# (In)-equality in the allocation of R&D resources for rare diseases

***Setti Raïs Ali***[1]

*Hospinnomics, Fondation Imagine for rare diseases, Paris 1 Panthéon-Sorbonne (France)*

***Sandy Tubeuf***

*Université Catholique de Louvain (Belgium) and University of Leeds (UK)*

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**Abstract**

This paper analyses the allocation of R&D investments within rare diseases and identifies the characteristics of rare diseases that appear to lead R&D resources. Rare diseases affect less than 1 in 2,000 citizens. With over 7,000 recognized rare diseases and 350 million people affected worldwide, rare diseases are not so rare when considered collectively. Rare diseases are generally underserved by drug development because pharmaceutical industries consider R&D investments in rare diseases too costly and risky in comparison with the low expected returns due to the small population involved. We use data on rare diseases research from Orphanet along with academic publications per rare disease from bibliographic databases. We test the existence of inequalities in R&D investments within rare diseases and identify the disease characteristics that appear to lead R&D investments using dominance tools and bilateral tests. We show that rare diseases in children and with a smaller prevalence, such as ultra-rare diseases, are underserved by R&D. R&D investments appear to be concentrated in more profitable research areas with potentially larger sample size and adult population.

**Keywords**: R&D; Inequality; FOSD; Rare Diseases; Orphan Drug
**JEL codes**: I11- I14- I18 - L65

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[1] Corresponding author contact details: Setti Raïs Ali – Hospinnomics (PSE/AP-HP) – 1, Parvis Notre-Dame, 75004 Paris – Phone number: +33 668303070 – Email: setti.rais@psemail.eu

# I. Introduction

A disease is characterized as rare if it affects less than 1 in 2,000 citizens, which represents 250,000 or fewer patients in the European Union (Drummond & Towse, 2014). While over 7,000 recognized rare diseases with 80% of them being genetic, a total of 350 million people are affected worldwide, and so patients with rare diseases are not very rare when considered collectively (Giannuzzi et al., 2017). The diagnostic 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 & 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 a poor health status 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 targeting 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 in comparison with the low expected returns due to the small population involved. Consequently, patients with rare diseases are underserved by drug development. The pharmaceutical sector is an highly regulated sector from the very first step of translational research to the market authorization of the drug and marketing (Scott Morton & Kyle, 2011). While pharmaceutical firms naturally pursue a revenue maximization exercise, the regulator is in position to endorse ethical considerations and impact the allocation of R&D investments by increasing firms' profitability in underserved research areas. Despite governmental initiatives providing incentives for pharmaceutical firms to invest in rare diseases enacted in 2000 with the European Union Orphan Drug regulation[2], it is estimated by the National Center for Advancing Translational Sciences[3] that 95% of rare diseases do not have treatment options in 2018.

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 to care in the whole population (Williams & 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 health status of patients with rare diseases.

[2] Regulation (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)

[3] See: https://ncats.nih.gov/

Several studies conducted on the relationship between pharmaceutical innovations and mortality, suggest that the launching of new drugs decreases mortality in various contexts and therapeutic areas (Lichtenberg, 2001, 2013, 2014, 2016).

There have been considerable discussions in the philosophical and political economy literature about the role of the welfare state in promoting efficiency and equity in the provision of certain goods and services (Cookson & Dolan, 2000; Hughes et al., 2005; Martin et al., 2002; Temkin, 2003). Most decisions about the reimbursement of health care interventions are based on their comparative cost-effectiveness where 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 cost-effective, the question of how much resources should be invested in R&D, especially rare diseases, is a moral dilemma for policymakers (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 healthcare systems. Since the allocation of pharmaceutical R&D resources is a major concern for policymakers, social justice theory will be relevant when policymakers 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 but we consider diseases as being the observations of importance and use data on R&D investments for rare diseases. Policymakers 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 prioritized by R&D are not disclosed. Here, we therefore aim to uncover which of the diseases 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 categorising them according to several characteristics. We firstly consider them individually, and then in combination with the population size to benefit.

The objectives are twofold. Firstly, 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. Secondly, 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 authorisation at the European level, the number of orphan drugs designations, and the number of published articles per rare disease on bibliographic databases. We appraise rare diseases 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 on 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 where there are higher chances 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 symptoms 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 2 proposes a conceptual framework for the study of the distribution of R&D investments for rare diseases. Section 3 introduces the data, and section 4 the method. Section 5 presents the empirical application on rare diseases. Discussion and concluding remarks are in Section 6.

# II. A conceptual framework to study the distribution of R&D investments for rare diseases

## a. The appraisal of healthcare 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 quality-adjusted life year (QALY), which is a generic outcome summarising both quality of life and survival. Quality of life is built based on assessment of multiple dimensions of a health state and utility weights for 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 to those life-years gained, which will be particularly relevant for treatments that extend life at the expense of side effects, for example.

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 the threshold are found 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 a fair and comparable decision-making. This means that a QALY is a QALY and there is anonymity towards whom get 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.

Healthcare decision is guided by a maximization principle (Bentham & Mill, 2004) according to which policymakers should aim at maximizing the total sum of health within the population. Hence, a particular attention should be given to capacity to benefit from public resources. No extra weight is given to any particular patients group, whatever the level of their health needs and the severity of the disease.

### b. The appraisal of healthcare treatments: ... to a special case.

While in theory egalitarian principles guide decision-making, policymakers sometimes distance themselves from the reference framework of health care technologies assessments and can mitigate or soften the use of the threshold, especially when it concerns rare diseases. For example, decision makers may consider diseases 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 (Thébaut & Wittwer, 2017). For example, 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 treatments[4] (Paulden, 2017).

Granting a special status to rare diseases and especially orphan drugs is supported by the World Health Organization[5] that recommends prioritizing "those with the greatest need", even in settings where resources are substantially constrained. Similarly the consideration of patients with needs for highly specialized treatments is emphasized in the European Commission[6], which explicitly mentions the right of patients with a rare disease to be entitled to the same quality of treatment as any other patients. Such view on fairness is relevant to prioritarian principles (Otsuka, 2013; Temkin, 2003), which give emphasis to health needs; these principles stipulate that the most severely ill categories of patients should receive

[4] See https://www.nice.org.uk/news/feature/changes-to-nice-drug-appraisals-what-you-need-to-know
[5] Human rights and health: http://www.who.int/news-room/fact-sheets/detail/human-rights-and-health
[6] European Commission memo: http://europa.eu/rapid/press-release_MEMO-14-141_en.htm

priority according to the “Rule of Rescue” (McKie & 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 towards the general public and taxpayers while including equitable considerations. A higher cost-effectiveness threshold for some healthcare treatments on the rational of burden of illness and wider societal impact violates "a key principle of 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 consider 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 gain differently because of specific individual characteristics. For example, interviews conducted on 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, regardless of the opportunity cost in healthcare provision and how priority-setting may divert resources away from other categories of patients (Brazier et al., 2013; Rogge & Kittel, 2016). In particular, it appears that people mostly agree that priority over others should be given to the young over the old as suggested in the ethical argument defended by fair-innings considerations (Williams, 1997a, 1997b). According to the fair innings argument, 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 regard, healthcare 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 longer benefit duration as younger patients comparatively have more years to live than older patients (Mossialos & King, 1999). Similarly, Aghion et al. (2010) argued that gains in life expectancy at young age and during active life (before the age of 40) matter more for economic growth than gains in life expectancy at older age because better health at young age has long-term consequences in terms of workers productivity.

### c. Which criteria guide the distribution of R&D investments for rare diseases?

As 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 patient" 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 into favouring R&D investments in rare diseases with an average age at symptoms onsets and/or an average at death within infancy, childhood or young adulthood.

Despite policymakers appear to explicitly endorse ethical considerations in the decision-making process and institutions like the WHO or the European Commission express recommendations on which patients to prioritise, neither of them discloses *ex-ante* where the investments for orphan drugs should be encouraged. However we can analyse the distribution of R&D investments across rare diseases *ex-post* and investigate whether R&D investments for rare diseases that are related to younger population, dominate other patients population.

We propose here to analyse the distribution of R&D investments across rare diseases. We study whether there is equality in R&D investments within rare diseases 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; neither provides a comprehensive set of the determinants of inter-individual differences in R&D investments across rare diseases. Our analysis is meant to identify the sub-groups of rare diseases, which appear to be under-served by R&D and which, could be targeted by policymakers 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.

## III. 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 (French National Institute for Health and Medical Research) in 1997. This initiative then became European from 2000 and gradually grew to a Consortium of 40 countries within

Europe and across the globe[7]. The Orphanet dataset comprises data about all rare diseases, granting them a unique Orphanet identification number to facilitate sharing information on each disease.

### a. R&D resources outcome measures

Orphanet provides us with four different outcomes 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 an inventory of clinical trials activities targeting rare diseases. Clinical activities include interventional studies treating or preventing a rare disease using drugs, 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 trials activities and research projects include both single-centre and national and international multicentre research projects at the European level. Third, Orphanet provides us with the number of orphan drugs designations that qualify for the financial incentives provided by the EU Orphan Drug legislation. Finally, we consider the number of drugs with marketing authorisation at the European level per rare disease (we refer to them as orphan drugs).

The four outcomes 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 PubMed search engine in July 2017 from its inception date to present using the MEDGEN unique identifier of the 8755 diseases classified as rare diseases and we 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 1 displays the descriptive statistics of the R&D resources outcome measures. There is a total of 9220 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 between 0.12 and 0.72, the median being 0 for each of the outcome. The **third quartile** is equal to zero for research projects, clinical trials, orphan designation and orphan drugs, suggesting the absence of any investments for a 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 diseases is approximately 578 [median=85], while the maximum reached for one of the rare diseases is 177,430 articles. We present in Table 2 the linear correlation coefficient between all the R&D resources outcome measures. Correlations range from 0.16 to

[7] See: https://www.orpha.net/consor/cgi-bin/index.php

0.69; this suggests that R&D resources 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 is equal to 0.63 and this is explained by clinical trial activities being a prerequisite for market approval.

### b. Rare diseases characteristics

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

The average age at symptoms appearance for each disease was not provided as a single age but as a category among a choice of four categories: *Infancy, Childhood, Adults & Elderly* and *All ages*. The average age at death for each disease was also available as a category including five possible categories: *Infancy, Childhood, Adults & Elderly, Normal Life Expectancy* 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 the uncertainty around the number of patients with the condition is high. We homogenised the values and intervals using intervals overlaps and the mid-point of each interval to construct a discrete variable of prevalence in 4 categories (<1 over 1,000,000; 1 to 9 over 1,000,000; 1 to 9 over 100,000; 1 to 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* equals to one when the age of first symptoms appearance equals the average age of death category. Second, we constructed a dummy variable measuring the *Uncertainty on Disease Evolution* equals to one if the age of symptoms appearance and/or the mean age at death is classified as unpredictable.

Table 3 presents the distribution of the average *age at symptoms 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* show great discrepancies in distribution across the age groups as displayed in Table 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 1 displays the frequency distribution for the *prevalence* variable and suggests that rare diseases prevalence is highly skewed toward 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.

In Table 3, we investigate the relationships between all the rare disease characteristics using the Cramer's

V[8] statistics. The age of symptoms onset is by construction related to the mean age at death in the sense that the patient cannot be at risk of death before symptoms' appearance 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 symptoms' onset.

All diseases 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 are visually described in Figure 2. All the R&D investments 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 symptoms 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 6 and suggest that when some diseases characteristics have missing values, the distributions of the R&D proxy outcomes among the missing data usually have a significantly lower average. Most of the rare diseases characteristics share the same missing values.

# IV. Methods

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

We detect inequalities comparing cumulative distribution functions (CDF) of the R&D investments devoted to rare diseases conditioned on a set of variables representing diseases characteristics. Our approach loosely follows Lefranc et al. (2009) and Lefranc and Trannoy (2016) and the diseases 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 $F_B(y)$, and A dominates at first order B, written $A \geq_{FSD} B$ 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 investments provided as a discrete outcome such as $y_j=\{$

[8] The Cramer's V statistics indicates how strongly two categorical variables are associated (Sheskin, 2003). The statistics is ranging between 0 and 1, the maximum value indicating perfect relationship.

$y_1, y_2, \ldots, y_k\}$.

It means that R&D investments is higher in distribution A than in distribution B and this is true at every points of the distribution. Graphically, the cumulative distribution function of R&D investments of the sub-group of rare diseases in B is always above that of rare diseases in A at any point of the distribution. For example, let us consider the CDF of the number of academic publications in rare disease with an average age at symptom onset classified in *Adult & Elderly*. If on the one hand, this CDF is clearly different than the CDF of the number of academic publications in rare diseases with an average age at symptom onset classified in *Infancy* and if, on the other hand, the difference is such that a rare disease has higher chance of being researched when the average age at symptom onset is classified in *Adult & Elderly*, we conclude that there is an inequality in R&D investments. Rare diseases with an older average age at symptom onset are favoured in comparison with rare diseases with an average age at symptom classified in *Infancy*.

We compare the cumulative distribution functions of each five proxy of R&D investments. The five proxy variables are (a) the number of research projects, (b) the number of academic publications, (c) the number of clinical trials, (d) the number of orphan designations and (e) the number of orphan drugs with marketing authorization across age class 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 equality of distributions is violated.

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

It is important to underline that this approach remains relevant even when all disease characteristics are not observed or cannot be combined. According to Lefranc et al. (2008; 2009), equality of distributions conditional on 'circumstances', here diseases characteristics, is a necessary condition even if diseases characteristics are not fully described. As a result, if the KS test shows significant differences between CDFs then we can say that equality of distributions is violated if we had the opportunity to measure perfectly all the diseases characteristics. This provides a rationale to perform first the non-parametric 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 diseases 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, otherwise 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 $\frac{prev\_i - prev\_min}{prev\_max - prev\_min}$.

# V. Results

## a. Non-parametric tests on each diseases 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 conclude on 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 7. They suggest that the distribution of all proxies of R&D investments targeting rare diseases occurring during *Infancy* are dominated by the distribution of any R&D investments of rare diseases with an average age at symptom onset classified in *All Ages* and in A*dult & Elderly*. All five proxies of R&D investments appear to favour 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 favour rare diseases in *Childhood* (p-values respectively 0.006, 0.012, 0.061) 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 authorisation (p-values respectively 0.234, 0.701).

The distribution of most of the R&D proxies for rare diseases in *Childhood* and *Infancy* are 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 publication) 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 respectively 0.771 and 0.990).

**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 8. 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 all R&D proxies, except for the distribution of the number of orphan drugs (p-values respectively 0.272, 0.417, 0.184). When rare diseases in *Infancy* are compared to rare diseases in *Childhood*, the distribution of the number of academic publications is in favour 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 designations and orphan drugs with marketing authorization (p-values respectively 0.136, 0.742, 0.832, 1.000). 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), favour 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 favours the category *All Ages* (p-value=0.065). We cannot conclude on dominance for the distribution 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 conclude 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 all proxies for R&D for rare diseases with *Normal Life Expectancy* dominate the distributions of R&D for disease in the category *All Ages*.

**Prevalence in the population -** Results for the two tailored KS tests comparing the distribution of R&D investments for rare diseases over the four prevalence categories are presented in Table 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 favour 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 favour 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 favour diseases in 1-9 over 10,000. We cannot conclude on dominance when we compare the distributions of the number of research projects, orphan designations and orphan drugs (respectively research projects, and orphan designations) 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 favour diseases in the higher prevalence category. The KS tests remain inconclusive for the number of research projects and of orphan drugs (p-value respectively 0.296 and 0.263).

**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 symptoms' onset and the mean age at death. We compare the distribution of the five proxies of R&D investments for those two groups of rare diseases. Results are presented in Table 10. They suggest that the distributions of R&D investments targeting diseases with an immediate danger of death are dominated by the distributions of R&D investments of diseases with non-immediate danger of death across most proxies of R&D investments, except for the distribution of the number of research projects and orphan drugs where the test is inconclusive (p-value respectively 0.886, 0.121).

**Uncertainty on Disease Evolution** - We now compare rare diseases according to whether there is uncertainty about their evolution. We consider that diseases for which both the average age at symptoms' onset and the average age at death are classified in "*All Ages*" category in the dataset are uncertain. The binary comparisons presented in Table 11 show that the distributions of two proxies of R&D investments (academic research, and orphan designations) of diseases with uncertainty on disease evolution are dominated by the distributions of the R&D investments of diseases with lower uncertainty (p-values respectively 0.006 and 0.001). The KS tests remain inconclusive for the distribution of the number of research projects, clinical trials, and orphan drugs.

## b. Non-parametric tests on each diseases characteristic weighted by disease prevalence

We performed the same analysis accounting additionally 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 12 suggest that the distribution of most of R&D investments targeting diseases with a lower category of average age at symptoms onset (*Infancy* and *Childhood*) are dominated by the distributions of R&D investments for all other categories of average age at symptoms' onset (*Adults & Elderly* and *All ages*). The distribution of most of the R&D proxies for rare diseases in *Infancy* are 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* where 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 favour rare diseases in *All ages*, however we cannot conclude 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 favour of diseases occurring in *Adult & Elderly* (p-value respectively 0.000 and 0.011). However we cannot conclude 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 respectively 0.001, 0.001, 0.044) . 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 investments for rare diseases over the five categories of the average age at death are presented in Table 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 respectively 0.366, 0.184). 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 favour of diseases occurring in *Childhood* (p-values respectively 0.000 and 0,000). However, the distribution of the number of academic research, orphan designations and orphan drugs are in favour of diseases with mean age at death in *Infancy* (p-values respectively 0.000; 0,000 and 0.032). The distribution of most of

the R&D proxies for rare diseases with mean age at death in *Childhood* are 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* dominate 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 investments targeting diseases with an immediate danger of death are dominated by the distributions of R&D investments of diseases without immediate danger of death. Results are displayed in Table 14.

**Uncertainty on Disease Evolution -** Results in Table 15 compare rare diseases according to whether there is uncertainty about their evolution. The results differ from the one computed in the absence of weights. More specifically, they suggest that the distributions of R&D investments targeting diseases with lower uncertainty are dominated by the distributions of R&D investments of diseases with higher uncertainty, when considering the following proxies: research projects, clinical trials, orphan designations (p-values respectively 0.000, 0.041, and 0.007). The KS tests are inconclusive for all the number of academic publications and orphan (p-values respectively 0.971 and 0.396)

## VI. Discussion

We investigated the distribution of R&D investments 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 investments across rare diseases with different average age at symptoms' appearance, it appeared than the life stages at which the disease occurs is associated with different levels of R&D investments. Results suggest that diseases with symptoms appearing during *Infancy* and *Childhood* are dominated in terms R&D investments by rare diseases with symptoms appearing among *Adult & Elderly*. When considering the average age at death of rare diseases, the same age groups of *Adult & Elderly* is favoured. Results suggest that diseases with an average age at death in *Infancy*, and in *Childhood* are dominated in terms R&D investments 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 sub-groups 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 investments for rare diseases is not a fair-innings argument but a market size argument. There is little money to make for pharmaceutical firms 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 paediatrics (Bavisetty et al., 2013). However, R&D investments in infancy are under-developed. 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 is also crucial issue, and therapies must embody the impact they may have on the reproductive system (Lathyris et al., 2014). The metabolization of drugs is heterogeneous across age groups within childhood and it makes it difficult to evaluate the optimal dosage for the therapy whilst it is necessary to prevent toxicity. Overall, the development of therapies for children is more costly and not 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 confirms that market share is a driver of R&D activities, which is in line with previous evidence (Dubois, 2015) as rare diseases in high prevalence categories are favoured by R&D investments. 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 the opportunity to pharmaceutical firms 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 symptoms, and when rare diseases show a high level of uncertainty in terms of 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 by drug development than other rare diseases. In the analysis with frequency weights based on prevalence levels, diseases with high level of uncertainty are favoured, but the risk of death surrounding rare diseases still do not foster further R&D investments.

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 number of 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 to 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 underline 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.

We summarised the average value for each of the proxies of R&D investments in Figure 4. The hierarchy in disease characteristics is rather stable across the proxies of R&D investments. The most deprived category over all R&D investments is the group of rare diseases with an average age at first symptoms during *Infancy* and *Childhood*. The second most deprived characteristic is uncertainty about rare diseases evolution then comes the group of diseases with an immediate danger of deaths. While the difference in average R&D investments is very low, it is somewhat dependent on disease characteristics. 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 sub-groups of rare disease could be a desirable form of compensation to prevent long-term discrepancies in health technologies availability and ultimately discrepancies in patients' opportunities to access care and treatment.

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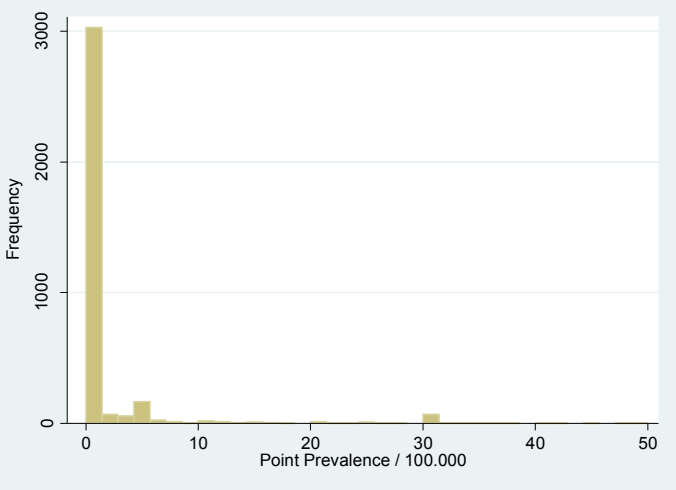
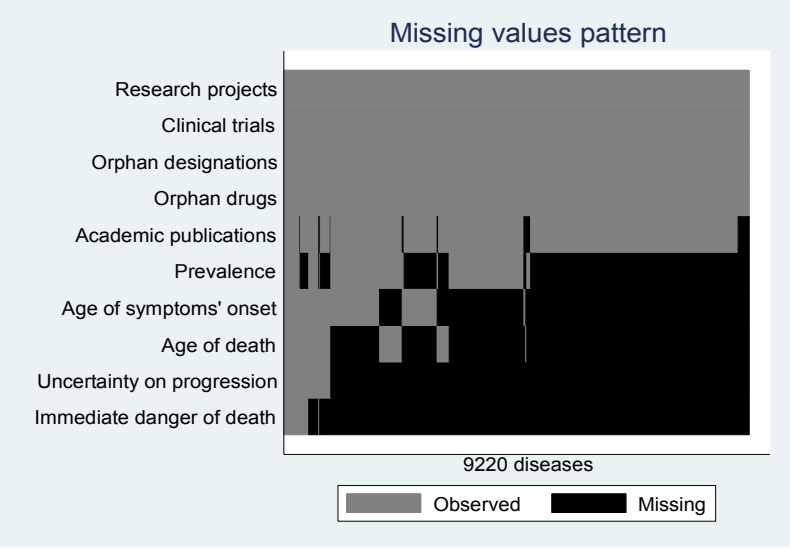
# VIII. Figures

**Figure 1: Frequency distribution of rare disease prevalence**



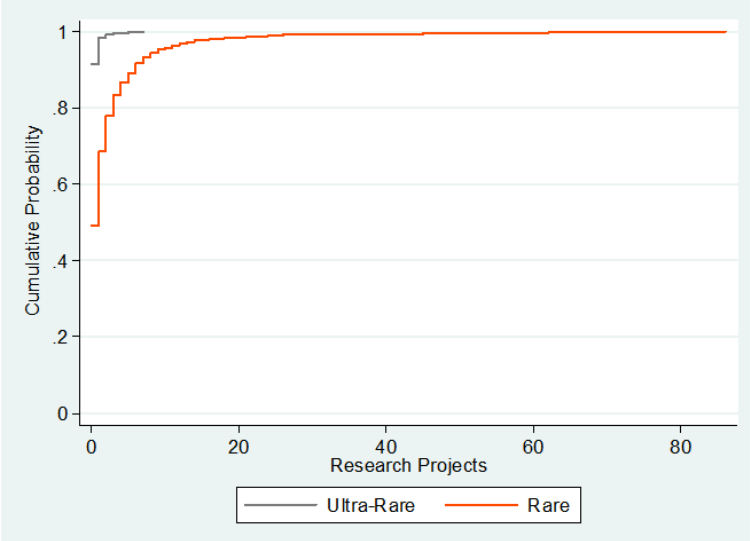

Source: Orphanet Dataset

**Figure 2 – Missing values pattern in terms of all variables of interest**



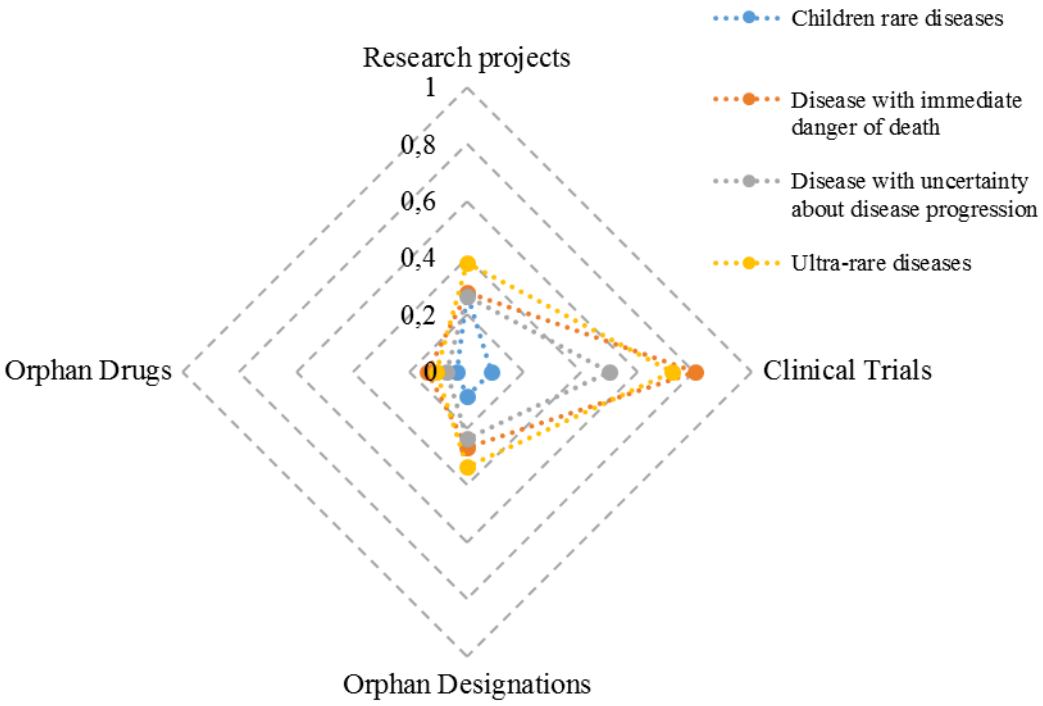

Note: This graph provides visual investigation of shared missing values between all variables considered in the analysis. Variables are displayed on the y-axis depending on the number of missing values in increasing order.

**Figure 3: Cumulative distribution of research projects of ultra-rare versus non ultra-rare diseases**




Source: Orphanet Dataset

**Figure 4: Mean R&D levels differentiated across disease characteristics.**




**Caption:** Yellow line indicates the mean number for each of the R&D outcomes (respectively Research Projects, Clinical Trials, Orphan Designations and Orphan Drugs) 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 very comparable to the one observed for Research Projects.

# IX. Tables

**Table 1 – Descriptive statistics of the 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 respectively: SD: Standard deviation; P25: First quartile; P50: Median; P75: Third quartile.
Source: Orphanet and authors' dataset containing MEDLINE disease-specific number of publications

**Table 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

**Table 3 - Distribution of the mean age at symptoms appearance for rare diseases**

| Mean age at symptoms' onset | Freq. | Percent. | Cumulative Freq. |
|---|---|---|---|
| Infancy | 536 | 20.36 | 20.36 |
| Childhood | 748 | 28.42 | 48.78 |
| Adult & Elderly | 743 | 28.23 | 77.01 |
| All ages | 605 | 22.99 | 100 |
| *Total* | **2632** | **100** | |

Source: Orphanet dataset

**Table 4 - Distribution of the mean age at death for rare diseases**

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

Source: Orphanet dataset

**Table 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 6 - Mean difference in R&D proxies between missing values and non-missing values for diseases' characteristics**

| Characteristics *'c'* | *R&D proxies 'r'* | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Research Projects** | | | **Academic Research** | | | **Clinical Trials** | | | **Orphan designations** | | | **Orphan Drugs** | | |
| | Mean *r* if *c* non-missing | Mean *r* if *c* missing | Diff | Mean *r* if *c* non-missing | Mean *r* if *c* missing | Diff | Mean *r* if *c* non-missing | Mean *r* if *c* missing | Diff | Mean *r* if *c* non-missing | Mean *r* if *c* missing | Diff | Mean *r* if *c* non-missing | Mean *r* if *c* 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 on disease* | 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 deaths* | 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: Table 6 displays the difference in the mean number of each of the R&D proxy (respectively: research projects, academic publications, clinical trials, orphan designations and orphan drugs) when each of the diseases' characteristic 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*_non-missing),
Ha: diff < 0; we display p-values as follows: *** p<0.01, ** p<0.05, * p<0.1
Source: Orphanet and authors' dataset containing MEDLINE disease-specific number of publications

**Table 7 - First-order stochastic dominance using mean age at symptoms onset** (reported p-values)

| Mean age at symptoms onset | | *Infancy* | | | | | *Childhood* | | | | | *Adult & Elderly* | | | | | *All ages* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| *Infancy* | RP | | | | | | **FSD 0.006** | | | | | **FSD 0.000** | | | | | **FSD 0.037** | | | | |
| | AR | | | | | | | **FSD 0.012** | | | | | **FSD 0.000** | | | | | **FSD 0.000** | | | |
| | CT | | | | | | | | **FSD 0.061** | | | | | **FSD 0.000** | | | | | **FSD 0.000** | | |
| | OD | | | | | | | | | ? 0.234 | | | | | **FSD 0.000** | | | | | **FSD 0.000** | |
| | MA | | | | | | | | | | ? 0.701 | | | | | **FSD 0.000** | | | | | **FSD 0.002** |
| *Childhood* | RP | . 1.000 | | | | | | | | | | **FSD 0.009** | | | | | ? 0.696 | | | | |
| | AR | | . 0.715 | | | | | | | | | | **FSD 0.000** | | | | | **FSD 0.003** | | | |
| | CT | | | . 1.000 | | | | | | | | | | **FSD 0.000** | | | | | **FSD 0.000** | | |
| | OD | | | | ? 1.000 | | | | | | | | | | **FSD 0.000** | | | | | **FSD 0.000** | |
| | MA | | | | | ? 0.996 | | | | | | | | | | **FSD 0.002** | | | | | **FSD 0.013** |
| *Adult & Elderly* | RP | . 1.000 | | | | | . 1.000 | | | | | | | | | | . 1.000 | | | | |
| | AR | | . 1.000 | | | | | . 1.000 | | | | | | | | | | . 0.963 | | | |
| | CT | | | . 1.000 | | | | | . 1.000 | | | | | | | | | | **FSD 0.031** | | |
| | OD | | | | . 1.000 | | | | | . 1.000 | | | | | | | | | | ? 0.771 | |
| | MA | | | | | . 1.000 | | | | | . 1.000 | | | | | | | | | | ? 0.990 |
| *All ages* | 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 | | | | | ? 0.233 | | | | | | |
| | MA | | | | | . 1.000 | | | | | . 1.000 | | | | | ? 0.895 | | | | | |

Note: 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 8 (to be continued 1/3) - First-order stochastic dominance with mean age at death** (reported p-values)

| **Mean age at death** | | ***Infancy*** | | | | | ***Childhood*** | | | | | ***Adult & Elderly*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| **Infancy** | RP | | | | | | ? 0.136 | | | | | **FSD 0.000** | | | | |
| | AR | | | | | | **FSD 0.036** | | | | | **FSD 0.000** | | | | |
| | CT | | | | | | | ? 0.742 | | | | | **FSD 0.000** | | | |
| | OD | | | | | | | | ? 0.832 | | | | | **FSD 0.013** | | |
| | MA | | | | | | | | | ? 1.000 | | | | | ? 0.272 | |
| **Childhood** | RP | ? 0.999 | | | | | | | | | | **FSD 0.009** | | | | |
| | AR | | . 0.998 | | | | | | | | | | **FSD 0.000** | | | |
| | CT | | | ? 1.000 | | | | | | | | | | **FSD 0.000** | | |
| | OD | | | | ? 0.872 | | | | | | | | | | **FSD 0.031** | |
| | MA | | | | | ? 0.998 | | | | | | | | | | ? 0.156 |
| **Adult & Elderly** | RP | . 1.000 | | | | | . 1.000 | | | | | | | | | |
| | AR | | . 1.000 | | | | | . 1.000 | | | | | | | | |
| | CT | | | . 1.000 | | | | | . 1.000 | | | | | | | |
| | OD | | | | . 1.000 | | | | | . 1.000 | | | | | | |
| | MA | | | | | ? 1.000 | | | | | ? 1.000 | | | | | |

Note: 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
Caption: RP: research projects, AR: academic research, CT: clinical trials, OD: orphan designations, MA: orphan drugs with market approvals

**Table 8 (to be continued 2/3) - First-order stochastic dominance with mean age at death** (reported p-values)

| Mean age at death | | *All Ages* | | | | | *Normal Life Expectancy* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| **Infancy** | 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 |
| **Childhood** | RP | ? 0.420 | | | | | **FSD 0.010** | | | | |
| | AR | | **FSD 0.065** | | | | | **FSD 0.000** | | | |
| | CT | | | ? 0.264 | | | | | **FSD 0.004** | | |
| | OD | | | | ? 0.590 | | | | | **FSD 0.012** | |
| | MA | | | | | ? 0.833 | | | | | **FSD 0.084** |
| **Adult & Elderly** | 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 |
| **All ages** | RP | | | | | | **FSD 0.019** | | | | |
| | AR | | | | | | | **FSD 0.003** | | | |
| | CT | | | | | | | | **FSD 0.020** | | |
| | OD | | | | | | | | | **FSD 0.002** | |
| | MA | | | | | | | | | | **FSD 0.039** |
| **Normal Life Expectancy** | RP | . 1.000 | | | | | | | | | |
| | AR | | . 0.992 | | | | | | | | |
| | CT | | | . 1.000 | | | | | | | |
| | OD | | | | . 1.000 | | | | | | |
| | MA | | | | | . 1.000 | | | | | |

Note: 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

Caption: RP: research projects, AR: academic research, **CT**: clinical trials, OD: orphan designations, MA: orphan drugs with market approvals

**Table 8 (to be continued 3/3) - First-order stochastic dominance with mean age at death** (reported p-values)

| Mean age at death | | *Infancy* | | | | | *Childhood* | | | | | *Adult & Elderly* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| **All ages** | RP | . 1.000 | | | | | ? 1.000 | | | | | **FSD 0.024** | | | | |
| | AR | | . 1.000 | | | | | . 0.998 | | | | | **FSD 0.003** | | | |
| | CT | | | . 1.000 | | | | | ? 1.000 | | | | | **FSD 0.000** | | |
| | OD | | | | . 1.000 | | | | | ? 1.000 | | | | | **FSD 0.016** | |
| | MA | | | | | ? 1.000 | | | | | ? 1.000 | | | | | ? 0.136 |
| **Normal Life Expectancy** | 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 | | | | | ? 1.000 | | | | | ? 1.000 | | | | | . 0.912 |

Note: 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 9 - First-order stochastic dominance using prevalence in class** (reported p-values)

| **Prevalence in class** | | ***<1 / 1 000 0001*** | | | | | ***1-9 / 1 000 000*** | | | | | ***1-9 / 100 000*** | | | | | ***1-9 / 10 000*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| ***<1 / 1 000 0001*** | 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** |
| ***1-9 / 1 000 000*** | RP | . 1.000 | | | | | | | | | | ? 0.738 | | | | | ? 0.247 | | | | |
| | AR | | . 0.998 | | | | | | | | | | **FSD 0.002** | | | | | **FSD 0.000** | | | |
| | CT | | | . 1.000 | | | | | | | | | | **FSD 0.038** | | | | | **FSD 0.000** | | |
| | OD | | | | . 1.000 | | | | | | | | | | ? 0.330 | | | | | **FSD 0.000** | |
| | MA | | | | | .1.000 | | | | | | | | | | ? 0.824 | | | | | ? 0.151 |
| ***1-9 / 100 000*** | RP | . 1.000 | | | | | ? 1.000 | | | | | | | | | | ? 0.296 | | | | |
| | AR | | . 0.999 | | | | | . 0.907 | | | | | | | | | | **FSD 0.005** | | | |
| | CT | | | . 1.000 | | | | | . 1.000 | | | | | | | | | | **FSD 0.042** | | |
| | OD | | | | . 1.000 | | | | | ? 1.000 | | | | | | | | | | **FSD 0.000** | |
| | MA | | | | | . 1.000 | | | | | ? 0.962 | | | | | | | | | | ? 0.263 |
| ***1-9 / 10 000*** | 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 | | | | | |

Note: 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 10 - First-order stochastic dominance tests with immediate danger of death** (reported p-values)

| **Immediate danger of death** | | ***Yes*** | | | | | ***No*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| ***Yes*** | RP | | | | | | ? 0.886 | | | | |
| | AR | | | | | | | **FSD 0.011** | | | |
| | CT | | | | | | | | **FSD 0.000** | | |
| | OD | | | | | | | | | **FSD 0.089** | |
| | MA | | | | | | | | | | ? 0.121 |
| ***No*** | RP | ? 1.000 | | | | | | | | | |
| | AR | | . 0.999 | | | | | | | | |
| | CT | | | . 1.000 | | | | | | | |
| | OD | | | | . 1.000 | | | | | | |
| | MA | | | | | ? 1.000 | | | | | |

Note: 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 11 - First-order stochastic dominance tests with high level of uncertainty on disease evolution** (reported p-values)

| **Uncertainty about disease evolution** | | ***Yes*** | | | | | ***No*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| ***Yes*** | RP | | | | | | ? 0.791 | | | | |
| | AR | | | | | | | **FSD 0.006** | | | |
| | CT | | | | | | | | ? 0.850 | | |
| | OD | | | | | | | | | **FSD 0.001** | |
| | MA | | | | | | | | | | ? 0.311 |
| ***No*** | RP | ? 1.000 | | | | | | | | | |
| | AR | | . 1.000 | | | | | | | | |
| | CT | | | ? 0.932 | | | | | | | |
| | OD | | | | . 1.000 | | | | | | |
| | MA | | | | | ? 1.000 | | | | | |

Note: 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 12 - First-order stochastic dominance tests using mean age at symptoms onset, observations weighted by prevalence** (reported p-values)

| Mean age at symptoms onset | | *Infancy* | | | | | *Childhood* | | | | | *Adult & Elderly* | | | | | *All ages* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| ***Infancy*** | RP | | | | | | **FSD 0.006** | | | | | ? 0.191 | | | | | **FSD 0.001** | | | | |
| | AR | | | | | | . 0.151 | | | | | | **FSD 0.000** | | | | | **FSD 0.000** | | | |
| | CT | | | | | | | | **FSD 0.001** | | | | | **FSD 0.000** | | | | | **FSD 0.000** | | |
| | OD | | | | | | | | | ? 0.234 | | | | | **FSD 0.000** | | | | | **FSD 0.000** | |
| | MA | | | | | | | | | | ? 0.701 | | | | | **FSD 0.000** | | | | | **FSD 0.002** |
| ***Childhood*** | RP | . 0.489 | | | | | | | | | | ? 0.088 | | | | | ? 0.011 | | | | |
| | AR | | **FSD 0.000** | | | | | | | | | | **FSD 0.000** | | | | | **FSD 0.000** | | | |
| | CT | | | . 1.000 | | | | | | | | | | **FSD 0.000** | | | | | **FSD 0.001** | | |
| | OD | | | | ? 1.000 | | | | | | | | | | **FSD 0.011** | | | | | **FSD 0.000** | |
| | MA | | | | | ? 0.690 | | | | | | | | | | ? 0.029 | | | | | **FSD 0.001** |
| ***Adult & Elderly*** | RP | ? 0.324 | | | | | ? 0.000 | | | | | | | | | | ? 0.148 | | | | |
| | AR | | . 1.000 | | | | | . 0.351 | | | | | | | | | | ? 0.963 | | | |
| | CT | | | . 1.000 | | | | | . 0.144 | | | | | | | | | | **FSD 0.001** | | |
| | OD | | | | . 1.000 | | | | | . 0.934 | | | | | | | | | | **FSD 0.001** | |
| | MA | | | | | . 1.000 | | | | | ? 0.045 | | | | | | | | | | **FSD 0.044** |
| ***All ages*** | RP | . 0.929 | | | | | ? 0.039 | | | | | ? 0.904 | | | | | | | | | |
| | AR | | ? 0.006 | | | | | . 1.000 | | | | | ? 0.667 | | | | | | | | |
| | CT | | | . 1.000 | | | | | . 0.592 | | | | | . 1.000 | | | | | | | |
| | OD | | | | . 1.000 | | | | | . 1.000 | | | | | . 0.548 | | | | | | |
| | MA | | | | | . 1.000 | | | | | . 1.000 | | | | | . 1.000 | | | | | |

Note: 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 13** ***(to be continued 1/3)*** **- First-order stochastic dominance tests with mean age at death, observations weighted by prevalence**
(reported p-values)

| **Mean age at death** | | ***Infancy*** | | | | | ***Childhood*** | | | | | ***Adult & Elderly*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| **Infancy** | 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** |
| **Childhood** | 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** |
| **Adult & Elderly** | RP | . 1.000 | | | | | . 1.000 | | | | | | | | | |
| | AR | | . 1.000 | | | | | . 1.000 | | | | | | | | |
| | CT | | | . 1.000 | | | | | . 0.800 | | | | | | | |
| | OD | | | | . 1.000 | | | | | . 1.000 | | | | | | |
| | MA | | | | | . 1.000 | | | | | . 1.000 | | | | | |

Note: 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
Caption: RP: research projects, AR: academic research, CT: clinical trials, OD: orphan designations, MA: orphan drugs with market approvals

**Table 13** ***(to be continued 2/3)*** **- First-order stochastic dominance tests with mean age at death, observations weighted by prevalence** (reported p-values)

| **Mean age at death** | | ***All Ages*** | | | | | ***Normal Life Expectancy*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| **Infancy** | 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 |
| **Childhood** | RP | **FSD 0.000** | | | | | **FSD 0.000** | | | | |
| | AR | | **FSD 0.000** | | | | | **FSD 0.000)** | | | |
| | CT | | | **FSD 0.000** | | | | | **FSD 0.000** | | |
| | OD | | | | **FSD 0.001** | | | | | **FSD 0.000** | |
| | MA | | | | | **FSD 0.095** | | | | | **FSD 0.007** |
| **Adult & Elderly** | RP | . 0.992 | | | | | . 1.000 | | | | |
| | AR | | . 0.182 | | | | | . 0.304 | | | |
| | CT | | | . 1.000 | | | | | . 0.794 | | |
| | OD | | | | . 0.992 | | | | | . 0.853 | |
| | MA | | | | | . 0.998 | | | | | . 0.911 |
| **All ages** | RP | | | | | | **FSD 0.000** | | | | |
| | AR | | | | | | | **FSD 0.002** | | | |
| | CT | | | | | | | | **FSD 0.006** | | |
| | OD | | | | | | | | | **FSD 0.087** | |
| | MA | | | | | | | | | | **FSD 0.216** |
| **Normal Life Expectancy** | RP | . 0.982 | | | | | | | | | |
| | AR | | . 0.580 | | | | | | | | |
| | CT | | | . 1.000 | | | | | | | |
| | OD | | | | . 0.988 | | | | | | |
| | MA | | | | | . 0.908 | | | | | |

Note: 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

Caption: RP: research projects, AR: academic research, **CT**: clinical trials, OD: orphan designations, MA: orphan drugs with market approvals

**Table 13** ***(to be continued 3/3)*** **- First-order stochastic dominance tests with mean age at death, observations weighted by prevalence**
(reported p-values)

| **Mean age at death** | | ***Infancy*** | | | | | ***Childhood*** | | | | | ***Adult & Elderly*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| **All ages** | 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** | |
| | MA | | | | | ? 0.438 | | | | | . 1.000 | | | | | **FSD 0.000** |
| **Normal Life Expectancy** | RP | . 1.000 | | | | | . 1.000 | | | | | **FSD 0.084** | | | | |
| | AR | | . 1.000 | | | | | . 0.835 | | | | | **FSD 0.000** | | | |
| | CT | | | . 1.000 | | | | | . 1.000 | | | | | **FSD 0.000** | | |
| | OD | | | | . 1.000 | | | | | . 0.554 | | | | | **FSD 0.000** | |
| | MA | | | | | ? 1.000 | | | | | . 1.000 | | | | | **FSD 0.043** |

Note: 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 14 - First-order stochastic dominance tests with immediate danger of death, observations weighted by prevalence** (reported p-values)

| **Immediate danger of death** | | ***Yes*** | | | | | ***No*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| ***Yes*** | RP | | | | | | **FSD 0.017** | | | | |
| | AR | | | | | | | **FSD 0.000** | | | |
| | CT | | | | | | | | **FSD 0.004** | | |
| | OD | | | | | | | | | **FSD 0.000** | |
| | MA | | | | | | | | | | **FSD 0.001** |
| ***No*** | RP | . 0.593 | | | | | | | | | |
| | AR | | . 0.994 | | | | | | | | |
| | CT | | | . 1.000 | | | | | | | |
| | OD | | | | . 1.000 | | | | | | |
| | MA | | | | | . 1.000 | | | | | |

Note: 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 15 - First-order stochastic dominance tests with high level of uncertainty on disease evolution, observations weighted by prevalence (reported p-values)**

| **Uncertainty about disease evolution** | | ***Yes*** | | | | | ***No*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Column Versus Row | | RP | AR | CT | OD | MA | RP | AR | CT | OD | MA |
| ***Yes*** | RP | | | | | | ? 0.971 | | | | |
| | AR | | | | | | | ? 0.019 | | | |
| | CT | | | | | | | | . 0.477 | | |
| | OD | | | | | | | | | . 0.191 | |
| | MA | | | | | | | | | | ? 0.396 |
| ***No*** | RP | **FSD 0.000** | | | | | | | | | |
| | AR | | ? 0.081 | | | | | | | | |
| | CT | | | **FSD 0.041** | | | | | | | |
| | OD | | | | **FSD 0.007** | | | | | | |
| | MA | | | | | ? 0.391 | | | | | |

Note: 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