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APPROACHES TO ESTIMATING INDIRECT COSTS IN HEALTHCARE: MOTIVATIONS FOR CHOICE

Abstract

When performing health economic evaluations all costs and expected benefits (in terms of clinical effectiveness, utility, monetary benefits) should be taken into account. Costs are direct and indirect: concerning the latter, two main methods have been developed. The Human Capital Approach (HCA) considers the gross salary in the days of absence from work due to illness; the method based on the Friction Costs (FC), instead, considers equally the value of productivity, but the losses are limited to the period of illness when it is necessary to replace the absent worker. This paper conducts a review of the literature contributions for European countries and aims at identifying common trends within geographical areas. Estimation of indirect costs in different European areas may reflect the real cost of health services across countries and schematize the conditions under which a certain method should be preferred. Overall, cost analyses applying HCA are the most frequent, while studies based on FC are more common in the Netherlands, where this method had been developed. The reasons to

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apply HCA or FC may depend on the institutional context, for example, the flexibility in the job market, and the epidemiologic environment.

Key Words:

indirect costs; human capital approach (HCA); friction costs (FC); European countries.

JEL: I18, J24, J32, J89, Y50.

2 tables, 95 references.

Problem Statement

The objectives of the economic evaluation in healthcare include the estimation of the costs associated with the health programmes and technologies that represent an essential step in the choice and application of methods with different characteristics. Let us consider these two aspects.

Relevance of cost estimation in health economics analyses

The information relevant to the decision-maker, on the one hand, regards the estimate of the resources needed to implement a given programme and, on the other hand, analyses the economic consequences produced by that programme, both from the point of view of the National Health Service (NHS), where this is present, and of the welfare system.

The resources needed to implement a health programme can be divided into three categories. First, there are the direct costs, i.e., the resources associated with medical treatments (such as drugs, medical examinations, support therapies, laboratory tests, possible hospitalizations, etc.). Second, non-health direct costs relate to the resources used by patients and family members (these in-

clude the cost of social services, domestic assistance, transport costs, assistance provided by caregivers outside the working hours). These are mainly the so-called *out-of-pocket expenses* that are sustained directly by the patient. Finally, the indirect costs are related to the impact that the disease has on the social life of the patient (for example, the working days lost for medical treatment, the working days lost by patients' family members, as well as the share of social security expenditure borne by the public sector).

A cost assessment that includes indirect costs can efficiently drive health policy planning (Puddu et al., 2016; Pederzoli & Gandini, 2008) and allow a better allocation of resources (Koopmanschap & Rutten, 1994).

Three fundamental components have been identified as the elements that contribute to the determination of indirect costs (van Roijen et al., 1996):

a) absences from work (which have to be paid);

b) reduced productivity at work;

c) production not remunerated, due, for example, to the lower possibility of carrying out the usual activities at home.

All these components depend on the state of illness. The choice of a suitable methodology to calculate all kind of costs, including indirect costs, is an issue open to different interpretations: in fact, there are no established guidelines and precise criteria universally recognised.

Productivity costs are often omitted from economic assessments, despite their, often considerable, impact in terms of cost-effectiveness (Krol & Brouwer, 2014, Krol et al., 2011). When a worker cannot work due to illness, production decreases, giving rise to immediately quantifiable losses from an economic point of view (Knies et al., 2010). The contributions that, in the economic literature, have carried out estimates of these losses usually employ two main techniques: the best known is the Human Capital Approach (HCA); more recently implemented is the method based on the calculation of the Friction Costs (FC).

Out of the two methodologies, which one should be preferred? This analysis compares HCA and FC. It has been carried out for European countries, distinguishing geographical areas. The survey has considered the studies carried out in the last decade.

The present analysis has been conducted to highlight how studies in the medical-economic literature have been oriented to carry out an evaluation of indirect costs. Applying the same research methodology in each country and in each examined reality may not be appropriate: the institutional context is different, the epidemiological scenario that occurs in various European regions is different too. Even if the prevailing analysis methodology in one geographical area was, for example, that based on FC, this choice may not be the one preferred in another area, characterized by a different legislative and institutional context.

Overall, the important indication that can be drawn from such a review, therefore, concerns the appraisal of the prevailing methodology according to different pathologies and the identification of the methodology to be preferred in various institutional settings.

Characteristics of evaluation methods

In general, both methods estimate the value of resources in monetary terms (represented by the salary value). While the HCA considers the gross salary in the days of absence from work due to the disease, the method based on FC considers the value of productivity losses, limited, however, to the period of illness when it is necessary to replace the worker absent due to the disease (Koopmanschap & Rutten, 1996; Sculpher, 2001). The loss of productivity is thus calculated for the period necessary to restore production levels within an organization (Koopmanschap & Rutten, 1996; Koopmanschap & van Ineveld, 1992). Since it is assumed that it is possible to replace workers by drawing on labour reserves (Koopmanschap et al., 1995), it has been argued that the FC method generates more realistic estimates of lost productivity than the HCA.

The timeframe considered differs for both approaches: while productivity losses may extend from the short term to some decades in the case of HCA, when the FCs are considered, they refer to a shorter period, although the time needed to train a new worker is not known in advance. The worker who needs to be replaced may, however, increase their productivity when back at work, to compensate for the initial loss due to the state of illness. Further, if the sick worker carries out the work they have not been able to do when they return to work (or their work is temporarily carried out by any colleague), it is possible that their absence will not result in any loss of production.

In the absence of an approach that is clearly preferred over another, the solution lies in choosing the perspective that suits the current political context, the regulatory framework or in using both methods and comparing the results achieved.

A review of the criteria that should be observed in calculating indirect costs has been carried out by Gianino et al. (2009), who, discussing characteristics of FC, outline some key elements that must be considered. Among these are: the frequency of friction periods determined by the recurrence and duration of the absence from work; the length of the friction period; the relationship between the loss of productivity and the time spent working.

Summarising, advantages and pitfalls of both methods can be observed in Table 1.

Table 1

Characteristics of HCA and FC

Characteristics	Human Capital Approach	Friction Costs Approach
Theoretical assumptions	Neoclassical theory of full employment; the value of work equals the value of the product	No robust theoretical basis
Perspective adopted	Employee	Employer
Time framework	Life of the individual	Time needed to train a new worker
Costs	Real wage	Real wage, training costs
Estimation of costs	Easier, but risk to overestimate costs	More precise, but need to take into account wage variations

HCA is the most daring method and has been developed in the context of labour economics studies. Over the last twenty years, it has often been applied to estimate indirect costs and productivity losses. The FC method, on the other hand, was initially developed by health economics scholars in the Netherlands and in the Anglo-Saxon countries; its main characteristics have been described in the works by Koopmanschap et al. (1995), Koopmanschap & van Ineveld (1992), Liljas (1998), and Sculpher (2001). Despite the advantages of the FC method when applied in countries characterized by a highly flexible labour market, few studies have employed this method to carry out economic evaluations in other countries (for example, Kigozi et al., 2017). This may be due to the absence of reliable data regarding the frictional period, although there are proposals on this drawn from contributions in the literature (Koopmanschap et al., 1995; Pritchard & Sculpher, 2000). The duration of the frictional period suggested by Pearce et al. (2015) varies from 10 weeks to 13 weeks for manual occupations. Likewise, the probability of replacement by a person who was previously unemployed may differ depending on the type of employment. For example, in the United Kingdom, only four studies (Andrews et al., 2008; Adams & Greig, 2002; Roper, 1988; Beaumont, 1978) have addressed the problem related to the quantification of the absence from work. However, these studies do not provide the information necessary to correlate the frictional period to the productivity costs. If the differences between types of employees in the labour market are ignored, it may lead to an imprecise assessment of productivity costs (Koopmanschap & Rutten, 1996; Koopmanschap et al., 1995).

Analysis of Economic Literature by European Geographical Areas

The diversity in the types of intervention and the methodologies followed can be seen by examining some of the studies that have discussed this topic, the objectives of analyses, the analysed pathologies, and the obtained results.

The literature contributions have been selected according to the following procedure. First, selection of the studies was carried out through Pubmed.org, including, the following keywords:

- [human capital approach + indirect costs + country], substituting «country» with each European country examined. From an initial search, where «Europe» has been added as third keyword, 324 studies were retrieved.
- [friction cost + indirect costs + country]. From this search, instead, considering «Europe» as third keyword, 28 studies were retrieved.

The studies that have been identified are largely related to case studies: several observational studies have been conducted as part of international research projects, some contributions concern the two methodologies of analysis and present the results obtained through the application of both HCA and the FC-based approach.

The European geographical areas, for which the results are obtained from the pharmacoeconomic literature, are the ones identified in the study by Gianino et al. (2009): (a) Eastern Europe (including countries like Hungary and Poland); (b) Western Europe (including Austria, Belgium, France, Germany, Netherlands, Switzerland); (c) Northern Europe (including countries like the United Kingdom, Finland, Sweden); and (d) Southern Europe (including Italy, Portugal and Spain).

The research was carried out from 2018 to 2021. There are more works that apply HCA for the calculation of indirect costs, although there is a clear prevalence of FC in the literature of Western European countries (primarily, the Netherlands).

The common elements that may be found in the various studies are:

- the use of prevalence data;
- higher frequency of top-down rather than bottom-up analyses;
- effectiveness data are collected through interviews and patient surveys;
- consideration of health costs related to the costs of treatment, hospitalization, drugs and medical devices; non-health costs comprised of indirect costs and concern absenteeism, presenteeism and loss of productivity because of the morbid condition;

- health policy considerations relate to the costs of care provision for the patients;
- difficulty in attempts to quantify the intangible costs that are also borne by patients and their caregivers.

Table 2 summarizes the reviewed studies and the indications for possible inclusion of indirect costs in health economics studies.

Table 2

Inclusion of indirect costs in economic evaluations

Geographic area	Country	No. of studies reviewed		Indications about calculations of indirect costs
		HCA	FC	
Eastern Europe	Hungary	1	0	Inclusion of indirect costs depending on the perspective of the study
	Poland	10	4	Inclusion of indirect costs depending on the perspective of the study
Western Europe	Austria	3	0	Included
	Belgium	6	1	Inclusion of indirect costs depending on the relevance of the project
	France	6	2	Included
	Germany	18	5	Inclusion of indirect costs depending on the perspective of the study
	The Netherlands	12	13	Included
	Switzerland	3	0	Inclusion of indirect costs depending on the perspective of the study
Northern Europe	The UK	12	1	Inclusion not required
	Finland	2	1	Inclusion of indirect costs depending on the perspective of the study
	Sweden	12	6	Inclusion of indirect costs depending on the relevance of the project
Southern Europe	Italy	14	0	Included
	Portugal	3	0	Included
	Spain	5	3	Inclusion of indirect costs depending on the perspective of the study

The literature contributions for Eastern Europe

The contributions carried out in the last five years about Eastern Europe are not many, but they allow us to draw conclusions regarding the inclusion of indirect costs in the economic evaluation. The prevailing criterion for the estimation of costs is HCA, rather than FC.

The pathologies that have called for investigation about costs, in this geographic area, concerned mainly metabolic diseases (Crohn's disease or ulcerative colitis). While information on productivity regarding the performance at work was collected, mainly, through questionnaires, the disability rates for the whole population derive from national databases (see, for example, Mandel et al., 2014; Holko et al., 2016, Kawalec, 2017). Some studies (e.g., Łyszczarz & Nojszewska (2014), a study carried out for Poland and related to oncology diseases) underline the importance of taking into account, the economic implications of cancer both for the patient involved and for the system, together with the health and social costs. HCA is employed to evaluate all pathologies that imply a personal involvement by the patient, for example, migraine (Lublóy, 2019), or neurological conditions such as epilepsy (Jędrzejczak et al., 2021). Overall, indirect costs caused by reduced productivity at work are strongly influenced by the disease, while the costs related to informal care are usually neglected by economic analyses and this leads to frequently underestimated or incorrectly calculated results (Schubert et al., 2015). Some studies do not examine specific pathologies: the study by Lasocka et al. (2013) aims to estimate annual productivity losses due to smoking by looking at a social perspective and comparing the results obtained for Poland with similar research carried out in other countries (Germany, Sweden and USA) through the method of HCA.

The estimation of the full costs of illness depends on the method chosen for the analysis. In a study concerning asthma, indirect costs determined from the perspective of the third party amounted to € 4,287.6 per patient applying HCA, but decreased to € 1,457.2 using the FC method (Jahnz-Różyk et al., 2015).

Conclusions reached for Eastern Europe are comparable those for all OECD countries. An aspect that should be considered in more detail concerns the financing of health expenditure; for example, in Poland 70% of health expenditure is financed through universal contributions that increase in the same way citizens' wages do.

The literature contributions for Western Europe

In the countries of Western Europe (Austria, Belgium, France, Germany, the Netherlands, Switzerland), most studies aimed at estimating indirect costs use the HCA method, although the FC methodology has been developed in the Netherlands. This tendency may stem from a more conservative attitude of re-

searchers, who may prefer a consolidated method like HCA over a more recent method like FC.

The majority of costs are attributable to the indirect costs resulting from lost productivity. It has been seen that estimates of costs obtained with FC method are 56% lower than those estimated with HCA (see Prast et al. (2013), who examine the costs of endometriosis versus Simoens et al. (2007), who apply the FC method obtaining lower indirect costs).

For Belgium, the identified studies are not numerous, and the attention of the literature is directed at assessing implications for costs determined by lifestyles (for example, smoking, use of drugs, etc.) rather than specific pathologies. For example, Lievens et al. (2017) examine the economic burden for both individuals and society caused by the use of both legal and illegal substances (including alcohol, tobacco, and illicit drugs): the use of illegal substances determines costs of law enforcement, loss of productivity and reduced quality of life. The studies concerning social aspects need to adopt a wider perspective, and this justifies the application of HCA, as it is not temporally limited to the period of absence from work and considers a longer timeframe than FC.

Evidently, in Western Europe countries, the analyses dealing with economic evaluations focusing on indirect costs are rather limited. This could be explained by the ISPOR indications which, for Belgium in particular, state that, when carrying out economic evaluation analyses the reference should include only the costs of direct health care, i.e., the costs directly related to the treatment of the disease and the direct costs of health care related to the disease in the years of life gained. Direct costs outside the health sector, productivity costs and healthcare costs associated with unrelated diseases should not be included in the reference case, and can be reported as a separate analysis.

According to the criteria established by the Haute Autoritè de la Santè (2012), the evaluation method to assess the indirect costs has to be chosen by the researcher and adequate motivations must be provided when there is no clear indication, as in France, because the pathologies for the economic evaluations considering the indirect costs are different (see, for example, Fautrel et al., 2007; Serrier et al., 2014; Chevreul et al., 2015).

In Germany, most of the literature recommends including productivity losses in calculating healthcare costs, and, therefore, indirect costs. In the German context, the inability to perform any working activity is associated with partial loss of income: consequently, since productivity losses due to the inability to work should be presented among costs, HCA for the estimation of indirect costs would be the preferred method (Bommer et al., 2017, Huebner et al., 2017).

Other examples not related to specific diseases but affecting the costs of care are described in studies using HCA. For example, although patients with injuries from an accident represent a significant medical and socio-economic bur-

den in the German healthcare system, there are few data describing costs in the period between the accident and the professional reintegration (Anders et al., 2013), so the analysis can only be considered a starting point for further studies. This might be a framework where the application of FC could be, indeed, evalutated. Often, it is the kind of disease that suggests an assessment of costs across time, as is the case in the study by Wolf at al. (2010) dedicated to a therapy programme concerning HIV-positive patients. It concludes that the administration of abacavir in HIV-positive patients reduces the risk of hypersensitivity reaction to the drug, and determines potential cost savings, measured with HCA). The study is not limited to examining the period needed to restore work skills, as in Dodel et al. (2010), for example, where the health burden of patients with Gilles de la Tourette syndrome (GTS) is assessed in Germany during a 3-month observation period, a time span necessary to identify the rational allocation of resources.

While HCA is a widely accepted method for measuring the loss of production for the society caused by a disease, as it evaluates the output generated by a person measured in market prices, this method is often criticized because it overestimates the «real» costs of the disease. In fact, it assumes a perfect labour market and an immediate substitutability of the workers.

Other conditions, as stroke, for example, absorb many resources. While studies on the costs of acute stroke treatment have been conducted in Europe, a thorough analysis of direct and indirect long-term costs is lacking.

Cancer also causes a high economic burden. Reis et al. (2006) compare the direct, indirect and social costs of the Hodgkin's disease, non-Hodgkin's lymphoma, plasmacytoma, and chronic lymphatic lymphoma. Direct, indirect, and social costs are calculated using the HCA method. Lung cancer shows highest incidence out of all cancers among men and an increasing incidence among women. The study by Weissflog et al. (2001) evaluates the economic burden of lung cancer in Germany and identifies the main cost factors. In a retrospective analysis, direct and indirect costs were calculated based on data from government institutions and the pharmaceutical industry: the HCA method was applied for the calculation of indirect costs.

Some studies examine mental illnesses. Konnopka and König (2009) perform a systematic review of the literature on the cost of the disease for schizophrenia in Germany. Indirect costs are mainly caused by early retirement or unemployment and the HCA method is used to calculate them. Krauth et al. (2000) evaluate the indirect costs of an outpatient rehabilitation programme for the Hanover medical school. In the economic assessment, the cost of time is expressed by the loss and reduction of working time, time for housework and leisure time. To estimate the actual loss of working time which results in a loss of production, it is possible to apply the HCA and FC methods. The time lost due to

housework can be estimated both considering the production of goods and services, and the opportunity cost of an equivalent working hour.

In Switzerland, the inclusion of indirect costs depends on the subject of the study; the studies carried out present particular cases and often evaluate general programmes rather than the impact of specific pathologies. The study by Pugliatti et al. (2007) estimates the cost of epilepsy in Europe (25 EU countries plus Iceland, Norway and Switzerland). The selected approach is based on a bottom-up cost estimate that employs HCA for the calculation of indirect costs. Another study considers the weight and burden of flu, which varies with age and the patient's state of health (Szucs, 1999). The disease imposes a significant burden on all individuals, but hospitalization and treatment occur more frequently in high-risk patients (the elderly and those with certain co-morbidities). For the measurement of indirect costs, the HCA method is preferred. Finally, Sagmeister et al. (1998) estimate the cost of premature mortality due to coronary artery disease for the working age population using HCA. Indirect costs are around 25% of the total costs generated by the disease. From the study it is possible to observe a reduction in costs from one year to the other, corresponding to a lower loss of productivity.

Conversely, the studies that apply the method based on FCs for the estimation of indirect costs are less numerous. The examined diseases include mainly rheumatic diseases, as well as oftalmic diseases and vaccination programmes. Huscher et al. (2015) estimate changes in direct and indirect costs caused by patients with rheumatoid arthritis in Germany between 2002 and 2011. Costs were updated and indirect costs were calculated using HCA and FC. There has been a significant increase in direct costs, attributable to the increase in the prescription of biological agents. However, such increase in expenses for medical treatment was accompanied by a reduction in hospital expenses and indirect costs. In a previous study, Huscher et al. (2006) had already estimated and compared the direct and indirect costs of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus, evaluating the impact of certain variables (gender and severity of the patients' conditions) on the various cost items, applying, for the calculation of indirect costs, HCA and FCs. With the FC method the estimated figures were lower, with a strong effect of the functional state on the total costs.

Overall, it can be argued that the indirect costs of chronic diseases are receiving increasing attention because recent diagnostic and therapeutic improvements have significantly augmented treatment costs, and it is therefore crucial to pursue cost savings. However, the methods of valuing indirect cost components still differ widely, leading to heterogeneous data that does not allow for direct comparison. This is the consideration advanced, for example, by Merkesdal et al. (2002) who compare the indirect costs calculated with the HCA and FC method, providing recommendations to improve the comparability of such costs.

The Netherlands represents the context in which the FC methodology has been developed and in which the studies applying this method are more numerous. The interest of scholars is in assessing the impact of indirect costs on the labour market: this is why productivity losses receive higher attention. In Politiek et al. (2016), a systematic review of the literature is carried out considering both HCA and FC. The study assesses the costs of eczema in the hand, the burden of which is considerable, estimating indirect costs that account for up to 70% of total costs and are mainly due to work absenteeism.

Concerning other pathologies, Cuijpers et al. (2007) have investigated the impact of depression in comparison with the costs of other mental illnesses. Direct medical costs, direct non-medical costs and indirect non-medical costs were calculated according to the latest Dutch guideline for health economic assessments based on FCs.

Postma et al. (2004) estimate the cost-effectiveness of vaccination against hepatitis A virus for children of ethnic minorities living in Amsterdam. The analysis was performed from a social perspective, as recommended in the Dutch drug-economy research guidelines, including the indirect costs of production losses. In fact, indirect costs have been calculated based on 40 days of sickness, concluding that vaccination does not represent a cost-saving but can have a favorable profitability and fits into the Dutch policy of providing vaccinations for ethnic minority groups. Van Beeck et al. (1997) assess the direct medical costs and indirect costs of injuries, which are an important source of medical costs as well as production losses in the Netherlands, using HCA and FC. Nearly two-thirds of the direct costs are the result of injuries among women (especially older women's domestic injuries). However, regardless of the method used, more than 80% of indirect costs are the result of injuries among males, mainly caused by a high frequency of accidents at work and sports injuries among young males. The application of the FC method confirms injuries as a source of production losses compared to other diseases.

All the other identified studies focus on a broad discussion of the advantages of each estimation method. The debate dates to the early 1990s, with the study by Koopmamschap and van Ineveld (1992), who warned that many researchers, when assessing health care, have doubts on the usefulness of estimates of indirect costs of disease in setting priorities in health care. The study seeks to respond to the criticism related to the definition of indirect costs as the value of loss of production due to the disease, by first proposing a new method for estimating indirect costs. The authors conclude that the method based on FCs for estimating indirect costs is promising but needs further development. However, it should be borne in mind that this article was published in the early 1990s.

At the same time, in the early 1990s, although HCA was commonly used to estimate indirect costs, a growing number of authors questioned its validity.

Koopmansch and Rutten (1993) illustrate the relevance of indirect cost estimates for health policy and stress various important issues and disputes concerning indirect costs (such as the reduction of productivity without absence from work, the influence of unemployment on loss of production, the relationship between health effects and indirect costs). Indirect costs are relevant to health policy, provided that their estimates reflect the actual changes in production due to the disease, including production by unpaid labor.

In economic evaluations, indirect costs, according to the studies carried out in the Netherlands, should preferably be presented separately from direct costs, health effects and other results. Koopmansch et al. (1995) describe the FC-based approach for estimating the indirect costs and provide some evidence: for the Netherlands, short-term FC in 1990 amounts to 1.5-2.5% of national net income, depending on the extent to which short-term absence from work leads to losses and production costs. The macroeconomic consequences of absence from work and disability in the medium term reduce the national net income by a further 0.8%. These estimates are significantly lower than estimates based on the traditional HCA approach, but, perhaps, reflect better the economic impact of the disease and should orient the choice of the analyst for FC methods. In the subsequent study by Koopmanschap and Rutten (1996), a practical guide is provided for the quantification and exploitation of indirect disease costs, both at the aggregate level of general cost of disease studies, and in an economic assessment of precise health programmes. In this context, while HCA estimates the potential value of production lost because of an illness, the method based on FC is aimed at deriving more realistic estimates of indirect costs, taking into account the scarcity of work.

The identified studies that apply FCs include that of Reurings et al. (2010), which evaluates the latest developments in colon surgery. The primary outcome parameters are the two main cost factors: direct medical costs (calculated through the actual cost) and indirect non-medical costs (estimated through the FC method). Postma et al. (1999) had already proposed a single case study, evaluating the cost effectiveness of the Chlamydia trachomatis (CT) screening of young women who go to primary care physicians. Data on the need for health care for CT complications and its costs are estimated through FCs.

Hutubessy et al. (1999) estimate the indirect costs of back pain in 1991 in the Netherlands based on both HCA and FC. The results of the study showed that the estimated short-term indirect costs with HCA were more than three times higher than the indirect costs estimated by the FC-based method (respectively, $4.6 billion vs. $1.5 billion). The lower amount of indirect costs when estimated with the FC method is mainly due to the fact that actual production losses were assessed during a relatively short friction period. In contrast to HCA, long-term absenteeism and disability do not induce additional costs when the FC method is applied. Policies aimed at reducing the indirect costs of back pain are increasingly focused on the development and evaluation of interventions immediately af-

ter the onset of the disease, taking also into account the possibility of reintegrating chronic patients into the workforce.

Recently, Dutch studies have shown an emerging greater openness to innovative methods, but also greater attention to the consequences on the labour market. Recommendation here would be that the implementation of measures of economic and health policy should be considered within the regulatory sphere.

The literature contributions for Northern European (United Kingdom, Finland and Sweden)

In Northern European countries (including, in this group, the UK and Scandinavian countries), HCA still remains the prevalent approach. In the UK, studies have evaluated pathologies such as cancer. For example, Round et al. (2016) consider people diagnosed in an advanced stage of neoplasia, who require a range of health care, both social and informal, during the final stages of life, with significant costs for health and social systems, patients and their families. As stressed in other studies, the adoption of HCA allows them to pay attention to the patient's condition; the choice of HCA for the estimation of indirect costs is justified in studies describing how the economic burden is borne by the individual, rather than the employer (as in the study by Ayres et al. (2011), who estimate the social costs of asthma in the United Kingdom).

One of the weaknesses of the HCA-based approach is that it could underestimate indirect costs. Costs, in fact, are estimated taking into account market prices and very low values are attributed to expenses incurred by retired older people or other frail people (as in the work by Mangalore and Knapp (2007), which conducted different estimates for categories of not working subjects, e.g., people living in families, institutions, prisons and homeless people). The considered costs include health and social care, informal care, private expenses, lost productivity, criminal justice services and other public expenditure, such as the social security system, leeading to an estimated burden of indirect costs almost double comparing to the direct costs.

In a study presenting both methods of estimation, Liu et al. (2002) assess the economic burden of coronary heart disease in the UK by using both direct and indirect costs. Having estimated indirect costs using the HCA, the productivity losses were adjusted for FC. The article presents some considerations on the friction period to consider for the analysis. However, in spite of some isolated works applying FC, the prevailing approach for the United Kingdom is based on human capital (HCA), without a consolidated tradition of literature based on FC.

Looking at Scandinavian countries, in Finland, the economic assessment studies are not many and look at individual case studies. Haikonen et al. (2016) examine the indirect economic burden of deaths caused by fires in Finland in the period of 2000-2010 and the HCA-based method is the main tool used to esti-

mate productivity losses, though the potentially lost lives are also estimated. Puolakka et al. (2009), on the other hand, prefer the FC-based approach. In a study aimed at estimating the loss of productivity due to rheumatoid arthritis, the loss of productivity was calculated with both HCA and FC.

A greater attention to the economic evaluation studies is observed in Sweden: here, the number of studies, which apply both methods for estimating indirect costs, is among the most copious in Europe.

Some studies are aimed at suggesting health policy indications. Ernstsson et al. (2016), observing studies on multiple sclerosis (MS), a disease whose prevalence in Scandinavian countries is higher comparing to other European countries, argue that studies centered on the cost of the illness are fundamental for planning adequate interventions. These considerations also apply to rheumatological diseases, such as rheumatoid arthritis, for which Hallert et al. (2014) use HCA to calculate indirect costs. The results can be used to analyse possible improvements in care, as in a paper by Persson et al. (2012), which estimates the economic burden related to the treatment of stroke.

Estimates of indirect costs associated with breast cancer are based on HCA, although it is suggested to use the FC method as an alternative: in a comparison of the two methods, it has been seen how FC produces smaller estimates of indirect costs (Lidgren et al., 2007). The assessment of the pathology itself concerns conditions like depression, which is among the most common causes of disability and is associated with substantial reductions in individual quality of life. A study by Sobocki et al. (2007), measures both the direct cost of providing healthcare to patients, and indirect costs, measured through HCA approach.

HCA and FC can be compared looking at the obtained results: some case studies looking at costs of informal care in the context of home care (Andersson et al., 2002) include both the HCA and FC approaches. While estimating indirect costs with FC, the amount is only 18% of total costs, whereas the HCA approach shows an amount equal to 44% of indirect costs. However, the main conclusion from the study is that the cost of informal care in evaluating home care programmes is often underestimated due to the exclusion of indirect costs. Another case, which sees the application of the FC, is investigated by von Thiele Schwartz and Hasson (2012), whose objective is to investigate the effects of physical exercise during working hours and the effect on the related direct and indirect costs.

Johannesson and Karlsson (1997) propose the FC method for the estimation of indirect costs, although they recognize that this method is based on hypotheses not supported by the neoclassical economic theory. An important point concerns the fact that the FC-based method for indirect costs should also be applied in estimating direct costs, with the consequence of substantially reducing the costs of health care programmes. In a study that is a corollary of those al-

ready conducted by the same authors, Koopmanschap and Rutten (1994) analyse the impact of including indirect costs of the disease in the economic evaluations of eight health care programmes. The impact of indirect costs varies widely between health programmes: in particular, indirect costs tend to play an important role if health programmes produce effects in the short term, if the absence from work is significantly affected, and if a significant part of the reference population is considered in the analysis. Finally, Liljas (1998) describes the elements to be included in the calculation of indirect costs. The proposed method is based on FC and excludes many aspects of the indirect cost components. For this reason, it should not be recommended in place of the HCA approach, if the economic evaluations aim at taking into account the patient's needs.

The literature contributions for Southern Europe. The Mediterranean area (Italy, Spain and Portugal)

The recommendation resulting from the guidelines developed for health economics studies is for the inclusion of the indirect costs in any case of economic evaluation analyses. There is a preference for the HCA approach, confirmed by the larger number of the conducted studies.

Examining the studies carried out for Italy, the recent work of Turchetti et al. (2017) estimated the average annual social cost per patient with chronic kidney disease and cost components in Italy. Productivity losses for patients and caregivers were assessed using HCA. Marcellusi, Viti, Incorvaria et al. (2015) calculate the burden of respiratory allergies; despite the consistent economic and social burden, there are no precise data on the costs associated with the management of allergic respiratory diseases in Italy. The study performs a systematic review of the literature to identify both the cost per case and the number of affected patients, applying an incidence-based estimation method. The direct costs are estimated by multiplying the admissions, the drugs and the management costs deriving from the literature with the Italian epidemiological data. Indirect costs are calculated on the basis of lost productivity estimated with HCA. This is the first study in which both direct costs (incurred by the health system) and indirect costs (incurred by the society) were taken into consideration to calculate the overall burden associated with respiratory allergies and their co-morbidities.

In another article, Marcellusi and co-authors (2015) estimate the impact of the hepatitis C virus and the economic burden of the disease, developing a probabilistic cost model. Indirect costs are calculated on the basis of lost productivity based on HCA. The relevance of the problem can be understood considering that Italy is one of the European countries with the greatest number of people suffering from chronic HCV infection, the main cause of cirrhosis, HCC and liver diseases. These diseases induced by HCV generate high costs for the Italian health system as well as high indirect costs.

Marcellusi et al. (2016) try to interpret available information on epidemiology of diabetes mellitus by estimating the average annual cost incurred by the health services and the society. Direct medical costs (drugs, hospitalizations, monitoring and adverse events) and indirect costs (absenteeism and early retirement) are estimated. The study is the first in Italy to assess the direct and indirect cost of diabetes (through HCA) with a probabilistic prevalence approach. The difficulty in finding the relevant information confirms that the real burden of diabetes is underestimated, especially with regards to indirect costs. Mennini et al. (2014) assessed the indirect costs and the impact of bipolar disorder with HCA. The study stressed the relevance of indirect costs of this pathology, which affects mainly employed people.

The objective of the study by Garattini et al. (2000) was to evaluate the indirect costs in pharmacoeconomic studies in Italy and the attitude of Italian pharmacists towards indirect costs. A literature review was conducted, focusing on studies about economic evaluation of drugs. Eighteen studies were available for review. Although the methods used to calculate the loss-of-production value due to morbidity were all based on HCA, there was great variability between studies in practical methods. The parameters used to evaluate production losses also varied widely: of the 25 respondents, 20 considered it important to include indirect costs in pharmacoeconomic studies; 56% of respondents said that health authorities should request indirect cost assessments. This, as stressed in several Italian studies, shows a misalignment regarding the methods used.

Another study carried out with the HCA method (Leardini et al., 2004) estimated the impact of osteoarthritis of the knee, which is one of the main causes of disability due to rheumatic diseases, and requires extensive use of health resources. The study involved 29 rheumatology institutes. Productivity losses to patients and caregivers and informal care were considered as indirect costs. The study confirmed that the direct and indirect costs attributable to osteoarthritis of the knee were substantial. The losses incurred by workers, assessed with HCA, were measured in terms of wage variations (including the tax burden charged to employers) under the assumption that income reflects productivity.

In Portugal, studies based on FC are more recent and focus mainly on specific diseases. Ferreira et al. (2017) estimated the cost of asthma in Portuguese children. Indirect costs were calculated using a bottom-up approach based on HCA for 208 children (<18 years). Laires et al. (2016) considered an older population in calculating the impact on early retirement due to self-reported rheumatic diseases. The study estimated the indirect costs and working years lost, employing a national database to calculate productivity values by gender, age and region, using HCA. The working years lost were estimated as the difference between the current age of each participant and the relative retirement age, while the potential years of working life lost were given as the difference between the age of the individual and the actual retirement age.

The same authors (Laires et al., 2015) evaluated the physical disabilities caused by rheumatic diseases, which can lead to a rapid exit from work and generate indirect costs to society. The analysis was based on prevalence of a bottom-up approach: health and sociodemographic data were collected for all people aged between 50 and 64, while an official national database was used to estimate productivity values by gender, age group and region, again using HCA. The early exit from work attributable to this condition amounted to about 0.4% of national GDP.

Finally, neurological disease was the object of the analysis by Reese et al. (2011). Health and economic assessments of Parkinson's disease for southern European countries are limited. In this study, carried out between 2004 and 2005, costs were assessed from the societal perspective using health and economic questionnaires. The HCA was employed to estimate the indirect costs, and the quality of life related to health was assessed using the EQ-5D. In general, the costs were lower than those reported in other Western countries. Overall, the economic burden of Parkinson's disease in Portugal is considerable, and the study emphasized that further research that would include indirect costs was needed to describe effective health models and to guide health policy decisions.

In Spain, according to the guidelines set by ISPOR, all costs, direct and indirect, should be included. The study by Ortega-Ortega et al. (2015) examined stem cell transplantation as a direct procedure for the treatment of malignant conditions in hematology. The aim of the study was to evaluate labour productivity losses associated with premature mortality due to blood cancer in recipients of stem cell transplants. The years of the potential life lost and the years of productive life lost were calculated using the HCA-based method; conversely, the FC-based approach was used as part of the sensitivity analysis. Oliva et al. (2005) estimated indirect costs due to productivity losses caused by mortality and morbidity of cervical tumors in Spain. Again, both HCA and FC methods were used, and the annual costs were much lower with the FC-based approach. The study emphasized that such analyses help to identify the real dimension of health problems. López-Bastida et al. (2003) evaluated the economic impact in terms of direct and indirect costs of cardiovascular disease and cancer in the Canary Islands in 1998, using a cost of illness approach. The direct costs were identified as hospitalization costs, outpatient costs, primary healthcare costs and drug costs, while the indirect costs were estimated using HCA and FC.

Martino et al. (2013) examined the complex intraoperative electrical stimulation procedure (IES) for the resection of GLO type II gliomas. Direct and indirect costs were measured as loss of labour productivity, while utility was measured in quality-weighted years of life. The surgical procedure is associated with an increase in direct costs; however, the initial costs are offset by the avoided medium and long-term costs and by a reduction in morbidity together with a longer patient's professional life.

Neurological conditions concerned other studies. For example, Pamias Massana et al. (2012) calculated the social cost of depression using the information contained in a European project against depression. In estimating indirect costs, it was not possible to calculate the cost of permanent disability at work (in the analysis, the highest weight corresponds to temporary work disability). However, the lack of knowledge of the total cost associated with permanent disability at work was an important limitation, since this category of costs represents the highest percentage for this disorder. Another neurological disease is amyotrophic lateral sclerosis (ALS). The study by López-Bastida et al. (2009) determined the economic burden (direct and indirect costs), as well as the quality of life related to health in patients with ALS in Spain. The approach of cost of illness used was based on a social perspective and the main categories of costs were informal care, early retirement, drugs and orthopedic equipment. A similar issue considered by López-Bastida et al. in 2008 estimated the economic burden (direct and indirect costs), as well as the quality of health care in patients diagnosed with spinocerebellar ataxia (SCA) in Spain. The approach was based on a social perspective; it was concluded that costs for patients' caregivers, as well as high indirect costs resulting from permanent disability in patients with SCA should become a priority for health authorities.

Some studies are directed at evaluating the impact of multiple sclerosis on indirect costs. Casado et al. (2006a) analysed data from 200 patients, who responded to a questionnaire on resource consumption, employment and economic status to estimate the amount of resources absorbed by the disease. The data of the questionnaires, hospital data, the statistics of the Catalan Health Service and the Catalan Statistical Institute were used to calculate the direct and indirect costs. Indirect costs were assessed in terms of lost productivity when patients cannot work, while direct costs accounted for around 60% of the total cost. In a similar study, Casado et al. (2006b) calculated the direct, indirect and intangible costs of a relapse of multiple sclerosis (MS). The HCA was used to estimate the indirect costs; quality measures were used to measure intangible costs.

Finally, some identified studies refer to the economic burden of specific conditions, such as headache (Badia et al., 2004). The direct costs (due to drugs, health care, specialist, etc.) and indirect costs (working days lost and work reduction) were calculated using the prevalence approach. The HCA was used to calculate indirect costs. As in many other developed countries, migraine determines a significant economic burden in Spain, particularly in terms of lost productivity. The recommendation from the study is that developing strategies aimed at reducing indirect costs may lead to the reduction of productivity losses.

The last works that have been identified for this review deal with assessing the economic impact of road accidents in Spain. Bastida et al. (2004) used the disease cost approach for their analysis. While direct costs referred to healthcare costs, insurance administration costs, and material damage costs to vehicles, indirect costs were calculated using the HCA-based approach. The high socio-

economic cost of road accidents indicated the need for the various administrations in Spain to implement preventive measures. The study by López-Bastida et al. (2001) assessed the economic impact in terms of direct and indirect costs of road accidents in the Canary Islands (Spain) in 1997 using HCA. Total indirect costs amounted to 18% of total costs due mainly to premature death and absenteeism from work. Although this study adopted a conservative approach, omitting the costs associated with pain and suffering, permanent disability and home-based care from the family, the frequency of road accidents and their consequences clearly showed the need for different Canary Islands administrations to implement preventive measures.

Conclusions

The examination of the existing literature on indirect costs and methods of their calculation has been carried out with the objective of identifying the method most likely to represent indirect costs. The following research keys: [human capital approach + indirect costs + country] and [friction cost + indirect costs + country] have been considered in this review.

Although the collected studies are not exhaustive, they indeed allow us identifying some common trends for geographical areas. While there is a higher number of studies that apply HCA for the calculation of indirect costs in Eastern and Southern Europe, there is a slight prevalence of analyses based on FC in the literature related to Western European countries (first of all, in the Netherlands where this methodology was first developed).

Health policy considerations that can be developed concern the costs for health assistance to plan for the patients. However, it is difficult to quantify the intangible costs incurred by patients themselves and their caregivers, as there is no consensus on the method to apply for the estimation of such indirect costs.

To sum up, the economic evaluation of health programmes is now a strongly consolidated practice in all industrialized countries and, specifically, in European countries. From the evidence reported in this survey, it is clear that the literature is now vast and robust with regards to the assessment of indirect costs and, especially, the estimation of the lost productivity, for different health conditions.

With the exception of the Netherlands and some other scattered studies, the prevalent use of HCA compared to FC is unequivocal. From the methodological point of view, HCA is more robust since it has roots in general economic theory and allows for a more comprehensive analysis. Thus, HCA is certainly preferable to FC for those countries where the labour market is characterized by rigid regulations. Hence, in carrying out economic evaluations, HCA may be

eventually accompanied, as some recent studies suggest, by a cost analysis based on FC, so as to confirm the results achieved.

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