presently available for research.

Finally, we use drug launches as our treatment variable but the impact of pharmaceutical innovation truly comes from drug utilization. Moreover, drug utilization is likely to differ between patient subgroups. The difference in the results between YPLL may be explained by the distribution of innovation in older categories of patients. It could be that innovation is available for older patients, but those patients might end up not accessing innovative technologies; literature shows that younger patients are more often prescribed innovative drugs than are older patients (Lublóy, 2014). It is also possible that innovation favors diseases affecting younger patients, who may benefit much longer from the drug's value-added. It could also be that older patients have co-morbidities and other treatments. They therefore face a trade-off between accepting an innovative treatment and bearing the risk of drug interference; they may strategically choose not to adopt an innovative treatment.

The literature on the health gradient indicates that younger and more educated patients are more likely to benefit from innovation. Further research could control for drug utilization among the patient population and explore the heterogeneity of innovation take-up depending of patients' social background and age.

5 Appendix

Figure III.5.1 – ADJUSTED-MORTALITY RATES (RARE DISEASES VS OTHER DISEASES)

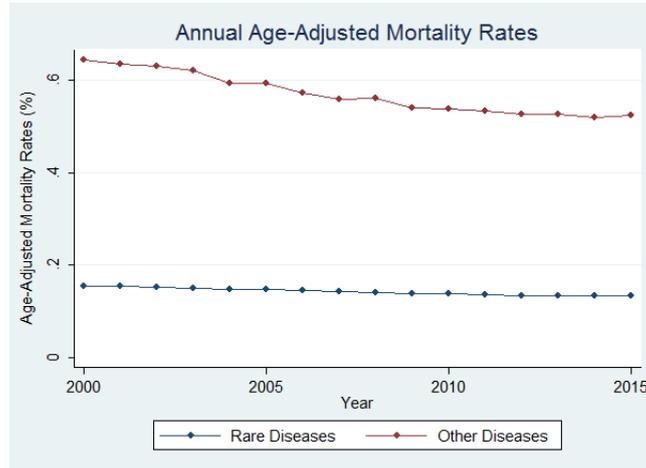


Figure III.5.2 – ADJUSTED-MORTALITY RATES (RARE DISEASES VS OTHER DISEASES) - TRENDS

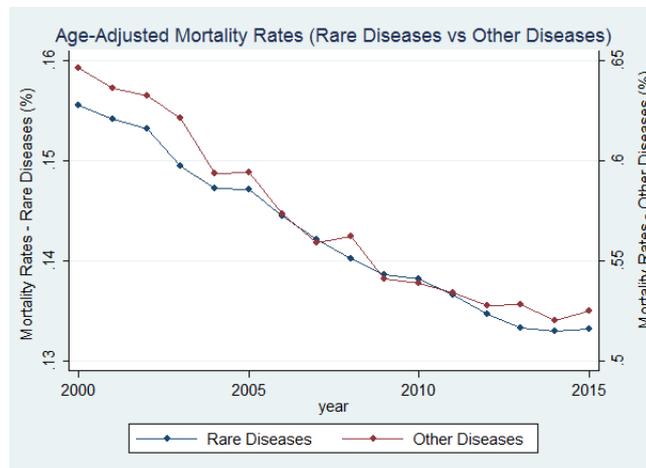


Figure III.5.3 – ADJUSTED-MORTALITY RATES WITH AND WITHOUT ORPHAN DRUG (RARE DISEASES) - TRENDS

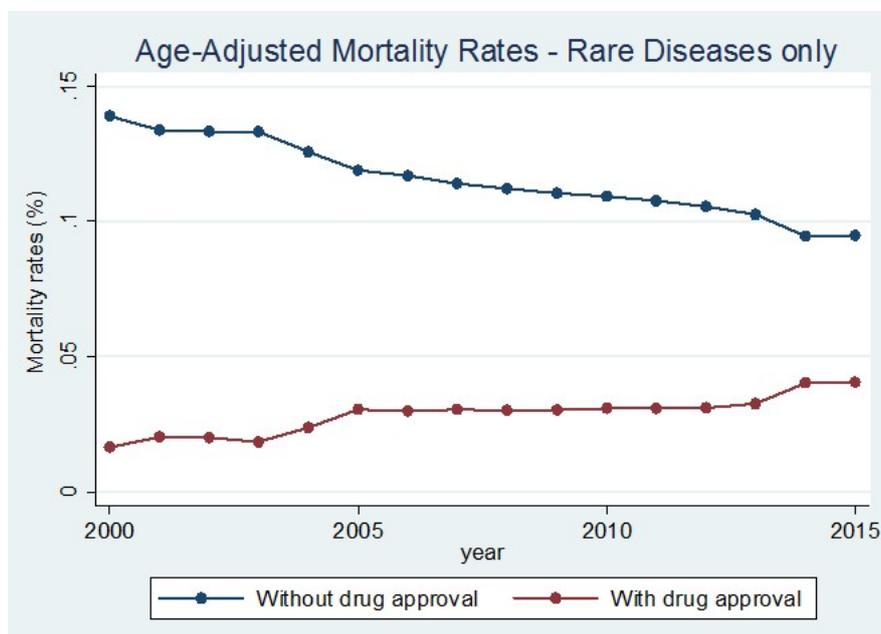


Table III.5.1 – DESCRIPTIVE STATISTICS

Variables	Whole sample			Treatment group		
	Treatment group	Control group	Diff.	Before	After	Diff.
YPLL65	5696	2192	-3505***	4153	5696	-1543**
YPLL70	8176	3135	-5040***	5963	8176	-2213**
YPLL75	11604	4393	-7211***	8360	11604	-3245***
YPLL80	16276	5997	-10278***	11506	16276	-4770***
YPLL85	22475	7940	-14535***	15495	22475	-6979***
Deaths	1815	484	-1331***	1061	1814	-754***
Academic Publications	353	108	-244***	172	353	-181***
Diagnostic Tests	0.50	0.13	-0.35***	0.10	0.50	-0.39***
Expert Centers	.44	.17	-0.27***	0.12	0.44	-0.32***
Observations	834	13150		752	834	
Nb Diseases	96	1179		96	96	

Note: This table shows the differences in means of all covariates between the treated and the control group, and in the control group before and after treatment based on t-tests. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.2 – YEARLY NUMBER OF APPROVED DRUGS

Year	# drugs	Mean # drugs / disease
1999	7	1
2000	7	1
2001	9	1
2002	2	1
2003	4	1
2004	7	1
2005	15	1
2006	6	1
2007	11	1
2008	4	1
2009	12	1
2010	7	1
2011	13	1
2012	16	1.2
2013	20	1.2
2014	21	1.1
2015	13	1.2

Note: # designates the number of approved drugs each year observed in the treatment group. Mean # drugs / disease designates the mean number of drugs per disease.

Table III.5.3 – IMPACT OF PHARMACEUTICAL INNOVATION ON YEARS OF POTENTIAL LIFE LOST

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
L.Drug Launches	-421*	-396	-353	-317	-275
	(246)	(344)	(474)	(629)	(809)
Disease fixed effects	Yes	Yes	Yes	Yes	Yes
Time fixed effects	Yes	Yes	Yes	Yes	Yes
Observations	11799	11799	11799	11799	11799

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.4 – IMPACT OF PHARMACEUTICAL INNOVATION ON YEARS OF POTENTIAL LIFE LOST

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
L.Drug Launches	-455** (246)	-450 (345)	-432 (477)	-424 (632)	-413 (813)
Expert Centers	11.4 (120)	63.9 (158)	143 (203)	206 (266)	255 (351)
Diagnostic Tests	269*** (135)	397*** (181)	559*** (247)	758*** (339)	971*** (449)
Disease fixed effects	Yes	Yes	Yes	Yes	Yes
Time fixed effects	Yes	Yes	Yes	Yes	Yes
Observations	11799	11799	11799	11799	11799

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.5 – TIME VARIATION — IMPACT OF PHARMACEUTICAL INNOVATION ON YEARS OF POTENTIAL LIFE LOST

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
years=[-4,-6[before adoption	-38.5 (193.1)	-39.8 (252.2)	-54.6 (328.5)	-94.1 (423.5)	-134.7 (543.0)
years=[-2,-4[before adoption	-163.3 (178.9)	-164.0 (240.9)	-178.5 (324.2)	-219.9 (425.6)	-285.5 (550.8)
years=[-2,0[before adoption	-204.4 (231.4)	-148.0 (315.7)	-58.3 (423.1)	64.5 (549.9)	219.8 (704.3)
years=[0,2[after adoption	-587.9 (368.7)	-565.1 (454.8)	-504.6 (569.4)	-398.4 (704.2)	-228.6 (867.3)
years=[2,4[after adoption	-665.1* (364.4)	-701.8* (420.4)	-744.0 (491.2)	-769.5 (568.8)	-736.2 (658.1)
years=[4,6[after adoption	-173.5 (421.0)	-128.8 (533.9)	-108.3 (689.4)	-119.1 (878.1)	-108.6 (1097.3)
years=[6,8[after adoption	-211.9 (578.0)	-76.0 (759.5)	60.1 (1004.6)	150.0 (1292.5)	272.8 (1619.2)
years=[8,10[after adoption	-392.3 (566.4)	-171.6 (777.3)	87.9 (1075.9)	306.6 (1432.7)	555.4 (1844.3)
years=[10,12[after adoption	-571.8 (551.3)	-367.5 (764.5)	-36.7 (1070.9)	294.2 (1458.6)	676.5 (1958.0)
years=[12,15[after adoption	-145.5 (371.9)	36.9 (551.6)	204.7 (748.2)	159.7 (890.9)	-168.9 (1114.4)
Expert Centers	22.3 (119.7)	81.4 (154.1)	165.8 (197.0)	234.2 (258.6)	291.1 (340.5)
Diagnostic Tests	253.6** (127.8)	362.9** (173.8)	501.1** (239.8)	673.4** (329.2)	856.2** (433.7)
Disease fixed effect	Yes	Yes	Yes	Yes	Yes
Year fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	13984	13984	13984	13984	13984

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.6 – IMPACT OF ACADEMIC INNOVATION ON YEARS OF POTENTIAL LIFE LOST

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
L.Academic Publications	-0.0 (0.1)	0.1 (0.1)	0.1 (0.2)	0.2 (0.2)	0.3 (0.3)
Disease fixed effect	Yes	Yes	Yes	Yes	Yes
Year fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	11799	11799	11799	11799	11799

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

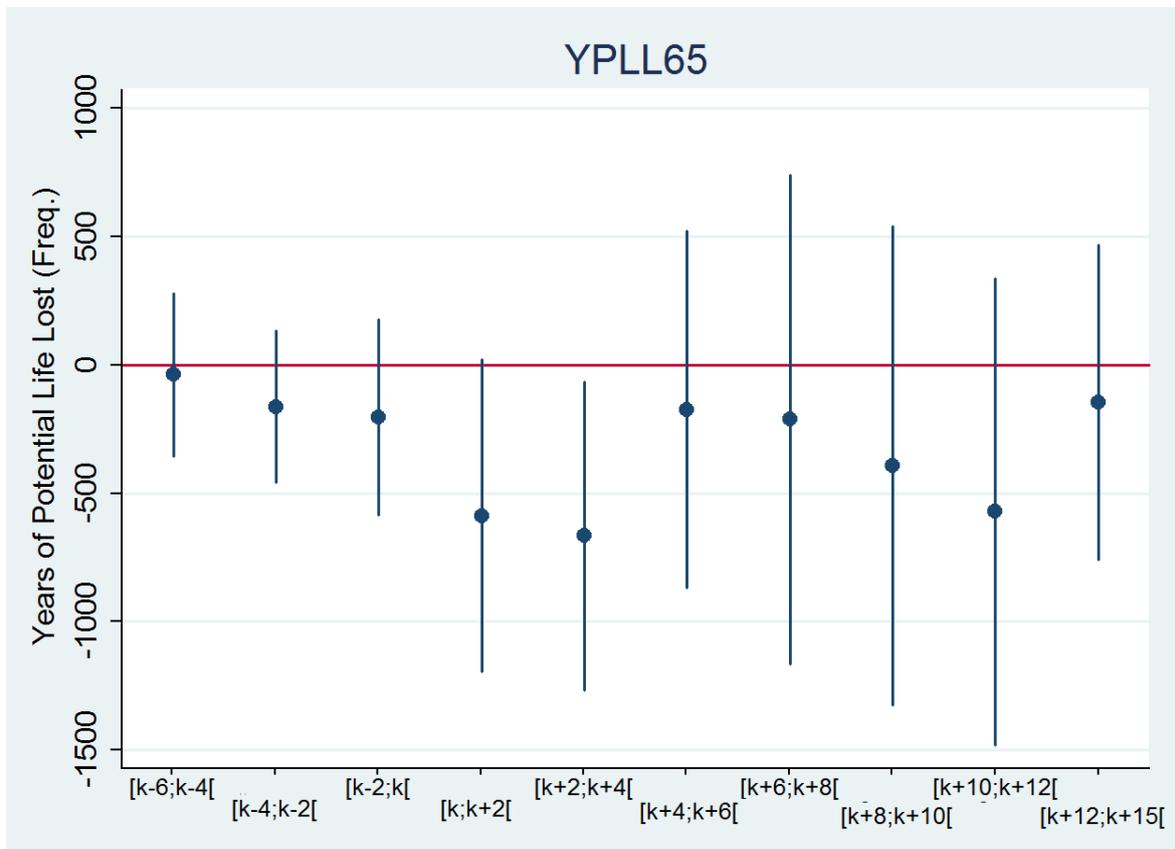
Table III.5.7 – IMPACT OF ACADEMIC PUBLICATIONS ON YEARS OF POTENTIAL LIFE LOST

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
L.Academic Publications	-0.0 (0.1)	0.0 (0.1)	0.1 (0.2)	0.2 (0.2)	0.3 (0.3)
Expert Centers	11.8 (78.6)	7.2 (110.1)	14.5 (153.4)	17.7 (205.3)	7.5 (269.4)
Diagnostic Tests	241.5 (213.1)	305.5 (269.3)	387.7 (344.4)	519.7 (469.0)	668.2 (622.1)
Disease fixed effect	Yes	Yes	Yes	Yes	Yes
Year fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	11799	11799	11799	11799	11799

Standard Errors in parentheses

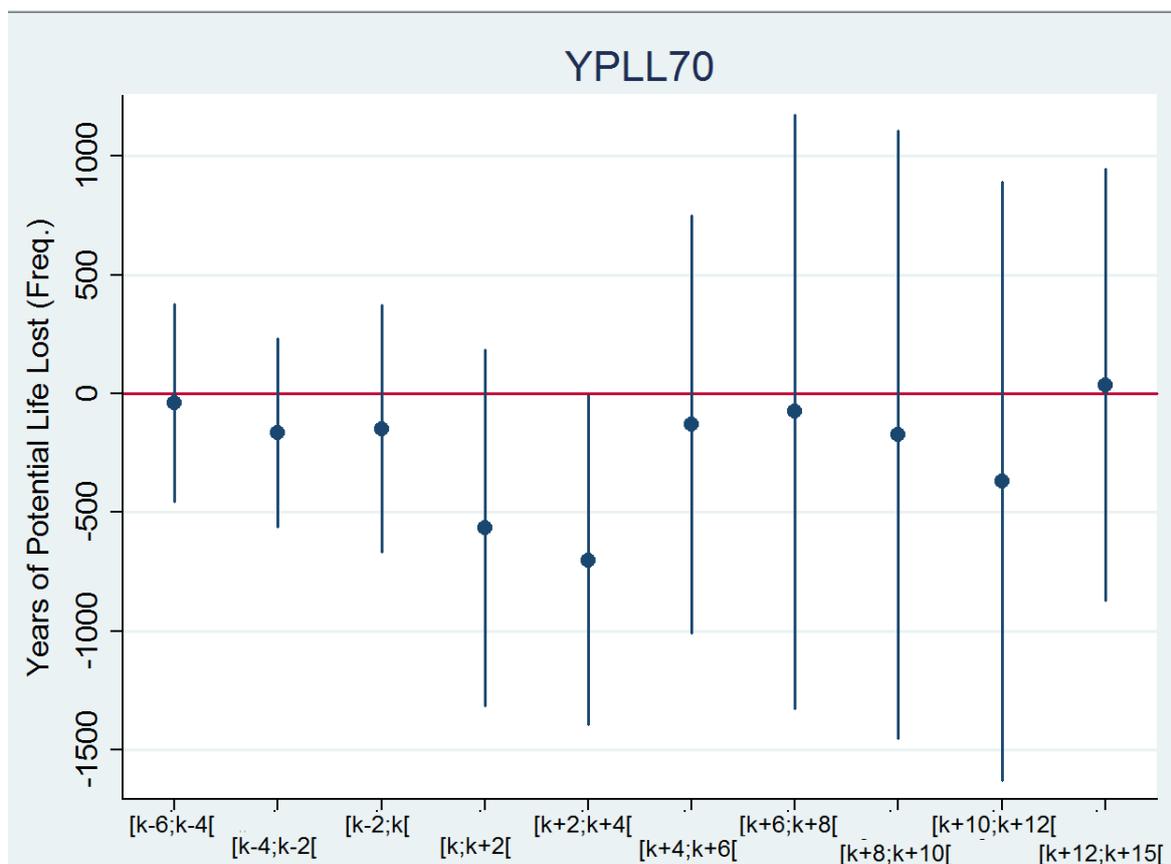
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Figure III.5.4 – TIME VARIATION — YPLL65



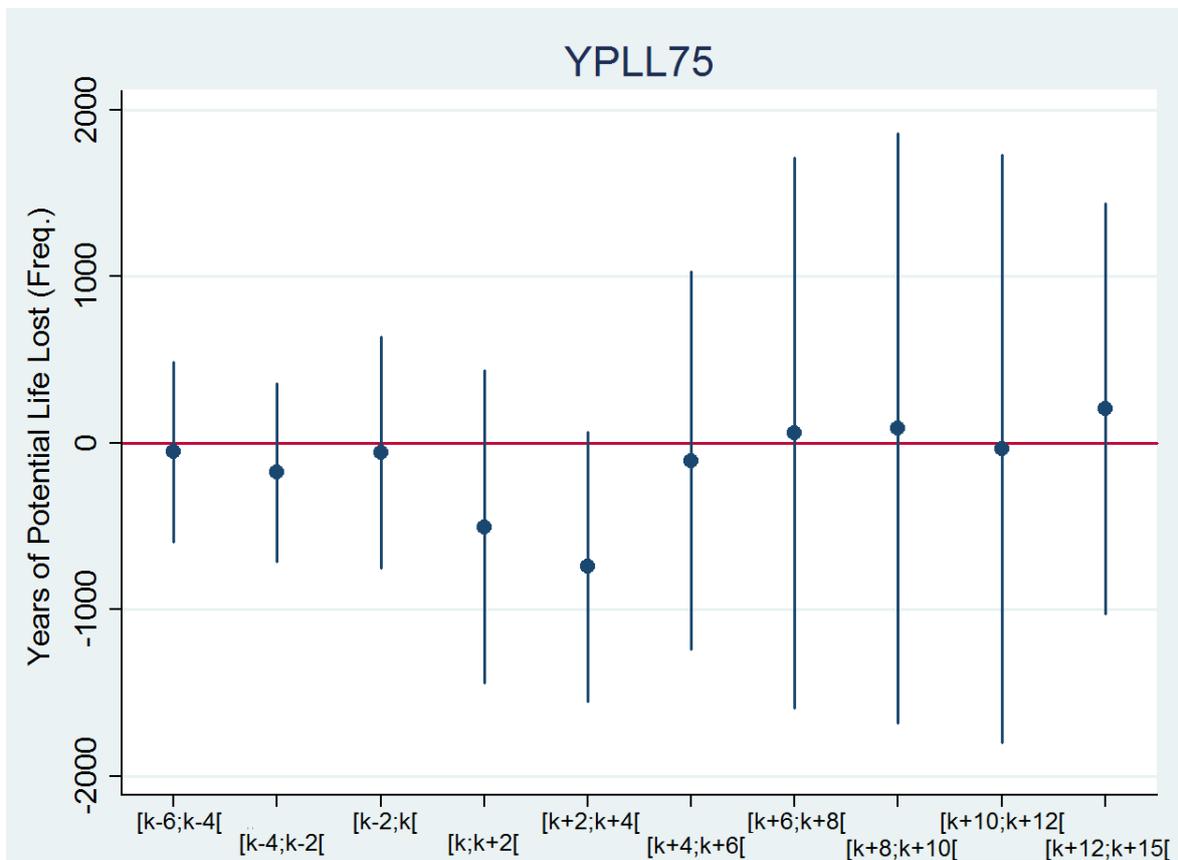
Note - This figure shows how Years of Potential Life Lost (age reference = 65) varies depending on the length of time to drug launch. The model includes disease fixed effects and year fixed effects. The graph includes 90% two-sided confidence intervals.

Figure III.5.5 – TIME VARIATION — YPLL70



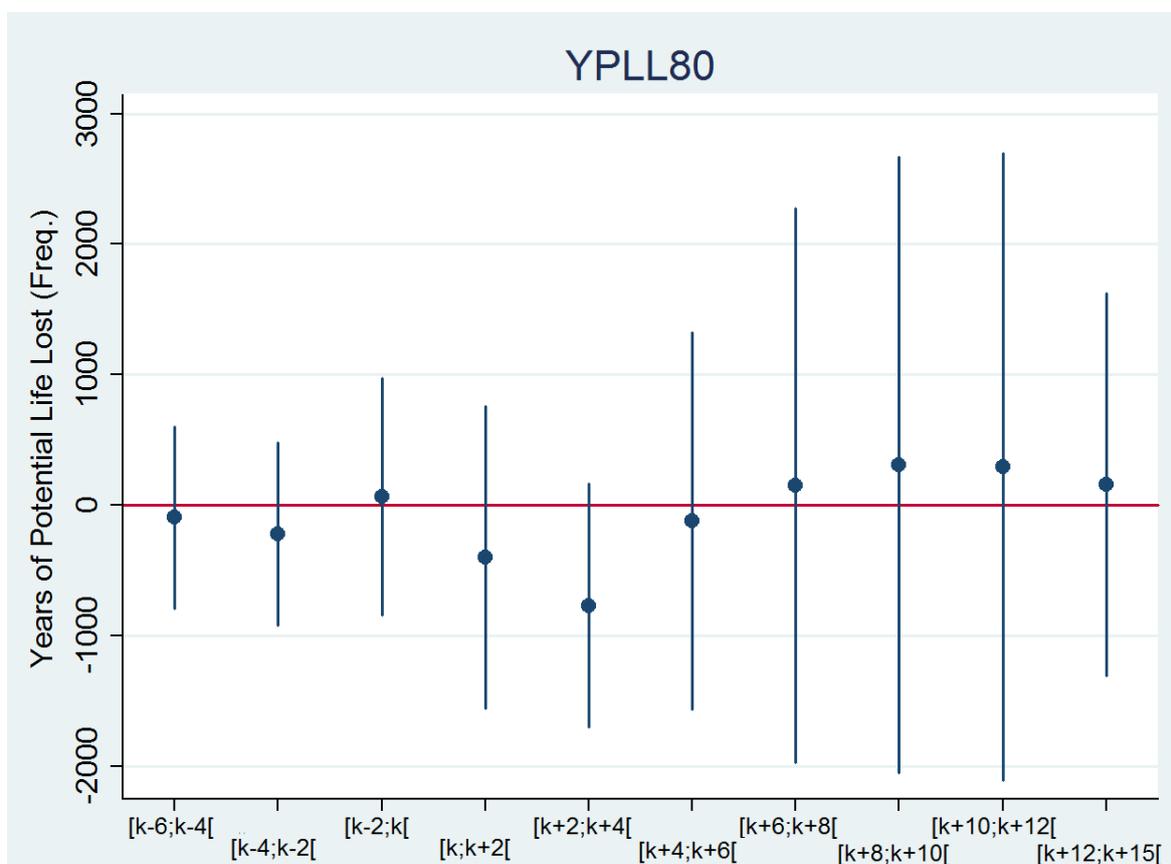
Note - This figure shows how Years of Potential Life Lost (age reference = 70) varies depending on the length of time to drug launch. The model includes disease fixed effects and year fixed effects. The graph includes 90% two-sided confidence intervals.

Figure III.5.6 – TIME VARIATION — YPLL75



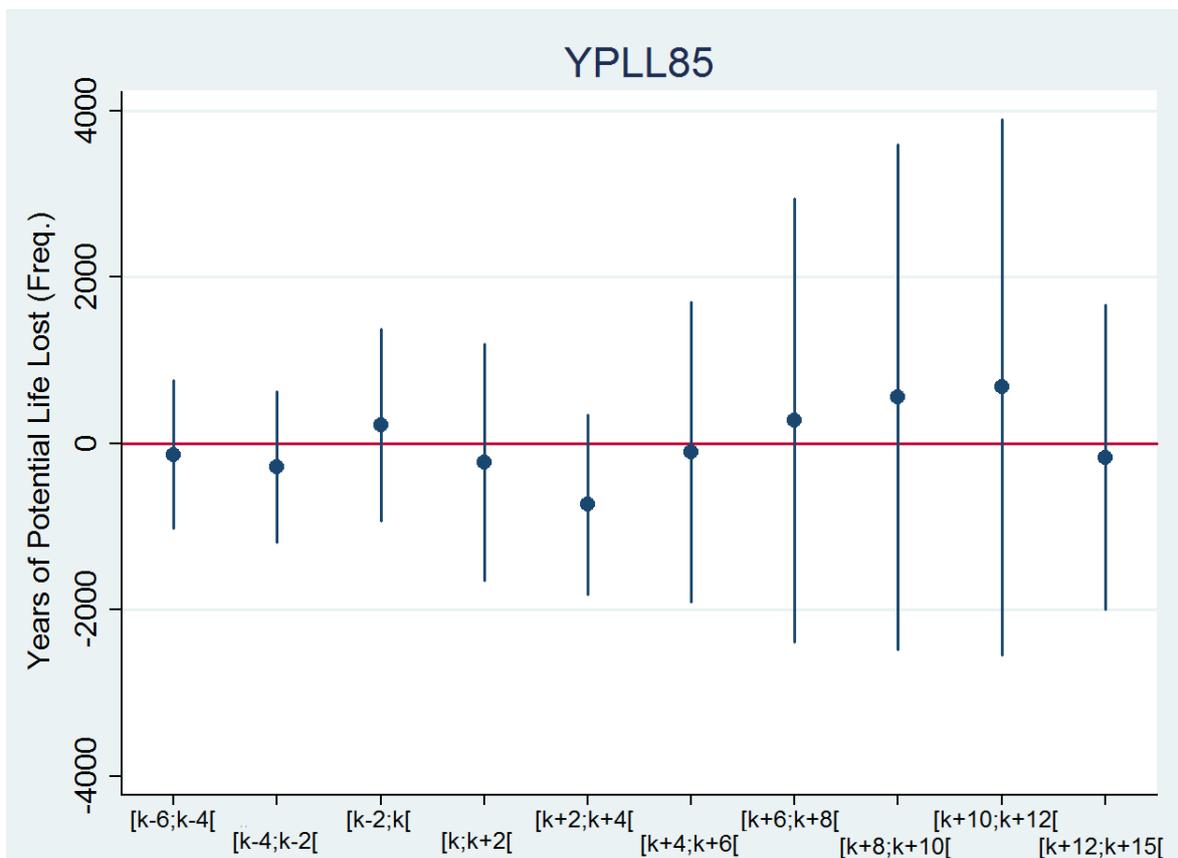
Note - This figure shows how Years of Potential Life Lost (age reference = 75) varies depending on the length of time to drug launch. The model includes disease fixed effects and year fixed effects. The graph includes 90% two-sided confidence intervals.

Figure III.5.7 – TIME VARIATION — YPLL80



Note - This figure shows how Years of Potential Life Lost (age reference = 80) varies depending on the length of time to drug launch. The model includes disease fixed effects and year fixed effects. The graph includes 90% two-sided confidence intervals.

Figure III.5.8 – TIME VARIATION — YPLL85



Note - This figure shows how Years of Potential Life Lost (age reference = 85) varies depending on the length of time to drug launch. The model includes disease fixed effects and year fixed effects. The graph includes 90% two-sided confidence intervals.

Table III.5.8 – ROBUSTNESS CHECK — IMPACT OF PHARMACEUTICAL INNOVATION ON YEARS OF POTENTIAL LIFE LOST, ONLY INCLUDING RARE DISEASES IDENTIFYING ICD-10 CODES

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
years=[0,2[after adoption	-1250.0 (812.0)	-1380.3 (880.8)	-1512.8 (953.6)	-1644.1 (1031.9)	-1783.3 (1116.1)
years=[2,4[after adoption	-1698.9* (953.8)	-1907.9* (1047.5)	-2133.9* (1151.5)	-2371.3* (1269.7)	-2618.1* (1403.0)
years=[4,6[after adoption	450.0 (1309.0)	415.6 (1438.1)	373.5 (1580.4)	323.2 (1741.5)	265.7 (1922.5)
years=[6,8[after adoption	860.9 (1640.2)	861.8 (1799.7)	844.6 (1980.4)	803.7 (2190.3)	763.6 (2430.4)
years=[8,10[after adoption	436.6 (1474.7)	378.7 (1646.0)	314.2 (1850.0)	238.5 (2095.2)	170.5 (2386.2)
years=[10,12[after adoption	118.4 (912.2)	88.2 (1061.8)	76.1 (1257.8)	72.8 (1512.0)	100.7 (1826.3)
years=[12,15[after adoption	-262.3 (763.0)	-377.1 (926.6)	-505.1 (1133.5)	-628.5 (1395.0)	-737.0 (1707.2)
Expert Centers	172.4 (146.8)	225.5 (177.8)	291.9 (227.7)	369.9 (302.0)	463.2 (404.6)
Diagnostic Tests	12.4 (159.6)	87.3 (230.0)	193.3 (338.3)	331.3 (489.1)	501.1 (685.5)
Disease fixed effect	Yes	Yes	Yes	Yes	Yes
Year fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	6101	6101	6101	6101	6101

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.9 – ROBUSTNESS CHECK — IMPACT OF PHARMACEUTICAL INNOVATION ON YEARS OF POTENTIAL LIFE LOST, ONLY INCLUDING DISEASES WITH ANNUAL AVERAGE NUMBER OF DEATHS BELOW 4,800

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
years=[0,2[after adoption	-1206.4 (790.7)	-1325.6 (857.6)	-1448.6 (928.0)	-1578.4 (1003.0)	-1717.3 (1083.4)
years=[2,4[after adoption	-1652.2* (913.5)	-1870.0* (1001.3)	-2114.4* (1098.1)	-2383.1** (1207.8)	-2666.9** (1332.3)
years=[4,6[after adoption	443.2 (1249.0)	407.2 (1373.4)	355.3 (1511.2)	279.4 (1667.5)	192.8 (1844.8)
years=[6,8[after adoption	765.8 (1541.8)	729.2 (1693.9)	644.4 (1868.3)	504.1 (2074.4)	347.9 (2314.2)
years=[8,10[after adoption	492.2 (1436.1)	458.0 (1600.8)	409.4 (1794.4)	325.1 (2023.7)	250.6 (2296.1)
years=[10,12[after adoption	209.6 (912.7)	193.3 (1046.2)	199.1 (1218.4)	185.2 (1439.5)	195.1 (1716.2)
years=[12,15[after adoption	-255.4 (749.4)	-371.2 (909.4)	-502.4 (1109.9)	-633.4 (1361.5)	-748.1 (1663.0)
Expert Centers	166.1 (144.5)	215.2 (175.0)	274.6 (224.3)	339.1 (298.0)	412.8 (399.9)
Diagnostic Tests	7.9 (161.6)	84.1 (229.4)	186.8 (334.2)	312.7 (480.9)	465.0 (672.4)
Observations	6135	6135	6135	6135	6135

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.10 – ROBUSTNESS CHECK — IMPACT OF PHARMACEUTICAL INNOVATION ON YEARS OF POTENTIAL LIFE LOST, ONLY INCLUDING DISEASES WITH ANNUAL AVERAGE NUMBER OF DEATHS BELOW 6,400

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
years=[0,2[after adoption	-1206.4 (790.7)	-1325.6 (857.6)	-1448.6 (928.0)	-1578.4 (1003.0)	-1717.3 (1083.4)
years=[2,4[after adoption	-1652.2* (913.5)	-1870.0* (1001.3)	-2114.4* (1098.1)	-2383.1** (1207.8)	-2666.9** (1332.3)
years=[4,6[after adoption	443.2 (1249.0)	407.2 (1373.4)	355.3 (1511.2)	279.4 (1667.5)	192.8 (1844.8)
years=[6,8[after adoption	765.8 (1541.8)	729.2 (1693.9)	644.4 (1868.3)	504.1 (2074.4)	347.9 (2314.2)
years=[8,10[after adoption	492.2 (1436.1)	458.0 (1600.8)	409.4 (1794.4)	325.1 (2023.7)	250.6 (2296.1)
years=[10,12[after adoption	209.6 (912.7)	193.3 (1046.2)	199.1 (1218.4)	185.2 (1439.5)	195.1 (1716.2)
years=[12,15[after adoption	-255.4 (749.4)	-371.2 (909.4)	-502.4 (1109.9)	-633.4 (1361.5)	-748.1 (1663.0)
Expert Centers	166.1 (144.5)	215.2 (175.0)	274.6 (224.3)	339.1 (298.0)	412.8 (399.9)
Diagnostic Tests	7.9 (161.6)	84.1 (229.4)	186.8 (334.2)	312.7 (480.9)	465.0 (672.4)
Observations	6135	6135	6135	6135	6135

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.11 – IMPACT OF PHARMACEUTICAL INNOVATION ON YEARS OF POTENTIAL LIFE LOST — SUB-SAMPLE ANALYSIS

	(1)	(2)	(3)	(4)	(5)
	YPLL65	YPLL70	YPLL75	YPLL80	YPLL85
L.Drug Launches	-640.8* (331.3)	-747.0* (433.1)	-865.3 (563.1)	-1013.0 (720.2)	-1161.2 (909.9)
Expert Centers	47.6 (169.4)	90.9 (265.2)	146.2 (397.4)	152.3 (533.1)	79.8 (681.4)
Diagnostic Tests	366.1** (165.6)	632.4** (246.1)	959.8*** (359.4)	1272.9*** (481.2)	1565.9** (627.0)
Observations	2061	2061	2061	2061	2061

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.12 – IMPACT OF PHARMACEUTICAL INNOVATION ON LN(YEARS OF POTENTIAL LIFE LOST)

	(1)	(2)	(3)	(4)	(5)
	ln(YPLL65)	ln(YPLL70)	ln(YPLL75)	ln(YPLL80)	ln(YPLL85)
L.Drug Launches	-0.3*** (0.1)	-0.3*** (0.1)	-0.3*** (0.1)	-0.3*** (0.1)	-0.2*** (0.1)
Disease fixed effect	Yes	Yes	Yes	Yes	Yes
Year fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	11799	11799	11799	11799	11799

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.13 – IMPACT OF PHARMACEUTICAL INNOVATION ON LN(YEARS OF POTENTIAL LIFE LOST)

	(1)	(2)	(3)	(4)	(5)
	ln(YPLL65)	ln(YPLL70)	ln(YPLL75)	ln(YPLL80)	ln(YPLL85)
L.Drug Launches	-0.3*** (0.1)	-0.3*** (0.1)	-0.3*** (0.1)	-0.2*** (0.1)	-0.2*** (0.1)
Expert Centers	-0.0 (0.1)	-0.1 (0.1)	-0.1 (0.1)	-0.1 (0.1)	-0.1 (0.1)
Diagnostic Tests	0.0 (0.1)	0.0 (0.1)	-0.0 (0.1)	-0.1 (0.1)	-0.0 (0.1)
Disease fixed effect	Yes	Yes	Yes	Yes	Yes
Year fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	11799	11799	11799	11799	11799

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III.5.14 – IMPACT ON ACADEMIC PUBLICATIONS ON LN(YEARS OF POTENTIAL LIFE LOST)

	(1)	(2)	(3)	(4)	(5)
	ln(YPLL65)	ln(YPLL70)	ln(YPLL75)	ln(YPLL80)	ln(YPLL85)
L.Academic Publications	-0.0* (0.0)	-0.0 (0.0)	-0.0 (0.0)	-0.0** (0.0)	-0.0** (0.0)
Disease fixed effect	Yes	Yes	Yes	Yes	Yes
Year fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	11799	11799	11799	11799	11799

Standard Errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

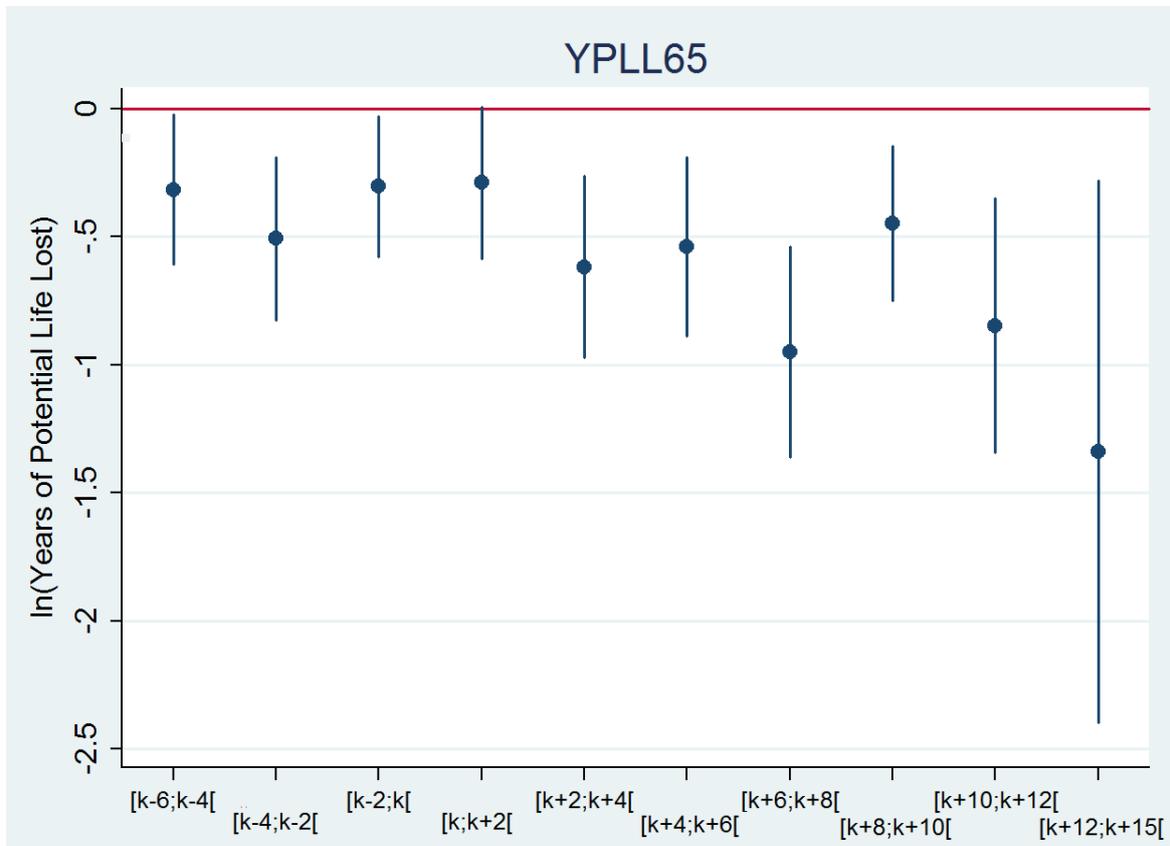
Table III.5.15 – IMPACT OF ACADEMIC PUBLICATIONS ON LN(YEARS OF POTENTIAL LIFE LOST)

	(1)	(2)	(3)	(4)	(5)
	ln(YPLL65)	ln(YPLL70)	ln(YPLL75)	ln(YPLL80)	ln(YPLL85)
L.Academic Publications	-0.0*	-0.0	-0.0	-0.0**	-0.0**
	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Experts Centers	-0.0	-0.1	-0.1	-0.1	-0.1
	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)
Diagnostic Tests	0.0	-0.0	-0.1	-0.1	-0.0
	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)
Disease fixed effect	Yes	Yes	Yes	Yes	Yes
Year fixed effect	Yes	Yes	Yes	Yes	Yes
Observations	11799	11799	11799	11799	11799

Standard Errors in parentheses

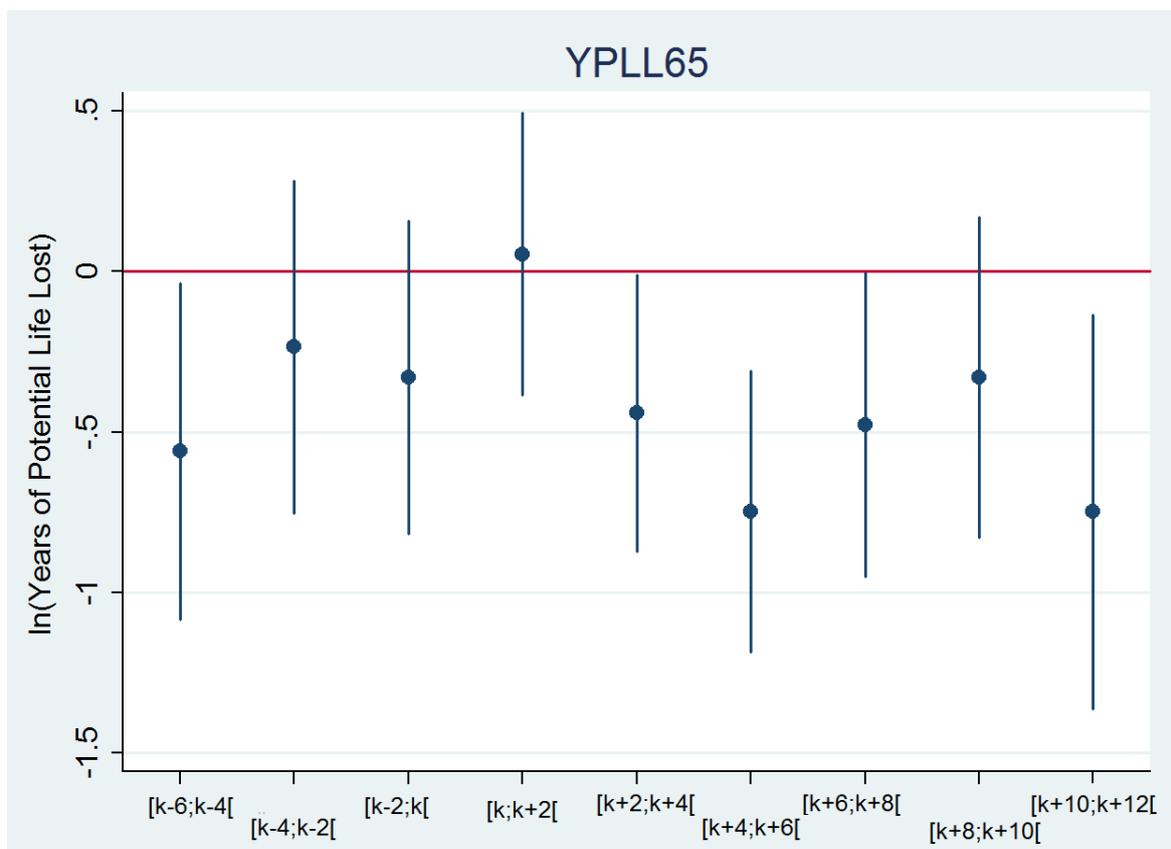
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Figure III.5.9 – TIME VARIATION — LN(YPLL65)



Note - This figure shows how ln(Years of Potential Life Lost) (age reference = 65) varies depending on the length of time to drug launch. The model includes disease fixed effects and year fixed effects. The graph includes 90% two-sided confidence intervals.

Figure III.5.10 – TIME VARIATION — LN(YPLL85)



Note - This figure shows how $\ln(\text{Years of Potential Life Lost})$ (age reference = 85) varies depending on the length of time to academic publication. The model includes disease fixed effects and year fixed effects. The graph includes 90% two-sided confidence intervals.

Table III.5.16 – LIST OF DRUG LAUNCHES PER YEAR WITH ICD-10

Disease name	ICD-10	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Botulism	A051					1										1			2
Cryptosporidiosis	A072				1														1
Coccidioidomycosis	B380													1					1
Aspergillosis	B440																	1	1
Zygomycosis	B460																	1	1
Squamous cell carcinoma of the oral tongue	C020																1		1
Hepatocellular carcinoma	C220							1											1
Gastrointestinal stromal tumor	C269			1												1			2
Pleural mesothelioma	C450						1												1
Desmoplastic small round cell tumor	C482											1			1				2
Embryonal rhabdomyosarcoma	C499			1															1
Malignant granulosa cell tumor of ovary	C56																1		1
Malignant tumor of fallopian tubes	C570											1							1
Familial prostate cancer	C61		1																1
Neuroepithelioma	C719							1				1							2
Familial medullary thyroid carcinoma	C73							1						1	1			1	4
Parathyroid carcinoma	C750						1												1
Nodular lymphocyte predominant Hodgkin's lymphoma	C810													1					1
Follicular lymphoma	C820															1	1		2
Mantle cell lymphoma	C831					1		1								1			3
Precursor B-cell acute lymphoblastic leukemia	C835																	1	1
Subcutaneous panniculitis-like T-cell lymphoma	C836											1						1	2
Localized pagetoid reticulosis	C840											1		1		1	1		4
Sézary syndrome	C841											1					1		2
Primary cutaneous unspecified peripheral T-cell lymphoma	C844											1					1		2
Waldenström macroglobulinemia	C880															1			1
Multiple myeloma	C900	1				1		1			1				1	1			6
Precursor T-cell acute lymphoblastic leukemia	C910			1			1	1	1					1			1		6
B-cell chronic lymphocytic leukemia	C911			1								1						1	3
Adult T-cell leukemia/lymphoma	C915											1						1	2
Chronic myeloid leukemia	C921			1					1	1									3
Acute promyelocytic leukemia	C924		1																1
Acute myelomonocytic leukemia	C925		1																1
Acute monoblastic leukemia	C927		1																1
Chronic myelomonocytic leukemia	C931			1															1

ORPHAN DRUGS AND LONGEVITY IN THE US REVISITED

Table III.5.16 continued from previous page

Disease name	ICD-10	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Acute megakaryoblastic leukemia in Down syndrome	C942		1																1
Mastocytosis	C962			1															1
Solitary fibrous tumor	D219														1				1
Cushing disease	D352														1				1
Bronchial endocrine tumor	D381												1						1
Polycythemia vera	D45													1					1
Refractory anemia	D467							1											1
Essential thrombocythemia	D473													1					1
Giant cell tumor of bone	D480															1			1
Lymphangi leiomyomatosis	D487																	1	1
Hemoglobinopathy	D560							1						1					2
Beta-thalassemia	D561							1						1					2
Sickle cell anemia	D570							1											1
Hemoglobin C disease	D582							1											1
Atypical hemolytic-uremic syndrome	D588									1									1
Paroxysmal nocturnal hemoglobinuria	D595									1									1
Idiopathic aplastic anemia	D610										1								1
Acquired purpura fulminans	D65									1									1
Hemophilia B	D67															1			1
Von Willebrand disease type 1	D680	1								1								1	3
Familial hypodysfibrinogenemia	D682	1						1	1	1		1		1		1			7
Acquired prothrombin deficiency	D684																1		1
Gray platelet syndrome	D691																1		1
Immune thrombocytopenic purpura	D693										1					1			2
Necrobiotic xanthogranuloma	D763													1					1
Hereditary angioedema type 3	D841										1	1		1					3
Familial parathyroid adenoma	E210						1												1
Pituitary gigantism	E220									1							1		2
Kallmann syndrome	E230									1									1
Autoimmune polyendocrinopathy type 1	E310																	1	1
Carcinoid tumor and carcinoid syndrome	E340									1									1
Laron syndrome	E343							1											1
Peroxisomal acyl-CoA oxidase deficiency	E713	1																	1
Hartnup disease	E720														1				1
Citrullinemia	E722												1						1
Glycogen storage disease	E740								1				1						2
Niemann-Pick disease type A	E752												1		1		1		3
Cerebrotendinous xanthomatosis	E755																	1	1
Mucopolysaccharidosis type 1	E760					1													1

Table III.5.16 continued from previous page

Disease name	ICD-10	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Mucopolysaccharidosis type 2	E761								1										1
Mucopolysaccharidosis type 3	E762							1									1		2
Sitosterolemia	E780														1	1		1	3
Cystic fibrosis	E840												1		1			1	3
Familial Mediterranean fever	E850											1			1				2
Alpha-1-antitrypsin deficiency	E880			1															1
Atypical juvenile parkinsonism	G20						1												1
Focal, segmental or multifocal dystonia	G243		1																1
Lennox-Gastaut syndrome	G404												1	1					2
CANOMAD syndrome	G618														1				1
Neuromuscular junction disease	G700									1									1
Dopamine beta-hydroxylase deficiency	G908																1		1
Idiopathic and/or familial pulmonary arterial hypertension	I270	1	1	1	1		1			1								1	7
Acquired aneurysmal subarachnoid hemorrhage	I609															1			1
Familial cerebral saccular aneurysm	I671															1			1
Juvenile idiopathic arthritis	M080	1						1											2
Infant acute respiratory distress syndrome	P220	1																	1
Congenital short bowel syndrome	Q438						1												1
Tuberous sclerosis complex	Q851												1						1
Pfeiffer-Palm-Teller syndrome	Q871							1											1
Hepatocellular carcinoma	C220																2		2
Familial medullary thyroid carcinoma	C73															2			2
Precursor T-cell acute lymphoblastic leukemia	C910														2				2
B-cell chronic lymphocytic leukemia	C911															2			2
Idiopathic pulmonary fibrosis	J841																2		2
Systemic-onset juvenile idiopathic arthritis	M082															2			2
Multiple myeloma	C900																	3	3
Chronic myeloid leukemia	C921														3				3
Total		7	7	9	2	4	7	15	6	11	4	12	7	13	16	20	21	13	174

Chapitre 6

Seuil d'acceptabilité des technologies
de santé : quel retour d'expérience
20 ans après ?

1 Introduction

L'existence de contraintes sur les ressources budgétaires pousse les pouvoirs publics à se doter d'outils d'aide à la décision afin d'optimiser le panier de biens et services remboursables aux assurés sociaux. Pour répondre à cet objectif de gestion efficace des ressources budgétaires, la considération du coût de chaque poste de dépenses est associée à celle des gains en santé espérés du nouvel investissement (Weinstein and Stason, 1977). Transposé au seul secteur de la santé, l'exigence d'une allocation efficace des ressources signe la genèse des méthodes d'évaluation des nouvelles technologies de santé comparant l'efficacité et le coût des technologies innovantes aux technologies conventionnelles. En particulier, le concept du QALY qui combine la dimension de durée de vie gagnée avec les préférences associées à la qualité de vie de ces années de vie, s'érige en instrument de comparaison des bénéfices de chaque traitement entre pathologies différentes et fonde l'application des études coût-résultat, ou plus précisément coût-utilité, dans le domaine de la santé. Une échelle de qualité de vie générique, comme par exemple le questionnaire de l'EQ-5D (Szende et al., 2007; Dolan, 2011), est utilisée pour évaluer un état de santé. Les mesures d'état de santé sont ensuite transformées en mesures d'utilité à partir d'estimations en population générale des préférences associées à chaque état de santé. En 1999, le premier organisme d'évaluation économique de produits de santé disponibles pour les patients du NHS s'établit en Angleterre et au pays de Galles. Le *National Institute of Care Excellence*, devenu en 2005 le NICE définit les recommandations nationales sur les traitements et les soins disponibles au sein du NHS anglais avec le double objectif d'excellence clinique et d'équilibre budgétaire. Le fondement social et scientifique de l'évaluation prend racine en 2005 par la publication du guide intitulé *Social Value Judgements : Principles for the NICE guidance* (Rawlins and Culyer, 2004). Parmi les responsabilités du NICE, le programme d'évaluation des technologies de santé a pour mission de réguler les dépenses liées aux médicaments onéreux, en recommandant ou déconseillant leur remboursement au sein du NHS, ou en redéfinissant l'indication remboursable par rapport à celle de l'Autorisation de Mise sur le Marché.

Les évaluations des technologies de santé peuvent prendre deux formes : la première, d'une durée d'un an, est une évaluation simple s'intéressant à une technologie innovante unique pour le traitement d'une pathologie. La seconde, évaluation multiple, compare différents traitements innovants élaborés par différents industriels du médicament l'évaluation peut alors durer jusqu'à deux ans. Le processus d'évaluation se caractérise par la succession de trois phases : durant la première phase de *scoping* (cadrage) s'opère la sélection de la technologie à évaluer. Cette phase est suivie par l'élaboration d'un rapport dit d'*assessment*

(appréciation) produit par une équipe académique indépendante à partir des données de preuve (médicales et médico-économiques) rendues disponibles par l'industriel porteur du dossier. Enfin, la troisième phase dite d'*appraisal* réside dans l'élaboration du rapport final d'évaluation et comporte la recommandation finale (pour une revue détaillée des différentes étapes de la procédure d'évaluation du NICE, voir (Tubeuf, 2010)). La décision relative à la prise en charge de la technologie de santé au sein du panier de biens et services du NHS repose sur les différents éléments de discussion débattus lors de la réunion du comité d'évaluation, dont notamment les résultats de l'analyse coût résultat. Celle-ci met en regard les bénéfices de santé en gain par QALY et les coûts engendrés par la technologie de santé (traitement et suivi) du point de vue du payeur, c'est-à-dire du NHS, par le calcul du ratio différentiel coût résultat, ICER) qui représente la variation des coûts en fonction des changements de la combinaison qualité de vie et survie des patients sous l'effet de la nouvelle technologie de santé. La valeur de l'ICER est alors confrontée à un seuil d'acceptabilité ou de coût-efficacité fixé de façon discrétionnaire par le NICE. Les décisions de prise en charge d'une technologie de santé sont opposables au NHS qui doit donner l'accès aux médicaments acceptés par le NICE dans les trois mois suivant la publication de leur recommandation. Les principes méthodologiques et la portée économique du processus d'évaluation des technologies de santé illustrent la philosophie et la volonté du E de maximiser l'utilité collective. Parmi les critères décisionnels du NICE, le seuil d'acceptabilité des technologies de santé joue un rôle central et représente le coût acceptable pour une année de vie en bonne santé, i.e. un QALY.

L'objet de cet article est de décrire les modalités d'application de ce seuil puis de discuter son utilisation par le NICE dans l'évaluation des technologies de santé.

Aujourd'hui, le Royaume-Uni est le seul pays qui utilise un seuil explicite pour la production des décisions en santé. Cependant d'autres pays utilisent un seuil implicite comme critère d'entrée dans le panier de soins. Par exemple, la Suède utilise le seuil de 57,000 par année de vie en bonne santé et les Pays-Bas utilisent le seuil de 80,000 par année de vie en bonne santé (Vallejo-Torres et al., 2016). En France, aucun seuil explicite n'est énoncé et la décision de remboursement ou d'inclusion dans le panier de soins est essentiellement fondée sur l'évaluation du service médical rendu et de l'amélioration du service médical rendu. Néanmoins, et ce depuis 2013¹, un avis d'efficience doit être produit par la Commission Évaluation Économique et de Santé Publique (CEESP) pour certains médicaments ou dispositifs médicaux jugés innovants et susceptibles d'avoir un impact significatif sur les dépenses de l'assurance maladie². Bien que ces résultats servent de critères dans la

¹Décret n2012-1116 du 2 octobre 2012 (article R.161-71-1 du Code de la sécurité sociale)

²Un avis d'efficience doit être formulé par la Commission Évaluation Économique et de Santé Publique

négociation de prix réalisée, le rôle de l'évaluation médico-économique dans le processus décisionnel - lui-même dans son ensemble peu transparent - reste méconnu. Pour autant, la CEESP commente les ratios différentiels coût-résultat des produits qu'elle considère et les qualifie "d'excessifs" ou "d'élevés", faisant par-là référence à l'existence implicite d'un seuil (HAS, 2018). Dans le débat d'experts, l'idée d'une évaluation médico-économique participant véritablement à définir le contenu du panier de biens et services remboursables émerge et remet en question l'utilisation purement consultative et informationnelle, aujourd'hui faite en France, des avis d'efficience.

Dans ce contexte, il apparaît crucial de revenir sur l'expérience britannique. Loin d'être un plaidoyer en faveur ou en défaveur de l'utilisation d'un seuil d'acceptabilité des technologies de santé, cet article apporte un éclairage sur les débats universitaires actuels et passionnés sur la place de l'évaluation médico-économique en santé qui éprouvent la Grande-Bretagne. Nous reviendrons dans une première partie sur la définition d'un seuil d'acceptabilité des technologies de santé, et de l'utilisation par le NICE de cet outil. Dans une seconde partie, nous évoquerons comment le NICE fait face à ses missions d'efficience et d'équité dans ses choix d'allocation en santé. Les dérogations prévues par le NICE ainsi que les écarts au modèle évaluatif de référence, comme observé dans le cas des médicaments orphelins, seront identifiés. De plus, la présentation des récents travaux mandatés par le NICE sur le coût d'opportunité des dépenses de santé nous permettra de discuter le niveau du seuil d'acceptabilité des dépenses de santé aujourd'hui employé par le NICE et de s'interroger sur l'opportunité de sa revalorisation. Enfin, une dernière section conclura notre article.

pour tout médicament ou dispositif médical remplissant les deux conditions suivantes : (i) La reconnaissance ou la confirmation d'une amélioration du service médical rendu ou du service attendu, majeure, importante ou modérée, au sens du 2 de l'article R.163-18 et du 3 de l'article R. 165-11, est sollicitée par l'entreprise; (ii) Le produit ou la technologie a ou est susceptible d'avoir un impact significatif sur les dépenses de l'assurance maladie compte tenu de son incidence sur l'organisation des soins, les pratiques professionnelles ou les conditions de prise en charge des malades et, le cas échéant, de son prix. (Site Web Haute Autorité de Santé (HAS), https://www.has-sante.fr/portail/jcms/r_1502595/fr/evaluation-medico-economique-des-produits-de-sante)

2 L'utilisation du seuil d'acceptabilité des technologies de santé

2.1 La définition du seuil d'acceptabilité des technologies de santé

Loin d'objectiver la seule résolution des décideurs publics à réduire les dépenses consenties en faveur du secteur de la santé, l'évaluation médico-économique est justifiée au NICE par la volonté de faire des choix d'investissements éclairés afin d'optimiser l'usage des ressources du système de santé par le déploiement des principes méthodologiques de l'analyse coût-efficacité. La transparence du processus d'évaluation des traitements innovants et des critères de décision quant à leur recommandation au sein du NHS permet également de renforcer la prise de responsabilité (*accountability*) des décideurs publics (Jeantet et al., 2014), et d'offrir une plus grande acceptabilité des recommandations finales de la part du grand public. C'est lors de l'interprétation du ratio différentiel coût résultat, représentant la variation des coûts en fonction des changements en termes d'années de vie pondérées par la qualité de vie sous l'effet de la nouvelle technologie de santé, que le seuil d'acceptabilité des technologies de santé est mobilisé pour guider la décision publique d'allocation des ressources collectives. Lorsque la technologie de santé est à la fois moins coûteuse et plus efficace, ou plus coûteuse et moins efficace que son comparateur, l'interprétation de l'analyse coût-efficacité est triviale et ne fait pas intervenir le seuil d'acceptabilité des technologies de santé. Cependant, lorsque la technologie de santé est à la fois plus efficace et plus coûteuse que son comparateur, l'interprétation du ratio différentiel coût résultat et la décision d'allocation des ressources doit juger de l'acceptabilité du surcoût monétaire estimé par rapport au gain de santé (Raimond et al., 2016).

Le seuil d'acceptabilité des technologies de santé correspond au montant maximum que la collectivité est prête à assumer pour une unité de santé supplémentaire. Au sein de la résolution d'un programme de maximisation des bénéfices santé sous contrainte budgétaire, le seuil d'acceptabilité des technologies de santé reflète le coût d'opportunité d'un QALY supplémentaire. Ainsi, le seuil d'acceptabilité des technologies de santé dépend du budget consacré à la santé, et s'élèverait à ce titre en phase d'expansion budgétaire et respectivement diminuerait en phase de restriction budgétaire. Dans le mesure où le seuil initialement fixé représente la productivité marginale du secteur, l'introduction de technologies de santé de plus en plus performantes dans le panier de biens et services de

santé remboursables devrait conduire à une diminution du seuil pour répondre à l'augmentation de la productivité du secteur de la santé (Claxton et al., 2013; Jeantet et al., 2014; Thokala et al., 2018).

2.2 De son utilisation par le NICE

Bien que l'évaluation des produits de santé se développe dès la fin des années 90 en Angleterre, c'est en 2004 que le NICE fait mention explicite d'un niveau de seuil d'acceptabilité des technologies de santé dans le *Guide to the Methods of Technology Appraisal* (NICE, 2004). La méthodologie d'évaluation et l'existence d'un seuil d'acceptabilité des technologies de santé ont des implications importantes en termes de choix de répartition des bénéfices en santé par les pouvoirs publics au sein de la population. Le calcul des utilités associées à chaque état de santé dans l'approche par QALY s'appuie sur des enquêtes réalisées en population générale et n'attribue pas de poids spécifique à chaque pathologie. A ce titre, le QALY comme outil de mesure du gain en santé garantit la comparabilité entre les pathologies et témoigne de la volonté de maximisation utilitariste du NICE ainsi que de sa responsabilité envers chaque patient. Autrement dit, en théorie, aucune augmentation d'un bénéfice en santé pour une catégorie de patient ne pourrait être consentie si elle conduit à la détérioration de la santé d'une autre. La fixation du seuil monétaire tel que décrit dans la section 2.1, rapportant le supplément de coût induit par la technologie de santé à son efficacité thérapeutique additionnelle, exige une connaissance exhaustive du coût par QALY de chacun des programmes de santé financés par le NHS. De telles données permettent de s'assurer qu'aucun programme de santé auparavant pris en charge par le NHS n'est abandonné (*displaced*) au profit d'une technologie moins efficace. Ce seuil s'apparente au coût d'opportunité de la dépense consentie au profit d'une nouvelle technologie de santé innovante, étant donnée la contrainte de budget du NHS (Claxton et al., 2013; McCabe et al., 2008). Il est cependant impossible d'avoir une information complète de l'état du budget et de la somme des gains en santé à disposition à chaque nouvelle recommandation. C'est la justification invoquée par le NICE, qui en 2004, a préféré opter pour un intervalle de coût-efficacité établi par un consortium d'experts du NICE, lui laissant une marge de manœuvre plus large (Rawlins and Culyer, 2004). Dans le cas où l'ICER d'une technologie de santé se situe en-deçà de la borne inférieure de £20,000 par QALY, la technologie est considérée très coût-efficace et fera l'objet *a priori* d'une recommandation positive de la part du NICE. Entre £20,000 et £30,000 par QALY la technologie innovante est considérée coût-efficace par le NICE mais la recommandation s'appuie davantage sur des critères tels que le degré

d'incertitude qui entoure le calcul de l'ICER, le degré d'innovation de la technologie de santé, la spécificité de la population à laquelle s'adresse la technologie de santé, les bénéfices sociaux espérés et non représentés au travers de l'analyse coût-efficacité (Claxton et al., 2015b). En particulier, si l'ICER de la technologie de santé étudiée excède la borne inférieure de l'intervalle, le NICE pourra exiger une plus grande certitude autour de la valeur de l'ICER, ou au contraire, considérer que la valeur de l'ICER et la valeur du seuil sont non significativement différentes (Towse et al., 2002). S'agissant de la population, de l'innovation et des bénéfices espérés, le NICE s'interrogera sur l'opportunité d'accorder une plus grande valeur aux gains de santé pour les technologies de santé remplissant ces critères. Au-delà de la borne supérieure de l'intervalle (i.e. £30,000 par QALY) la technologie de santé sera jugée *a priori* inefficace et fera l'objet d'une non-recommandation.

Des travaux académiques menés rétrospectivement sur les décisions du NICE et en particulier sur le seuil d'acceptabilité des technologies de santé, confirment que les technologies de santé dont les ICER ne respectaient pas l'intervalle du seuil définis par le NICE avaient une probabilité plus importante de faire l'objet d'une non-recommandation (Devlin and Parkin, 2004; Dakin et al., 2015). Plus précisément, Dakin et coauteurs (Dakin et al., 2015) ont récolté les décisions relatives à 229 technologies de santé, correspondant à 763 décisions³ rendues entre 1999 et 2011 de recommandation de prise en charge de la part du NICE et ont prédit dans cet échantillon la probabilité de rejet de la technologie en fonction du niveau de l'ICER. Leurs résultats montrent qu'à mesure que la valeur de l'ICER de la technologie de santé augmente et s'éloigne de la borne inférieure, la probabilité de faire l'objet d'une recommandation positive de la part du NICE diminue, et par analogie, le NICE a recommandé 75% des technologies de santé dont l'ICER est inférieur ou égal à £27,000 par QALY. Toutefois, bien que l'intervalle d'acceptabilité des technologies de santé joue un rôle crucial dans la décision finale, il apparaît qu'une technologie dont l'ICER excède la borne supérieure de l'intervalle (i.e. £30,000 par QALY) ne fait pas automatiquement l'objet d'un refus, et la probabilité de rejet a été estimée à 50% pour l'intervalle £39,417 - £43,949 par QALY. Ainsi, bien que le seuil de décision ait été rendu explicite par le NICE afin de maximiser les gains de santé au sein de la population, le rejet des technologies de santé dont l'ICER excède la borne supérieure du seuil d'acceptabilité et qui seraient donc jugées non efficaces, n'a pas un caractère systématique.

³En effet, un seul médicament peut faire l'objet d'un dossier au titre de plusieurs indications thérapeutiques.

2.3 De seuil, je n'ai que le nom

La mise en perspective de la définition formelle du seuil d'acceptabilité des technologies de santé et de la description de l'outil couramment utilisé par le NICE dans le cadre des évaluations des produits de santé fait apparaître un certain nombre de discordances. D'une part, pour reprendre le vocable du NICE lui-même, le niveau du seuil n'a pas de "fondement empirique" (Claxton et al., 2015a; Rawlins and Culyer, 2004). Ce niveau s'explique, comme discuté précédemment, par le volume et la spécificité des données à produire pour estimer empiriquement la valeur d'un seuil d'acceptabilité des dépenses de santé. A ce problème de faisabilité s'ajoute la volonté du NICE de ne pas s'imposer une contrainte trop rigide par une valeur de seuil d'acceptabilité unique dans ses décisions de recommandation et de s'autoriser à considérer un intervalle d'acceptabilité de £20,000 à £30,000 par QALY. Enfin, la pérennité de cet intervalle est également à souligner, puisqu'il est resté identique depuis 2004 et n'a varié ni avec la productivité des technologies de santé ni avec la conjoncture économique au Royaume-Uni. De fait, si la valeur de l'intervalle s'approchait d'un coût d'opportunité de chaque nouvelle décision dans les dépenses de santé du système anglais, cet intervalle n'aurait aucune raison d'être resté constant au cours d'une si longue période. L'on en vient alors à s'interroger sur la pertinence de l'outil dont le fondement théorique et la dynamique pratique sont en contraste.

3 Le paradigme efficience-équité

3.1 La différenciation des exigences d'efficience

Le caractère non automatique des décisions de rejet d'une technologie de santé au regard de sa seule efficience illustre la poursuite d'autres objectifs que celui de la seule maximisation des gains de santé sous contrainte de revenus. La promotion de l'innovation et les besoins de santé de populations de patients spécifiques, tels que les patients atteints de maladies rares ou les patients en fin de vie, sont autant d'arguments invoqués par le NICE pour justifier des dérogations dans les décisions de prise en charge des technologies de santé. Par exemple, depuis le rapport Kennedy en 2009 (Kennedy, 2009), les traitements en fin de vie, touchant moins de 7,000 patients, dont l'espérance de vie est estimée à moins de 24 mois et ne disposant pas de traitement d'au moins la même efficacité, font partie d'un cas particulier et leur seuil de coût-efficacité peut aller de £50,000 à £70,000 par QALY. De même, les anticancéreux innovants disposent depuis 2010 d'une enveloppe spécifique (*Cancer Drugs Fund*) de 200 millions de livres sterling par an (Dixon et al., 2016). Enfin, les médicaments orphelins⁴ et ultra-orphelins font l'objet depuis 2012 d'un traitement réglementaire spécifique qui leur permet de faire l'objet d'une recommandation positive par le NICE pour des ICERs s'élevant jusqu'à £100,000 par

⁴Les médicaments dits "orphelins" sont destinés au traitement de maladies rares

QALY, un seuil d'acceptabilité qui a été revalorisé à £300,000 par QALY en mai 2017 (NICE, 2017). Ces revalorisation du seuil d'acceptabilité des dépenses de santé, s'élevant jusqu'à dix fois le seuil couramment employé, apparaissent comme un procédé de soutien à l'innovation en faveur des catégories de patients desservis par les options thérapeutiques, et dont les molécules innovantes peuvent avoir un véritable retentissement sur leur qualité de vie (*Life Transforming Gains*) (Garrison et al., 2017). La tarification basée sur la valeur (*Value-Based Pricing*) se situe dans la continuité de ses dispositifs dérogatoires, et prône la prise en compte du fardeau de la maladie (*Burden Of Illness*) et des gains sociétaux potentiellement générés par la technologie de santé (*Societal Benefit*) dans les choix d'allocation des ressources en santé. Cette démarche d'utilisation de références plus larges que le seul gain de santé dans l'évaluation des technologies de santé a notamment été soutenue sans succès⁵ par les défenseurs de l'évaluation basée sur la valeur (*Value-Based Assessment*) pour échapper aux décisions de non-recommandation du NICE.

En particulier, l'utilisation d'une nouvelle méthode de pondération des QALYs ((Stolk et al., 2004)) avait été proposée afin de prendre en compte la sévérité de la pathologie dans les choix d'allocation des ressources. Celle-ci consistait à calculer un *Proportional Shortfall*, soit le ratio du nombre de QALYs perdus en raison de la pathologie et du nombre de QALYs espérés en l'absence de la maladie. L'objectif était de privilégier les patients dont le *Proportional Shortfall* serait plus important. Le *Proportional Shortfall* est un raffinement de l'*Absolute Shortfall*, qui représente la différence entre les années potentielles de vie en bonne santé en l'absence de la maladie et les années potentielles de vie en bonne santé avec la pathologie, toutes deux évaluées par QALY. L'*Absolute Shortfall* a été jugée par le NICE trop défavorable aux personnes âgées et de ce fait discriminatoire et donc illégal (Towse and Barnsley, 2013). Les méthodes d'évaluation des technologies de santé ne se fondent donc pas sur une seule doctrine utilitariste mais intègrent les besoins de santé individuels. La différenciation des exigences d'efficacité et des ressources collectives consenties en faveur de ces traitements innovants reflètent la disposition à payer supérieure du décideur pour les gains de santé d'une population de patients dont les besoins sont importants, et ce, au prix d'une diminution de la quantité de santé dans la collectivité.

3.2 Désinvestissement et coût d'opportunité des dépenses de santé

De récents travaux britanniques (Claxton et al., 2013) ont permis d'évaluer les effets de la mise en application des recommandations du NICE par le NHS sur la santé de la population dans son ensemble. Ils ont réalisé une étude rétrospective des données de dépenses et de taux de mortalité par pathologie et estimé l'impact dans le système de santé anglais de l'utilisation de

⁵Cette requête sera écartée par le NICE en 2014 après une vive période de débat dans le cadre de la rediscussion des procédures de dérogation pour les traitements de fin de vie.

la borne supérieure du seuil d'acceptabilité des dépenses de santé (i.e. £30,000 par QALY) (Claxton et al., 2013). Leur approche se fonde sur le concept de coût d'opportunité et considère la contrainte budgétaire fixe du NHS sur laquelle le NICE n'a pas de prérogative. Chaque recommandation du NICE et son remboursement au sein du NHS affectent deux groupes d'individus: les patients bénéficiant de cette technologie de santé et les patients qui supportent le coût d'opportunité de ce nouvel investissement. Si les bénéfices en santé liés à l'introduction de la technologie de santé sont mis en évidence dans le cadre de l'évaluation des produits de santé, les QALY (i.e. unités de santé combinant années de vie et qualité de vie) qui seront perdus pour réaliser cet investissement à partir du budget du NHS sont ignorés, c'est ce que les auteurs appellent le *displacement*). Leur analyse empirique s'appuie sur des données rétrospectives de morbidité et de mortalité ainsi que des données budgétaires issues des recueils du NHS entre 2008 et 2010, ils estiment le lien entre les modifications des dépenses du NHS, et les changements de morbidité et de mortalité par pathologie. Les résultats suggèrent qu'une dépense de santé de £10 millions supplémentaires par an, permettant un gain de santé de 333 QALY, se traduit par une perte nette de 440 QALY par année, distribués à l'ensemble des patients du NHS⁶ (Karnon et al., 2018). Ces années de vie de bonne santé perdues sont notamment dues à l'augmentation de la mortalité dans les cancers, les maladies circulatoires, respiratoires et gastro-intestinales. S'intéressant plus précisément au *Cancer Drugs Fund*, les auteurs mettent en évidence que l'enveloppe dédiée aux anticancéreux innovants en 2014-2015 s'est traduite par une perte collective de 21,645 QALY. Dans la continuité de ces travaux, Claxton et al. (2015a) ont estimé quelle devrait être la valeur du seuil d'acceptabilité des technologies innovantes qui garantirait que chaque recommandation ne conduise pas à une perte nette collective de santé du fait du *displacement*. Leur étude suggère qu'une technologie innovante de santé devrait être considérée coût-efficace et faire l'objet d'une recommandation positive de la part du NICE si son ICER est au plus égal à £12,936 par QALY. Ainsi, Claxton et al. (2015a) concluent que même la valeur inférieure de l'intervalle de coût-efficacité actuellement utilisé entraîne une perte en QALY supérieure aux QALY gagnés.

La publication des résultats de ces travaux a fait l'objet d'une importante couverture médiatique soulignant que le NICE recommande des traitements que le NHS ne peut se permettre de financer.⁷

Cependant, le préjudice substantiel causé à l'ensemble des patients du NHS, en dépit des gains en santé de ceux qui recevront le nouveau traitement recommandé, doit être mis en regard des pressions croissantes subies par le décideur pour un assouplissement de la borne supérieure du seuil d'acceptabilité des technologies de santé⁸ La borne haute de l'intervalle £20,000 à £30,000

⁶Pour davantage d'information sur les méthodes permettant d'identifier l'impact des dépenses du NHS sur les états de santé, consultez Claxton et al. (2018)

⁷Voir par exemple: <https://www.theguardian.com/society/2015/feb/19/nhs-buys-expensive-new-drugs-nice-york-karl-claxton-nice>;

⁸Voir par exemple: <https://www.theguardian.com/society/2017/apr/11/gamechanging-cancer-drug-rejected-for-use-on-nhs>.

par QALY étant aujourd'hui largement plébiscitée lors des comité d'évaluation des technologies de santé au NICE avec un quart de décisions dépassant ce seuil (Dakin et al., 2015), industriels du médicament et associations de patients tendent à pousser pour un seuil revu à la hausse en mettant en avant le seul groupe des patients qui bénéficieraient de la nouvelle technologie et en ignorant le reste des patients du NHS qui amortissent le coût d'opportunité. Il est important dans ce contexte de rappeler les travaux de Cohen et Looney (Cohen and Looney, 2010) qui ont rappelé que sur le marché anglais la disposition à payer du décideur étant révélée, les industriels du médicament ont essentiellement pour objectif de maximiser leur surplus de producteur. Ainsi la soumission de nouvelles technologies qui présentent un ratio différentiel coût résultat proche de la borne supérieure est accru.

3.3 “Compromis fait bon parapluie mais mauvais toit”⁹

La question de l'accès aux technologies de santé est une problématique économique mais également éminemment politique. La différenciation des exigences d'efficience par la création du *Cancer Fund*, ou encore par la procédure spécifique pour les traitements en fin de vie (*End Of Life Care*) font figure de “débordements institutionnalisés” (Benoît, 2016) pour répondre à la pression croissante exercée par les industriels du médicament et les représentants de patients pour assouplir la borne supérieure de la définition du seuil de coût-efficacité selon le NICE. La prise en compte des dépenses de recherche et de développement des technologies de santé ainsi que l'adoption de références plus larges que le seul gain de santé, tels que la réduction du fardeau de la maladie (*Burden Of Illness*) et les gains sociétaux¹⁰ générés par la technologie de santé (*Societal Benefit*) sont autant de requêtes formulées par les défenseurs de l'évaluation basée sur la valeur (*Value-Based Assessment*) pour échapper aux décisions de non-recommandation. L'on peut alors s'interroger sur le bien-fondé de cette approche. Est-ce l'objet du prix d'une technologie de santé que de récompenser et protéger l'innovation, quand des dispositifs tels que les brevets ou crédits d'impôts sur la R&D sont déjà couramment utilisés par l'industrie du médicament ? Est-il légitime de conférer un poids plus important aux gains de santé de certaines populations de patients au détriment d'autres ? Bien que ce type de choix puisse être acceptable d'un point de vue normatif, les choix de priorisation adoptés doivent être transparents et ne pas être le reflet de préférences des groupes d'intérêt. Car s'il est une population dont les intérêts ne sont pas représentés par ces lobbyistes, c'est celle des patients subissant le coût d'opportunité des dépenses de santé et en particulier le désinvestissement dont ils font l'objet dans une grande opacité.

⁹Citation empruntée à James Russell Lowell (poète du 19^{ième} siècle) et tirée de *On Democracy* (1884): “Compromise makes a good umbrella, but a poor roof.”

¹⁰Il s'agit des gains au-delà du budget du NHS, par exemple une réduction de l'aide formelle d'un patient dont le coût serait supporté par les services sociaux ou une reprise d'activité professionnelle qui solde un congé maladie.

4 Conclusion

Chaque nouvelle décision d'investissement en santé est consentie au détriment d'autres décisions collectives telles que l'éducation ou la justice. Ainsi l'utilisation d'un critère d'efficience dans la détermination du prix des technologies de santé est nécessaire pour éclairer la décision publique dans un contexte de ressources budgétaires contraintes. Alors que le NICE est doté d'un outil de décision explicite et transparent qu'est le seuil explicite d'acceptabilité des technologies de santé compris entre £20,000 et £30,000 par QALY, reflétant la contrainte des dépenses de santé du NHS, la France ne fait pas usage des mêmes principes méthodologiques mais poursuit les mêmes objectifs d'allocation efficiente des dépenses des santé.

En France, la question de la définition d'un seuil d'efficience est largement abordée dans le débat public et l'expérience britannique, ainsi que les travaux universitaires menés sur le NICE sont sans aucun doute de nature à l'alimenter fructueusement.

Les faiblesses qui ont été discutées ici fournissent des éléments éclairants pour ce débat.

En premier lieu, il ne répond pas strictement à la définition d'un seuil d'acceptabilité des dépenses de santé, puisque qu'il n'admet pas de fondement empirique, et ne varie ni avec le budget, ni avec la productivité du système de santé. Par ailleurs, l'intervalle de £20,000 à £30,000, représentant la disponibilité à payer révélée du décideur, est suspecté d'être inflationniste sur les prix revendiqués par les industriels des médicaments. Cet outil n'a pas un caractère automatique et fait l'objet de nombreuses dérogations, permettant à certains médicaments, parmi lesquels les médicaments orphelins, d'obtenir des recommandations pour des ICERs atteignant jusqu'à 10 fois la valeur du seuil d'acceptabilité des technologies de santé. Bien qu'il soit sur le plan normatif acceptable de prendre en considération les patients dont les besoins de santé sont supérieurs, le manque de transparence sur les investissements consentis en faveur de ces populations de patients -à la fois en termes d'acceptation des technologies de santé, mais également en mettant en évidence leur coût d'opportunité du point de vue collectif- est indéniable. Entre 1999 et 2014, le pourcentage de décision de non-recommandation rendue par le NICE s'élève à 16%, chiffre chutant entre 6 et 7% une fois les dispositifs de dérogations pris en compte (Benoît, 2016). De plus, les travaux portant sur l'identification du seuil d'acceptabilité des technologies de santé garantissant l'absence de préjudice du point de vue de la collectivité convergent sur une valeur du seuil bien en deçà de celle couramment utilisée (Claxton et al., 2015a). Il est trompeur d'affirmer que la seule adoption d'un seuil d'acceptabilité des technologies de santé suffit à garantir l'efficience des décisions en santé. Ce constat pousse notamment de nombreux économistes à s'interroger sur une question analogue, celle du désinvestissement en santé. A mesure que des technologies innovantes sont intégrées au panier de biens et services remboursables, il semble nécessaire d'actualiser les choix d'allocation

des ressources (McCabe et al., 2008).

Une autre question qui prend toute sa dimension dans ce débat est l'implication sur les choix d'investissement des industriels du médicament dans la recherche et le développement de nouvelles thérapies des procédés de dérogation au seuil d'acceptabilité des technologies de santé évoqués dans cet article. Se pourrait-il qu'ils redirigent le développement de thérapies sur des pathologies pour lesquelles le décideur suggère des préférences plus marquées de recommandation, telles que les cancers ?

Au niveau international, en raison de l'inflation des prix des médicaments et en dépit d'une résistance historique à adopter un critère d'efficience pour guider la décision en santé, de nombreux pays s'orientent vers la définition d'un seuil ou d'un intervalle similaire d'acceptation des technologies de santé.

General Conclusion

Main Results and Contributions

This dissertation emphasizes the challenges raised by the management of rare diseases, and is structured around three key actors of the diagnostic and therapeutic “*odyssey*”: (1) patients and their social environment, especially during the patient’s experience receiving a diagnosis for his or her pathology; (2) pharmaceutical firms’, and their motivation to conduct R&D in rare disease areas, and (3) regulators facing challenges when granting patients access to orphan drugs.

Patients’ social determinants of time to diagnosis: Social capital and education

In Chapter 1, the thesis specifically highlights the social determinants of time to diagnosis. It focuses on the impact of patient characteristics on time to diagnosis, using a unique dataset of self-reported patient level information, collected for the purpose of this thesis through a collaboration with a French patient social network.

We measure time to diagnosis starting from symptom onset and ending at final diagnosis because we believe this is a robust measure of time to diagnosis in that it fully captures patients’ help-seeking behaviors. Findings suggest that social support and social participation significantly reduce the probability of experiencing longer time to diagnosis. Educational attainment, on the contrary, is associated with an increase in the probability of experiencing longer time to diagnosis. Further investigations reveal that this result was mediated by differences in help-seeking behaviors between more educated and less educated patients. More educated patients are more likely to visit a specialist as a first medical contact. However when compared to general practitioners, specialists appear to delay referrals to hospitals services, which are better equipped to reach a final diagnosis.

The first chapter identifies two key characteristics of patients that are associated with a smaller time to diagnosis. First, the enhancement of individuals’ social capital could reduce time to diagnosis, and ultimately prevent health deterioration caused by delays in accessing appropriate care. This result is in line with literature that highlights the potential of social capital enhancing interventions, such as the participation in collective activities (Guo et al.,

2018) for improving health. Second, results encourage the use of gate keeping and general practitioner referral systems to foster diagnostic workups.

This first chapter is focused on the patient's experience of the period prior to diagnostic workup, and suggests that a patient's social network may facilitate reduced delays in accessing diagnoses. We then turned our interest to uncover other aspects of importance in the relationship between patients and their support structure.

On health spillovers: Child's health externalities on the health of the mother

The main contribution of Chapter 2 is to document the causal impact of diseases, not on patients themselves, but on the direct support system of patients. More specifically, we investigate the causal impact a shock on a child's health has on the health of his or her mother.

We define a health shock as the occurrence of a longstanding disease and a subsequent drop in the child's self-reported health status. We use data from a large and longitudinal (eight wave) survey on child-mother pairs in Scotland. We find that mothers are significantly more likely to report a lower category of self-reported health as a result of a shock on the child's health. The findings suggest that mothers' physical health is significantly impacted by a shock in their child's health, while their mental health is not significantly affected. The impact of a shock on a child's health on the mother's physical health increases significantly with the duration of the shock, while the absence of effect on mental health is observed for the entire period of observation.

Results suggest that the deterioration of health is significantly stronger when the child has a disease that is more time-consuming, as opposed to money-consuming, for the mothers. In that case, mothers see their probability of reporting a higher health category reduced by 49%, everything else in the model held constant. This confirms the existence of persistent spillover effects from the child's health to the mother's health status. It also points to how specific mothers are in their reactions to caregiving responsibilities given their pivotal role in parenthood. This is of particular interest given that 75% of rare diseases are pediatric (Bavisetty et al., 2013). These findings call upon the refinement of policies regarding informal care. This could include, for example, the provision of respite care and advice. By doing so, such policies could improve both the health status for both mother and child.

Chapter 1 and Chapter 2 were devoted to patients and their social network; we then continue to invest the diagnostic and therapeutic odyssey by analyzing the efficiency and equity aspects of policies aimed at fostering pharmaceutical innovation in rare diseases. Pharmaceutical firms' private investment decisions are thus key aspects of Part II.

The orphan drug legislation: Efficiency and equity considerations

In Chapters 3 and 4 we discussed the efficiency of incentive schemes promoting R&D in rare disease arenas and the distribution of R&D between rare diseases. Chapter 3 considers the orphan drug legislation that was introduced in 2000 at the European level and offers supply-side market incentives to stimulate R&D investment levels in rare diseases arenas.

The OD legislation may also have had an impact on non-rare disease drug markets since clinical trials that tailor a subset of patients within traditionally non-rare disease populations fall within the scope of the orphan drug legislation. Thus, after the policy adoption, firms may have increased the number of clinical trials qualifying for orphan drugs to benefit from supply-side incentives. This differentiation between rare diseases and rare therapeutic indications allows us to investigate and compare the effects of the orphan drug policy on these two groups.

In this chapter, we study the causal impact of the orphan drug legislation by examining the variation in the number of new clinical trials and new academic publications from 1997 to 2015, and we compare the effect of the orphan drug policy on rare diseases and rare therapeutic indications. We rely on longitudinal data constructed on the basis of the Orphanet databases along with data we collected ourselves on academic publications from MEDLINE. We find a causal positive impact of the orphan drug policy on the number of clinical trials from 2004 and this impact increases over the 10 years following the legislation implementation. The causal effect of the orphan drug legislation on academic publications was significant and immediate after the introduction of the policy. Findings suggest that the pharmaceutical industry largely responded to financial incentives when allocating R&D resources, and that rare therapeutic indications were also promoted through the scheme, while much of the within variation in R&D is observed among rare diseases.

In Chapter 4, we investigate the existence of inequalities in the allocation of R&D resources within rare diseases and identify the characteristics of rare diseases that appear to lead R&D investments. There have been considerable discussions in the philosophical and political economy literature about the role of the welfare state in promoting equity in the provision of goods and services, especially the need for public health actors to tackle health inequalities and prioritize the most disadvantaged groups. Using the same longitudinal dataset from Orphanet and MEDLINE, along with stochastic dominance and bilateral tests, we show that (1) there is indeed inequality in R&D and treatment allocation between rare diseases, (2) rare diseases in children and those with a smaller prevalence are underserved by R&D. R&D efforts appear to be concentrated in more profitable research areas with potentially larger sample sizes for trial design and adult population.

The implementation of policies aimed at supporting innovation and research strategy for therapy development are a step forward in sustaining the health of patients with rare diseases. But innovation needs to be disseminated in order to have a positive impact on the patient's therapeutic "*odyssey*." That is why Chapter 5 and Chapter 6 are focused on the issue of access to innovation for patients and the moral dilemma for policy makers when deciding the conditions of access to innovation.

Addressing the unmet needs of patients with rare diseases, at any price? And to what end?

In Chapters 5 and 6, we focus on access to drugs after their approval. In Chapter 5 we choose to discuss what the benefit of drug approvals is for patients with rare diseases. In particular, we measure the causal impact of pharmaceutical innovation on premature mortality, taking into account variation in diagnostic ability. We then investigate the time variation of the impact of pharmaceutical innovation on longevity.

We appraise premature mortality by computing Years of Potential Life Lost at age 65, 70, 75, 80, and 85 from longitudinal data containing all US death certificates in the period 1999-2015. Results suggest that pharmaceutical innovation as measured by the cumulative number of lagged approved drugs significantly reduces the number of YLPP65 by an average of 455 years per disease. The investigation of the time variation in the impact of drug approval on premature mortality suggest that the drug approval significantly decreases the number of YPLL65 and YLPP70 between two and four years after approval.

In Chapter 6, we introduce the cost-effectiveness threshold for health technologies and discuss how it is possible to meet the challenging objective of providing access to orphan drugs while still considering equity for society as a whole. The NICE, when making recommendations on treatments and health care availability within the basket of goods and services, is pursuing a dual objective of clinical excellence and a balanced budget.

As part of the evaluation of new health technologies, health gains and induced costs are compared by calculating an incremental cost-effectiveness ratio (ICER) expressing a cost per quality adjusted life years (QALY). The value of the ICER is then faced with the cost-effectiveness threshold for health technologies defined by NICE since 2000. This threshold is between £20,000 and £30,000 per QALY. This chapter offers a critical discussion of (1) the cost-effectiveness threshold for health technologies, by highlighting the differences between its use and its foundations, and (2) the way NICE deals with the cost-effectiveness threshold for health technologies when orphan drugs are doomed to fall outside this range. We show in this critical discussion that the access to orphan drugs comes with a renouncement of the philosophy

behind the cost-effectiveness threshold for health technologies and a more generous threshold or funding thought parallel schemes is proposed when appraising such treatments.

The final chapters of the thesis highlight the challenges for policy makers in making innovation accessible while accounting for opportunity costs borne by the rest of the society and the concerns related to the appraisal of patients' benefits.

The major contributions of this thesis are (1) the generation of two original primary datasets: one with patient level information on the pre-diagnostic experience of chronic diseases, and one which offers precision in disease identification and offers the most comparable existing knowledge across the largest number of rare diseases; (2) new results on underdocumented research questions such as demand-side sources of delay in access to receiving a diagnosis or a mother's health status in the context of childcare; and (3) an overview of the disparities between rare and non-rare diseases as well as differences between rare diseases of different types.

Research Agenda

The results originating from this dissertation leave many questions open for future research. This section identifies a research agenda to extend the work that would complement this thesis.

Determinants of Time Period to Diagnosis in Rare Diseases

The main objective of Chapter 1 was to investigate the determinants of time to diagnosis and explore the existence of social inequalities in access to diagnostic services. The approach developed in Chapter 1 is relevant to rare diseases given the complexity of the diagnostic process. It was impossible to provide evidence on the time to diagnosis for rare diseases exclusively. Paris Public Hospitals are developing an innovative health data repository (in French, *Entrepôt de Données de Santé*), allowing access to patients' files including textual content. This information will be of invaluable importance for future research and could represent a unique opportunity to evaluate the time to diagnosis of patients with rare diseases. The link between patient characteristics and health care pathways will allow a deeper investigation into the social determinants of time to diagnosis.

Moreover, a networking structure was built following the implementation of the French Rare Diseases Plan 2005-2008 and expert centers have involved health professionals with extensive expertise on one or several rare diseases in order to facilitate the diagnosis of rare diseases. In the long term, an evaluation of the impact of this French Rare Diseases Plan 2005-2008 on diagnosis finalization would also be a valuable contribution to this research area.

Pharmaceutical Innovation and Mortality: A Re-revisit

The objective of Chapter 5 was to assess the impact of approved orphan drugs on premature mortality from rare diseases. There are two limitations to this work: (1) it does not measure current drug utilization by patients with rare diseases but only orphan drug approval, and (2) it uses ICD-10, which are imperfect in properly identifying rare diseases.

We propose to address those two limitations in future work by using drug hospital utilization from the French Technical Agency for Information on Hospitalization (ATIH) database. Orphanet announced the implementation of ICD-11 codes in their database. The principal gain of this change is to endorse the precise representation of 5,400 rare diseases. The ICD-11 codes are expected to become available late 2019. Moreover, a French early access scheme allows pharmaceuticals, which have not yet obtained their marketing authorization, to be administered and reimbursed for a pre-defined population of patients. This scheme is called *ATU*¹¹; it facilitates access to a number of orphan drugs before their market approval for a defined patient population. Finally, hospital mortality data and French death certificates will enable us to measure the impact on mortality and premature mortality of such therapeutic innovations. Following this work, we envision addressing the diffusion of pharmaceutical innovation by geographical area and age class. This would document inequalities in access to therapies between patients with rare diseases.

Multiplier Effect of R&D Investments

R&D investments allocated to rare diseases are often described as high given market sizes. However this comment fails to acknowledge that part of the R&D investments allocated to rare diseases also benefit patients with more common diseases. The identification of genetic mutations has led to dramatic advances in the management of very common diseases, such as breast cancer. This project proposes to examine the multiplier effect of R&D expenditure allocated to rare diseases by using a bibliometric analysis. The comprehensive database of academic publications identified at the pathology level collected from the MEDLINE literature database will enable us to identify cross-referencing within bibliographies for rare versus non-rare conditions. The objective will be to measure the multiplier effect of R&D investments allocated to rare diseases. This future research agenda only represents a minor contribution to the broad potential academic research that could help to meet the critical unmet needs faced by patients, caregivers, families, and health professionals in the management of rare diseases. While concluding this thesis, we hope to have successfully aroused and awakened interest to the importance and wealth of what we truly believe is a compelling object of study.

¹¹For a presentation of the scheme, see [Raïs Ali et al. \(2018\)](#).

Appendix

0.1 A. Webscraping - MedGen UID

```
#CODE1: how to recuperate MEDGEN UID
```

```
from bs4 import BeautifulSoup
from urllib2 import urlopen
import pandas as pd
import time
import json
import re
import os, datetime
import requests

import numpy as np
from selenium import webdriver

import urllib2
#urllib2.urlopen("http://example.com/foo/bar").read()

urlcsvcsv="(link to the file containing the list of orphanet code)"

os.chdir("(main directory)")

urlcsv=pd.read_csv("urlcsv.csv")
urlcsv=urlcsv.values

database=[]
for i in urlcsv:
    # try:
        print(i[0])
        id=str(i[0])
        url="https://www.ncbi.nlm.nih.gov/pubmed?LinkName=medgen_pubmed
&from_uid=%s" %(id)
        #driver=webdriver.Chrome()
        #driver.get(url)
        soup=urllib2.urlopen(url).read()#driver.page_source
        soup=BeautifulSoup(soup)
        #print soup
        numberofpage=int(soup.find("h3", class_="page").find("input").get("last")+1)
        print i, numberofpage
1Tttttttttttt          a_page = requests.get(url)
```

```

soup_2 = BeautifulSoup(soup)
#for page in range(1,numberofpage):
#    print page
#    b=str(i)
#element=driver.find_element_by_id("pageno")
#element.clear()
#element.send_keys("%s" %b)
#element.send_keys( u'\ue007')
#?soup=driver.page_source
#    soup=BeautifulSoup(soup)
liste=soup.find_all("p", class_="details")
liste2=soup_2.find_all("p", class_="details")
print liste
a={}
a["id"]=id
a["list"]=liste
#    print(a)
database.append(a)
#except:
#    print "oups"
#    a={}
#    a["id"]=id
#    a["code"]=np.nan
#    database.append(a)

```

```

Medic_DB = pd.DataFrame.from_dict(database)
Medic_DB.to_csv("database.csv", encoding="utf-8", sep=";")

```

0.2 B. Webscraping - PubMed content

#CODE2: Retrieve citation content from PubMed corresponding to a unique MedGen UID.

```

from bs4 import BeautifulSoup
import os, datetime, sys
import numpy as np
from selenium import webdriver, common
#from pyvirtualdisplay import Display
from scrap_general_info import non_zero_conditions
import matplotlib.pyplot as plt

low_research = np.array([(x, y, z, k) for x, y, z, k in non_zero_conditions
                        if y < np.mean(non_zero_conditions[:,1])])

database=[]

```

```

urlcsv = []
detailed = open('detailed_info.csv', 'r')
scrapped = np.array([map(float, x.split(';')[3]) for x in detailed.readlines()])
detailed.close()

p = plt.plot(scrapped[:,0], scrapped[:,2])
plt.savefig('scrapped.png')
temps_moyen = np.mean(scrapped[:,2])
print "Total time spent scrapping: %.3f" % sum(scrapped[:,2])
print "Mean time %.2f" % temps_moyen
last_condition, pageindex, _ = scrapped[-1]

for i, line in enumerate(low_research):
    test = False
    condition_code, pagenumber, _, _ = line
    if condition_code == last_condition:
        test = pageindex == pagenumber
        print last_condition, pageindex, pagenumber
        break

if test:
    condition_index, pageindex = i + 1, 1
else:
    condition_index, pageindex = i, pageindex + 1
print last_condition

def scrapping_pubmed(condition_index=0, pageindex=1):

    #display = Display(visible = 0, size = (400, 400))
    #display.start()
    timeleft = sum(low_research[condition_index:][:,1])*temps_moyen
    print timeleft
    print "Estimated total time: %.2f hours" % (timeleft/3600.)

    for maladie_code, numberofpage, y, z in low_research[condition_index:]:
        driver = webdriver.Chrome()
        print "Driver loaded."
        fobj = open('detailed_info.csv', 'a')
        maladie_code, numberofpage = int(maladie_code), int(numberofpage)
        driver.get("https://www.ncbi.nlm.nih.gov/pubmed?LinkName
=medgen_pubmed&from_uid=%s" % maladie_code)

        for i in range(pageindex,numberofpage):

```

```

t1 = datetime.datetime.now()
print maladie_code, i
try:
    element=driver.find_element_by_id("pageno")
except common.exceptions.NoSuchElementException:
    driver.quit()
    print "Impossible to get page index dialog driver quit."
    time.sleep(60)
    driver = webdriver.Chrome()
    print "Driver reloaded."
    driver.get("https://www.ncbi.nlm.nih.gov/pubmed?LinkName=
medgen_pubmed&from_uid=%s" % maladie_code)
    element=driver.find_element_by_id("pageno")

    element.clear()
    element.send_keys("%i" % i)
    element.send_keys( u'\ue007')
    soup=BeautifulSoup(driver.page_source, "lxml")
    resultlist=";".join([str(x) for x in soup.find_all("p", class_="details")])
    dt = (datetime.datetime.now() - t1).total_seconds()
    fobj.write("%i;%i;%.3f;%s\n" % (maladie_code,i,dt,resultlist))

pageindex = 1
driver.quit()
print "Driver quit."
fobj.close()
timeleft += - numberofpage*temps_moyen
print "Estimated time left: %.2f mins" % (timeleft/60.)
# display.stop()

scrapping_pubmed(condition_index, int(pageindex))

```

0.3 C. Identification of dates

```

#CODE3 : Identify publication dates by MedGen UID

# -*- coding: utf-8 -*-
"""
Created on Tue Nov 14 18:54:11 2017

@author: utilisateur
"""
#open

```

```

logfile = open('failed_dates.log','a')
recognizable_dates = ["2015 Jun", ]
recognizable_months = ["Jan", "Feb", "May", "Jul",
"Aug", "Sep", "Oct", "Nov", "Dec", "Jun",
"Mar", "Apr", ";"]
def find_dates_in_text(texte):
    possible_dates = []
    texte = texte.replace("-", " ").replace(";", " ;")
    mots_in_text = texte.split()
    for i, mot in enumerate(mots_in_text):
        quatre_caracteres = len(mot) == 4
        try:
            suivi_d_un_mois = any(x in mots_in_text[i+1] for x in recognizable_months)
        except IndexError:
            suivi_d_un_mois = False
        chiffres = all(x.isdigit() for x in mot)
        if all([quatre_caracteres, suivi_d_un_mois, chiffres]):
            #si on a quatre caracteres
            #si on que des chiffres
            #si il y a un mois apres
            possible_dates.append(mot)
    # il retourne la premiere date qu'il rencontre

    # mais si on veut la plus ancienne ou la plus recente, il faut:
    # la plus ancienne = min(map(int, [x for x in possible_dates]))
    # la plus recente = max(map(int, [x for x in possible_dates]))
    try:
        return possible_dates[0]
    except IndexError:
        logfile.write(texte + "\n")
        #return ''

def compare_dates(date):
    return date
detailed = open('detailed_info.csv', 'r')

maladies = {}
#readlines
for line in detailed.readlines():
    code_maladie, page_index = line.split(';')[2]
    texte = line.split('>;<')
    print code_maladie, len(line.split('>;<'))
    if code_maladie in maladies.keys():

```

```
        maladies[code_maladie] += map(find_dates_in_text, texte)
    else:
        maladies[code_maladie] = map(find_dates_in_text, texte)
detailed.close()

publication_dates = open('publication_dates.csv', 'w')
for code_maladie, liste_dates in maladies.iteritems():
    publication_dates.write("%s;%s\n" % (code_maladie,
";".join([x for x in liste_dates if x is not None])))
publication_dates.close()
logfile.close()
```

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Diagnostic and Therapeutic Odyssey: Essays in Health Economics

This dissertation emphasizes the challenges raised by the management of rare diseases and is structured around three key actors of the diagnostic and therapeutic “*odyssey*” of patients with rare diseases. Part I is devoted to *patients and their social networks*. Chapter 1 considers demand-side sources of delay in receiving a diagnosis; Chapter 2 explores the health spillover effects from patients’ health to their direct support structure. Part II considers *pharmaceutical firms* and examines how firms’ decisions to allocate R&D investment to rare diseases are impacted by innovation policies in rare arenas. Chapter 3 evaluates the causal impact of the EU Orphan Drug policy on R&D efforts in orphan drugs, while Chapter 4 investigates the inequality in allocation of R&D investment within rare diseases. Part III focuses on *policy makers* and addresses the issues in measuring pharmaceutical innovation benefits along with costs in rare disease arenas, while considering the opportunity cost of healthcare expenditures. Chapter 5 measures the causal impact of pharmaceutical innovation in rare diseases on longevity, while Chapter 6 is a critical discussion of decision-making tools for rational allocation of healthcare resources, and the use of a cost-effectiveness threshold.

KEYWORDS: Diagnostic; R&D; Health Inequalities; Rare Diseases; Pharmaceutical Innovation; Orphan Drugs; Orphan Drug Policy

Errance Diagnostique et Thérapeutique: Essais en Économie de la Santé

Cette thèse de doctorat met l’emphase sur les défis rencontrés par les patients atteints de maladies rares. Elle est structurée en trois parties, chacune d’entre elles dédiée aux enjeux d’un acteur au cœur de l’Odyssée diagnostique et thérapeutique des patients atteints de maladies rares. La première partie de la thèse s’intéresse au patient et à son réseau social. Le chapitre 1 considère les sources de délai à l’accès au diagnostic, et explore notamment l’effet du capital social sur le délai d’obtention du diagnostic. Le chapitre 2 évoque les externalités négatives sur la santé maternelle d’un diagnostic d’une maladie chronique chez l’enfant. La seconde partie de la thèse est dédiée à l’industrie pharmaceutique et s’intéresse aux décisions d’investissements de R&D ciblant les maladies rares. Le chapitre 3 évalue l’effet causal de l’*Orphan Drug Policy* sur l’effort de recherche, et le chapitre 4 envisage les inégalités d’allocation des investissements de R&D entre les maladies rares. La partie 3 est dédiée aux décideurs publics et discute des enjeux d’évaluation des bénéfices de l’innovation thérapeutique et de la définition des conditions d’accès à cette innovation. Le chapitre 5 évalue l’effet causal de l’innovation thérapeutique sur la longévité des patients atteints de maladies rares. Le chapitre 6 est une discussion critique relative à l’utilisation d’outils d’aide à la décision en santé, et l’utilisation d’un seuil de cout-efficacité des technologies de santé.

MOTS-CLÉS: Diagnostic; R&D; Inégalités de santé; Maladies Rares; Innovation Thérapeutique; Médicaments Orphelins; Orphan Drug Policy