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Cost Variability in Medical Treatments: A Value-Based Healthcare Perspective

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"Education is the most powerful weapon which you can use to change the world."

- Nelson Mandela (Tata Madiba)

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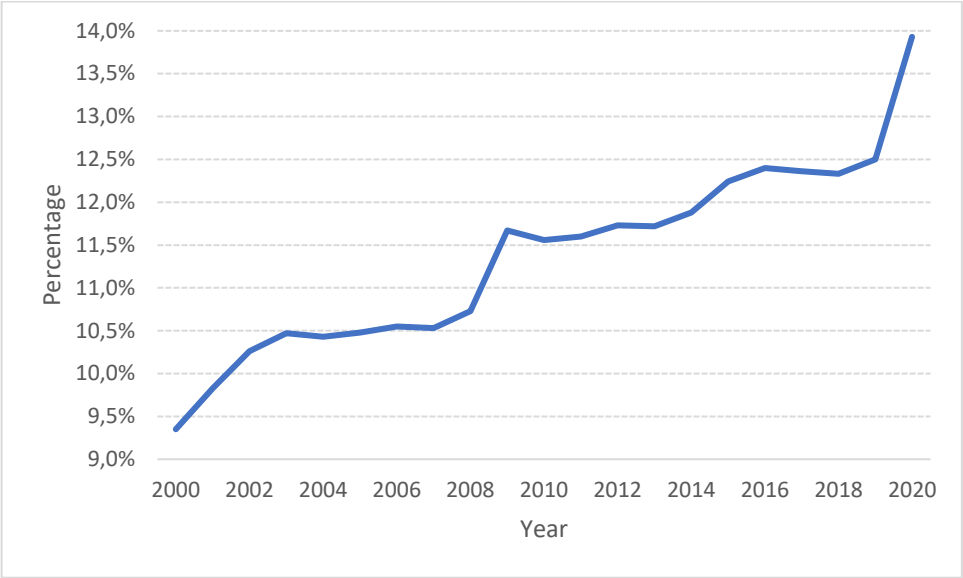
1. Introduction

1.1. Current healthcare landscape

Over the last few decades, the healthcare sector has enjoyed tremendous advancements, which have had resounding effects on how we provide care and the overall quality of care. If we categorize this progress, several broad themes arise. Firstly, medical research across disease disciplines has evolved. For instance, precision medicine has and will continue to alter how we tailor medical treatments for individuals [1]. Furthermore, developing immunotherapy to fight infectious diseases has nearly eradicated viruses such as smallpox and polio [2], which wreaked havoc on previous generations. Secondly, we see vast progress due to the emergence of technological innovations, such as using artificial intelligence for interpreting image results from scans, synthesizing laboratory results, and analysing and interpreting extensive clinical databases [3]. Other technological expansions, for example, on the level of medical devices, have ensured the migration towards using minimally invasive procedures, which positively impact patients through reduced physical trauma [4, 5]. Thirdly, we see a push toward preventative measures and interventions; for example, the global fight against HIV/AIDS has reduced the disease burden [6] and elevated some pressure on the healthcare sector. While we recognize the revolutionary changes the industry has enjoyed, it would be naïve of us to overlook some fundamental challenges, emphasizing that more work is necessary.

As the global pandemic, Covid-19, becomes but a distant memory, we cannot ignore the issue of rising healthcare expenditures. According to data from the World Bank, current health expenditure as a percentage of gross domestic product for OECD countries has increased from 9.34% to 12.53% over the past 20 years (from 2000 to 2019) (Figure 1). While this increase seems fair in percentage terms, if we translate that into expenditure per capita (current US$), this has more than doubled from $2,152.25 to $4,955.69 per person [7]. These increases could stem from several factors: for one, we see a shift in demographic characteristics, namely the rise in the aging population resulting in increased chronic illnesses; and two, costs associated with the advancement of medical technology [8–10], among several other reasons. To further add to the pressure regarding rising healthcare costs, providers face significant financial strain regarding their budgets. For example, in Belgium, general hospitals face a cap on their annual finances [11]. While these ceilings prevent government spending from running rampant, they could potentially impact the level and quality of care provided to society.

Figure 1. Current healthcare expenditure as a % of GDP (OECD Members)



Source: World Health Organization Global Health Expenditure database (apps.who.int/nha/database)

The second concern facing healthcare relates to inefficiency and waste within the sector. According to Health Care Without Harm (HCWH), an international organization, the healthcare sector is the fifth-largest emitter of greenhouse gases worldwide [12, 13]. While waste can occur on many levels, the OECD provides three broad definitions: (1) clinical level (patients receive care that adds little or no value), (2) operational level (unnecessary use of specific resources), and (3) governance level (relating particularly to administrative issues) [14]. These factors ultimately impact the quality of care delivered to patients.

A lack of patient-centred care is another hurdle, further impacting quality. It is essential to acknowledge clinician efforts at addressing this issue; however, room for improvement, particularly regarding patient concerns, the acceptance of beliefs, and the practice of sharing all treatment options with patients, still exists [15–17].

With these and many other challenges, there is growing recognition that transformation is necessary for the healthcare system. With that, we see the emergence of approaches such as increased use of digital healthcare technologies, the exploration of alternative payment models, and initiatives centred around care coordination; however, one that has gained prominence in the literature is Value-Based Healthcare (VBHC).

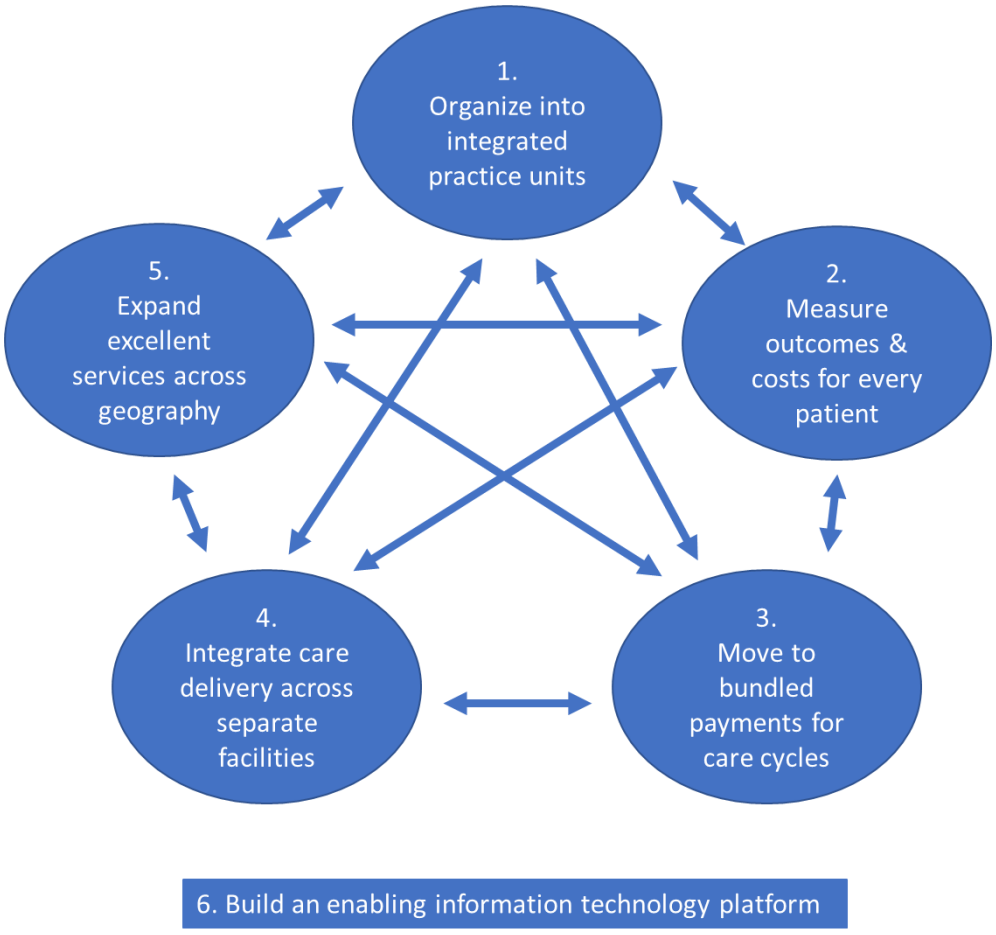
1.2. Value-based healthcare framework

Michael E. Porter and Elizabeth O. Teisberg introduced the concept of VBHC in *Redefining Healthcare, Creating Value-Based Competition on Results* (2006). The VBHC framework aims to improve healthcare outcomes while lowering costs by focusing on the value obtained for patients [18]. Thus, we express value as an equation whereby the numerator refers to healthcare outcomes, and the

denominator represents the dollar cost spent to provide individual care [19]. To further elaborate on the components of the equation, Porter described the outcomes as being specific to a condition and stressed that the cost should reflect the complete cycle of care for an individual. Through this narrative, value enables improvements regarding performance as it encourages a culture of accurate measurement, moves the sector from the volume of services towards a results-oriented mindset, and drives efficiency, as one cannot simply reduce costs without considering its impact on outcomes [20]. Porter and Teisberg laid the foundation for fundamental sector reform by focusing on value.

While we define value via an equation, the VBHC framework encompasses several elements representing a collective agenda to move the sector toward a more sustainable future (Figure 2). These elements cover the following aspects: (1) organize into Integrated Practice Units (IPU), (2) measure outcomes and costs for every patient, (3) move to bundled payments for care cycles, (4) integrate care delivery across separate facilities, (5) expand excellent services across geography, and (6) build an enabling information technology platform [21]. We discuss each element of the value agenda briefly.

Figure 2. The Value agenda (Porter and Lee, 2013)



Source: Lee T, Porter M. The strategy that will fix healthcare. Boston: Harvard Business Review; 2013 Oct 10.

1.2.1. Six agenda points of the VBHC framework

Michael E. Porter and Thomas H. Lee outline six interrelated components to advance the sector toward a VBHC narrative [21]. While we discuss these elements individually, ideally, we should focus on all aspects collectively to see real change.

The first component relates to measuring health outcomes and costs for each patient. Porter and Lee recommend that when measuring outcomes, it is vital to measure them for a medical condition. Furthermore, the outcomes must reflect the patient's perspective, i.e., what is critical to the patient, and be calculated over the complete care cycle. The cost measurement should reflect the overall care cycle for a medical condition and a patient. The suggested technique for measuring costs is a cost accounting technique known as Time-Driven Activity-Based Costing (TD-ABC) [22].

The second component discusses the need to organize into IPUs. IPUs call for a restructuring whereby the providers arrange themselves around the patient to treat the disease and the corresponding complications and comorbidities. The intention is that IPUs will encourage providers to work more closely as a unit instead of siloed departments to achieve better outcomes [23].

The third element corresponds to reform on the level of reimbursement, i.e., to move away from the current fee-for-service (FFS) system towards bundled payment schemes. Porter and Lee argue that FFS further perpetuates the sector's problems in that providers get reimbursed for the number of services provided rather than obtaining high-quality care, thus calling for an alignment between reimbursement and value. They do this by encouraging payment systems like bundles that cover all the necessary disease treatment services [24].

The fourth factor on the agenda refers to integrating care delivery services. The discussion, driven by the high volume of multisite care delivery institutions, suggests a possible duplication of services resulting in waste. Therefore, it is imperative to consider who provides which services, consolidate services to fewer locations, seamlessly coordinate care across various places, and select the appropriate location for service delivery [25].

The fifth factor focuses on expanding geographic reach, thus offering services to a larger population of patients. Porter and Lee suggest two ways to do this: (1) the construction of "satellite facilities," where physicians from larger organizations visit these sites on a rotating basis, thus expanding the reach; (2) through affiliations, whereby IPUs and community providers (situated in communities outside of the regular geographic circumference) partner up by allowing physicians from the IPU to use facilities, for example, to offer services that would not otherwise be available [21].

The final component, which refers to building an enabling information technology platform, is the empowering force necessary for the five factors to reach the value agenda. For the ICT platform to encompass the value perspective, it should focus on the patient (i.e., the patient through care services), capture all patient-relevant data (i.e., test results, physician notes, etc.), use standard definitions of collecting data (i.e., descriptions and data fields, etc.), be configured with templates and assist with

further treatment steps, make patients medical records accessible, and finally, extract information relating to outcomes, costs, and risk factors, which is easily achieved because of the system architecture [21]. The six factors will collectively ensure fundamental sector transformation; however, to narrow the focus of my thesis, we focus specifically on two aspects. The first is the component of measuring patient outcomes and costs. However, given our limited medical background and knowledge and access to medically reported outcomes (data remains limited), we focus on measuring costs and their implications for stakeholders and, second, how using accurate measurement of costs can move towards bundled payments for care cycles.

1.2.2. Measurement of costs

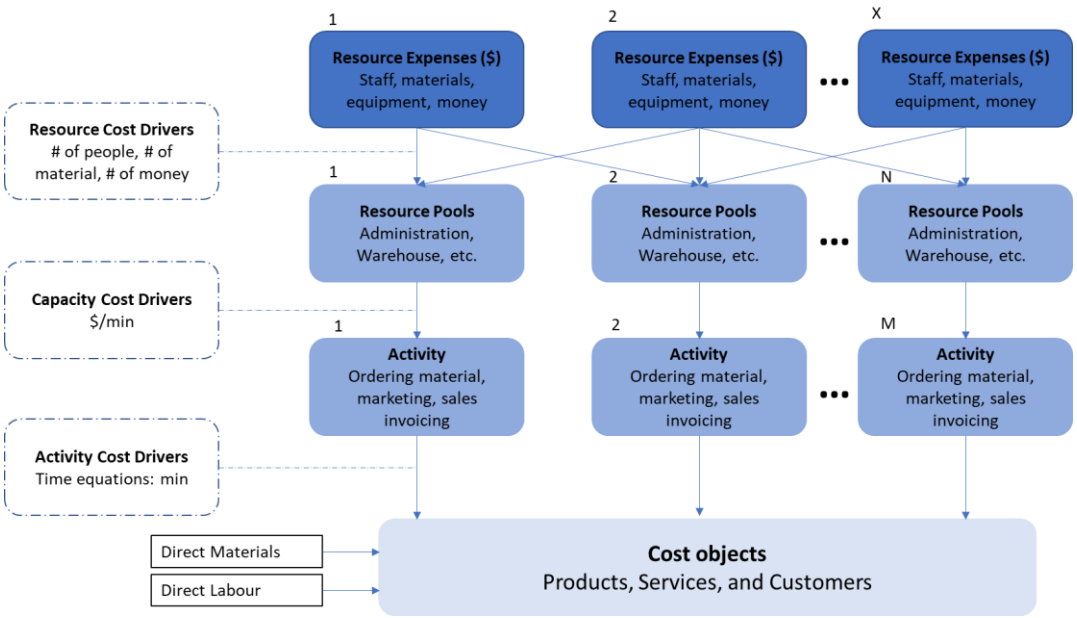
As mentioned above, TD-ABC, introduced by Kaplan and Anderson in 2003, represents the suggested method for accurately measuring costs [26]. TD-ABC served as an adaptation to Activity-Based Costing (ABC) because of its implementation limitations. ABC, first used in healthcare in the '90s, represents the first big push towards using process-oriented cost-accounting methods to track costs in the sector; however, given the sheer complexity of healthcare organizations and the enormous amount of resources needed, using the system proved to be harder than initially anticipated [27] hampering efforts to advance the system. TD-ABC, on the other hand, conveniently only requires two key parameters: (1) the capacity cost rate (CCR) of a resource and (2) the time that a cost object requires a resource [28].

To obtain the numerator, we must divide the total cost of supplying the resource by its available practical capacity. The total cost is a summation of all costs relating to the supply of a particular resource within a process, such as personnel, equipment, and facilities. We define practical capacity as when employees can work minus their idle capacity [29]. Practical capacity is measured by (1) taking a percentage of the theoretical capacity; a rule of thumb is 80% for personnel (i.e., all breaks, training, meetings, etc.) and 85% for machines (i.e., repairs, maintenance, cleaning, etc.), or (2) calculating the practical capacity using values obtained by the organization. One can interview staff members or directly observe the necessary activities to determine the denominator (no survey requirements exist). It is essential to mention that Kaplan and Anderson did not emphasize precision; they merely argued that a rough estimation is sufficient as resource surpluses/shortages are easily identifiable through TD-ABC implementation [28].

Furthermore, a fundamental difference between the ABC and TD-ABC systems relates to the time-based approach, where the cost of activities is estimated based on the required time for TD-ABC [26]. Unlike the ABC model (which utilizes activity pools), TD-ABC employs time equations, which sum individual activity times with their time drivers. By constructing time equations, one can easily represent the full range of activities and all their potential combinations. The cost of an activity is allocated to cost objects by multiplying the time required for the activity by the cost per time of the

resource. Figure 3 provides an overview of the TD-ABC mechanism (based on Everaert, Bruggeman, Sarens et al., 2008).

Figure 3. The TD-ABC model (based on Everaert, Bruggeman, Sarens et al., 2008)



Source: Everaert, P., Bruggeman, W., Sarens, G., Anderson, S.R., and Levant, Y. (2008), "Cost modelling in logistics using time-driven ABC: Experiences from a wholesaler," International Journal of Physical Distribution & Logistics Management, 38(3), 172–191. doi:10.1108/09600030810866977.

In 2011, Kaplan and Porter presented a seven-step process to assist with implementing TD-ABC in health care [30] (Table 1). We further elaborate on the steps below.

Table 1. Overview of the seven steps for the implementation of TD-ABC

Step 1	Select a medical condition
Step 2	Define the care delivery value chain (e.g., outline all relevant activities performed within the value chain)
Step 3	Develop process maps for each activity in the care pathway (i.e., identify all direct and indirect capacity-supplying resources)
Step 4	Obtain time estimates for each of the different processes
Step 5	Estimate the cost of supplying the resource (i.e., all the costs associated with the direct and indirect resources in the care delivery chain)
Step 6	Estimate the capacity of each resource and measure the capacity cost rate
Step 7	Calculate the total relating to the patient care

Source: Keel G, Savage C, Rafiq M, Mazzocato P. Time-driven activity-based costing in health care: a systematic review of the literature. Health Policy. 2017 Jul 1;121(7):755-63.

First, we select a medical condition and ensure all necessary steps are considered, from diagnosis to final consultation and interventions relating to complications and comorbidities. Second, we define the care delivery value chain based on the medical condition to identify the main activities needed within the care cycle and the respective locations. Third, we develop process maps for each activity identified in the care cycle. We distinguish between capacity-supplying resources (i.e., personnel, facilities, equipment, and machinery) and consumable resources (i.e., syringes, bandages, etc.). Fourth, we measure the time estimates for each activity; the exact time is recommended for longer/time-consuming activities, and estimates can be used for shorter processes. Fifth, we estimate the cost of supplying the necessary resources by calculating the direct cost of the resource for personnel related to compensation; for machines and equipment, we estimate depreciation or leasing costs. Additionally, we estimate the costs of supplies and all other operating expenses. Sixth, we estimate the capacity of each resource and calculate the CCR for the personnel, machines, and equipment using the methods described above. Finally, we calculate the total cost of patient care using the information obtained from steps three to six. We then estimate the total cost by multiplying the capacity cost rates of each resource with the required time to get the total cost [30].

While Kaplan and Anderson advocated for using this method in VBHC, many scholars across different sectors further support the approach in measuring costs. For example, studies conducted in the manufacturing sector found evidence that TD-ABC allowed for more accurate information regarding product profitability, capacity utilization, and strategic managerial decisions [31, 32]. If we focus specifically on logistics, we see that TD-ABC allows for capturing transaction complexity using time equations [33] and further improving complex processes and operations [33–36]. Furthermore, scholars have pointed out that TD-ABC helped identify the profitability of customer segments and idle resources in the hotel and manufacturing industries [37]. Another study supported these findings of idle capacity; the authors conclude TD-ABC is a superior costing model in identifying idle resources compared to ABC [38]. A service industry study concluded that TD-ABC is easier to implement than other costing methods [39]. Additionally, the costing method proved helpful for managers applying cost-cutting initiatives relating to information technology services [40].

These findings further highlight why TD-ABC is the suggested costing model for improving cost measurement in the healthcare sector. As a result of its usefulness, growing popularity thanks to VBHC, and two-step implementation, we find several studies in the healthcare sector applying TD-ABC to many different disease domains [27, 41]. For one, some stress that the bottom-up approach ensures costs are measured more accurately at the level of patients than at a service level [42]. Given the inherent complexity of patients, this perspective creates flexibility and allows for additional activities when necessary [43]. Moreover, the dynamic nature of TD-ABC provides opportunities for in-depth analysis of population variability. It helps identify cost drivers, making it easier to move towards risk stratification for future alternative payment models [44]. In one of the earliest applications of TD-ABC in healthcare, Demeere et al. (2009) highlight the effectiveness of information obtained

after applying TD-ABC to an outpatient setting for managers. They argue the application led to an improvement in managerial understanding of organizational processes, encouraged meaningful competition between departments on an operational basis, and resulted in changes in how administrative staff is organized [45]. Initially, literature in healthcare used TD-ABC to measure the costs relating to the entire care cycle for a particular disease [46–48]. They found that they could make meaningful cost reductions once they measured costs from this broader perspective [46]. If we look at studies focused on activities conducted within a department (radiology, for example), TDABC allowed providers to identify opportunities for improved efficiency by measuring costs for one particular tomography [49].

Several studies showed cost comparisons between medical interventions, such as radiation therapy techniques, and two types of heart surgeries [50, 51]. Of course, as mentioned above, the rise of medical technology makes these cost comparisons at the procedure level highly relevant, given the massive costs associated with these devices. Additionally, if we consider the evidence found when comparing TD-ABC to traditional costing methods, TD-ABC outperforms these systems in measuring costs more accurately [52–54]. At the Boston Children's Hospital, through a pilot study using TD-ABC, hospital management was able to redesign its processes to create greater efficiency [55]; an additional study comparing the costs of two interventions identified opportunities to optimize resource utilization in the operating room [56]. Through the focus on high-turnover operating lists, authors identified ways to reduce patients' surgery times and waiting times [57]. Another study improved its clinical process by implementing TD-ABC within its organization [58]. The findings of these studies show that by utilizing TD-ABC's aerial perspective of costs, it becomes possible to evaluate and analyse costs to inform strategies for enhancing care pathways and reducing wasteful resources.

Furthermore, TD-ABC helps identify the main cost contributors even in high-variability disease settings. After implementing TD-ABC, the Brigham and Women's Hospital orthopaedics department found that ICU costs accounted for 28% of the total care cycle costs. The department then moved toward a step-down unit (i.e., ICU monitoring is done by the nurse rather than the physician), which had resounding impacts on expenses. Utilizing a step-down approach could reduce costs by 8%, according to the authors [46]. Tan et al. 2016, used TD-ABC to investigate the impact of incorporating an additional medical physician into its process at a cancer genetics clinic; as a result, they could increase the number of patients they assisted [59]. These findings from prior literature show the tremendous positive impact TD-ABC can have on the entire sector.

While we typically only consider TD-ABC from a provider perspective, we find evidence of additional stakeholders who benefit from using the costing method to conduct important investigations. One example is the Canadian government, which defined the overall cost of endoscopic sinus surgery. By doing so, the government could estimate payer costs for this disease [60]. Pharmaceutical companies have also benefited from investigating the use of this cost technique. After applying TD-ABC to measure services, they could pass information to pharmacy managers, pharmacy professional

organizations, and policymakers about the most costly pharmaceutical services and identify opportunities to improve pharmacy management [61].

While TD-ABC has advantages, mentioning some of the method's drawbacks is essential. As mentioned previously, one should measure the time of more extended time-consuming activities and estimate the time for shorter activities [30]; however, Cardinaels and Labro (2008) refute these findings and conclude that overestimation bias is prevalent when participants provide their time estimates in minutes. Of course, from a TD-ABC perspective, these findings are problematic, as many studies use estimates provided by organizations for measuring the time of a specific activity [62]. Based on the systematic review of Keel et al. (2017), using time from experts seems to be common practice and effective in generating initial insights into costs [27]. In the earliest application of TD-ABC, Demeere et al. (2009) used stopwatches to measure times for activities, representing a potential solution to this issue [45].

Additionally, Gervais et al. (2010) argue that collecting data is still challenging under the TD-ABC method [36]. While these factors represent essential disadvantages of the costing method, we still believe TD-ABC has tremendous value on a broader scale. One worth mentioning is the development of the TD-ABC consortium, which represents a collective alliance of researchers and institutions committed to enhancing the calibre of endeavours employing the TDABC methodology within the healthcare sector. The consortium is driven by the objective of disseminating methodological advancements related to TDABC on a global scale, aiming to advance the principles of VBHC. Developments of international institutions to incorporate VBHC on a broader scale are vital for promoting change in the sector.

The preceding literature has primarily emphasized process enhancements and cost reduction strategies when analysing costs through TD-ABC. However, it's crucial to acknowledge another decisive dimension of cost investigation: reimbursement reform. Utilizing TD-ABC as a vital tool for dissecting cost intricacies positions us to navigate the complex landscape of reimbursement methodologies, mainly focusing on bundled payments. Therefore, we contemplate how our understanding of cost measurement and analysis can steer the discourse on reimbursement reform toward adopting bundled payments. This strategic shift aligns with the overarching goal of value-based healthcare whereby the elements are interconnected. Nevertheless, before delving into how we intend to do this, it's imperative to understand the reimbursement landscape comprehensively, the potential avenues for its advancement, and how bundled payments fit within the broader context of VBHC.

1.2.3. Reimbursement reform

The fee-for-service (FFS) system is the dominant worldwide reimbursement system [63]. Within this system, providers receive a predetermined fee per service performed. As the financial crisis within the sector becomes more prominent, we start to see many cracks in the FFS system. Firstly, many argue that under its structure, providers' remuneration is not aligned with what is beneficial for the patient, i.e., they are rewarded for the number of services they provide and not the value these services

bring to treating a patient [64]. Additionally, the system does not move us toward multidisciplinary organisms; instead, departments can continue to operate as standalone structures [24]. The lack of communication often results in poor service delivery and, in some instances, duplication of services, which further adds to the unnecessary financial burden of the sector [65]. As a result of these issues, many other payment systems are suggested and explored in the literature.

A notable example is using a capitation method or population-based model. Under this method, we shift from the individual to the overall health of the greater population. Thus, we move towards a system that emphasizes prevention and promotes the overall health of its citizens [66, 67]. Regarding the payment structure, insurers pay providers a fixed fee per population member [68]. In addition to this method, we have the Value-Based Payments system, whereby payments are linked to the provider's improved performance in treating patients. This system holds healthcare providers accountable for costs and the quality they reach [69].

As discussed in the value agenda, bundled payments are the proposed reimbursement system. Though not a new concept, they have gained popularity as a promising method that could restrict rising financial expenditure and link reimbursement to value rather than the number of services provided [70]. Bundled payments aim to address the shortfall of the current system; thus, it seeks to incentivize quality improvements and cost reduction through increased accountability and better care coordination [41, 71]. Furthermore, it aims to better align providers' interests via the fixed payment for all services provided.

Essentially, bundled payments represent a lump sum paid to hospitals to reimburse a patient's entire episode of care [72]. The payment is allocated to all services and providers across various care activities (inpatient, post-acute care, etc.) [73]. Providers receive the payment either retrospectively or prospectively. Under a retrospective agreement, providers operate under a fee-for-service arrangement; however, payments get reconciled against a target price after a fixed period. For the prospective payment system, providers receive a lump sum upfront to treat patients [74]. The division of bundles is at the discretion of the facilities and departments [75] and covers three parts: a fixed part, a risk-adjusted part, and a reward for quality obtained. While the objectives of bundled payments may appear straightforward, the implementation, specifically the design, remains challenging [75]. The literature on the effectiveness of bundled payments is ambiguous, with some studies reporting lower medical spending and improved quality of care while others report adverse effects [76]. Some argue that there are no clear recommendations on how to design them and that the current methods for developing bundled payments must be standardized [77]. Through our direct focus on costs and their variability, we investigate how cost transparency and insights can advance the discussion around bundled payment implementation, linking two important components of the value agenda.

1.3. Medical disease domains

To further investigate cost variability and make advancements toward VBHC payment reform, we use two disease domains as the basis of our investigations. Firstly, we focus on breast cancer in the medical field of oncology. Secondly, in the disease area of dermatology, we focus on psoriasis. We provide more detail on why we selected these diseases below.

1.3.1. Breast cancer

Breast cancer, classified as a type of cancer, grows in malignant cells found in glandular tissue in the breast [78]. According to the latest cancer incidence and mortality rates estimates by the International Agency for Research on Cancer (GLOBOCAN 2020), breast cancer is the most diagnosed cancer globally. In 2020, breast cancer accounted for 11.7% of all diagnosed cancer cases worldwide [79]. By estimate, we anticipate an increase to 3.2 million newly diagnosed patients annually by 2025 [80].

While we see an increase in prevalence, significant advancements, particularly in therapeutic options, have drastically reduced mortality rates, resulting in a longer life expectancy [78, 81]. Like all diseases, a diagnosis is necessary to select the correct treatment option for patients. Through standardized medical guidelines, patients follow a diagnosis pathway to determine the progression of the disease [82]. Clinicians and health providers employ a specific classification scheme consisting of luminal A, luminal B, HER2-enriched, and triple-negative cancers-based expressions of genes and proteins to determine the cancer stage [83]. Once the stage is determined, the appropriate treatment pathway is selected: either neo-adjuvant and/or adjuvant therapy plus a surgical intervention [82, 84].

If we consider the financial burden of the disease economically, the global estimated cost was roughly INT $2.0 trillion in 2017 [85]. These numbers will likely continue to rise with the growth in cases in the coming years. Given our focus on VBHC, it is also essential to consider the financial cost of the disease from the patient's perspective. Not only do patients face high medical costs, given the massive expenses associated with adjuvant therapy interventions like chemotherapy. According to Oestreicher et al., prices for chemotherapy interventions could increase to $23,019 (year 2003 values) in the first nine months post-diagnosis [86]. Hassett et al. reported slightly higher costs, around $31,143 (year 2002 values) per patient for adjuvant chemotherapy [87]. Patients face additional losses due to reduced productivity levels, not to mention the emotional burden this has on them and their families [88–90].

In addition to the financial burden both on a global and patient level, we still see limited studies focusing on the actual costs (not claims or charge data) of the disease. Research calls for widening the scope and considering real costs over the entire cycle of breast cancer treatment [91, 92]. The disease's prevalence, financial expenses, and limited knowledge of actual costs form the basis for why we want to dig deeper into costs and make significant academic contributions.

1.3.2. Psoriasis

Psoriasis is a well-known inflammatory chronic skin disease that impacts the skin and joints of roughly 2-3% of the world's population [93]. The condition typically appears as red, scaly plaques on the elbows, knees, lower back, scalp, and other areas of the body [94]. As a result of its visible nature, the disease negatively affects people's quality of life [95]. Given the disease's close associations with comorbidities like diabetes, psychological disorders, arthritis, and other cardiovascular-related illnesses, we classify it as systemic [94].

To determine the severity of the disease, clinicians use the Psoriasis Area and Severity Index (PASI) [96–98], whereby the body is divided into four regions: the head, the trunk, and the lower and upper extremities [99], to obtain a score. The same four areas are then examined based on the redness of the skin, surface area, scale, and thickness [100]. A score between 0 and 6 is given, thus resulting in a final score between 0 and 72; consequently, the higher the score, the higher the disease severity [101]. The second commonly used measure, which represents a patient-reported outcome, for diagnosis is the Dermatology Life Quality Index (DLQI) [102]. The DLQI is a simple questionnaire with ten questions scored between 0 and 3. The questionnaire covers a broad range of topics such as treatment, feelings, symptoms, daily routine, social environment, and factors about personal relationships [103]. Patients have either mild, moderate, or severe psoriasis, depending on severity. Once the severity is determined, appropriate treatment is assigned based on three broad drug options: (1) topical treatment (i.e., topical creams), (2) targeted phototherapy (i.e., UV light), and (3) systemic treatments (i.e., oral medications or biological drugs) [104].

While we see the tremendous impact of psoriasis both socially and psychologically, it is also important to discuss the enormous financial burden of the disease on a societal and individual level.
In 2013, the annual cost of treating all patients with psoriasis in the USA ranged between $112 billion and $135 billion [105]. At the time, the USA had roughly 2-3% of its population diagnosed with psoriasis [106]. In a European context (only Germany, Spain, France, Italy, and the UK), the annual patient cost was between $2,000 and $13,000 [107]. According to estimates, the lion's share of these costs comes from drug prices, particularly biological expenses, which range from $7,993 to $48,000 per patient annually [108]. Studies support using these expensive drugs because they reduce psoriasis severity [109]. Considering these high expenses, we still see limited studies investigating these costs from an economic perspective. Articles looking at prices typically take a societal perspective; for example, they focus on the impact the disease has on the loss of work and family income [110, 111]. The closest we have come to understanding actual costs is a study by Papadaki and Popesko in 2016, who used ABC as a measurement tool and compared the ABC and traditional cost calculation systems within the hospital. The authors highlighted the value of costing methods in measuring costs but provided no additional information about cost variability drivers. Thus, from an academic perspective, little is still known about the actual costs linked to psoriasis [112]. This gap in the literature and the vast

financial pressure of the disease underpins our reasoning for wanting to explore costs and their drivers in more detail.

1.4. Research objectives and outline of the dissertation

From the above, we see a significant advancement in the literature, particularly in measuring costs across disease settings and exploring the implementation and design of bundled payments to advance the VBHC agenda. However, it is essential to acknowledge that several gaps remain, particularly on the level of cost measurement for the specific disease domains in question and how these findings could assist in identifying process improvement opportunities and transforming the reimbursement system. This thesis aims to add to the current narrative about cost transparency by focusing on the accurate measurement of costs and how a better understanding of costs can assist providers in reorganizing themselves for optimal care delivery and provide essential considerations for policymakers. To do this, we utilize a mix of methodological strategies, both quantitative and qualitative, for collecting and analysing data. By exploiting the benefits of a mixed-methods approach [113, 114], we measure costs across disease settings to understand the drivers of costs and how valuable cost insights can be in the quest to achieve greater value within two Belgian hospitals.

This dissertation seeks to contribute to the literature on healthcare management in several ways. On a disease-specific level, we strive to generate relevant academic and practical insights into measuring costs for a cycle of care, identify their potential cost drivers, and explain how these findings assist the relevant stakeholders in making more informed cost-reduction decisions through process improvements and impact reimbursement reform for the previously mentioned disease domains. Furthermore, by systematically investigating existing literature on cost variability, we provide insights into future research potential and suggestions for advancing the costing literature in the field. Finally, we discuss the challenges of implementing and designing bundled reimbursement reform and offer tips for moving forward to affect reimbursement transformations.

To make these contributions, we divide the thesis into five chapters: (1) a specific focus is given to the costing literature in healthcare to gauge a better understanding of the current state of the art, the potential research gaps and provide suggestions for future research; (2) we show the usefulness of costing methodologies in determining the costs of a disease domain on a limited data set; (3) and (4) we empirically investigate the drivers of costs for different disease areas to identify process improvement opportunities and considerations for reimbursement changes; and (5) we critically reflect, by analysing the literature, on the potential challenges faced for implementing bundled payments generically. An outline of each chapter, with the corresponding title, research question, and research methodology, is presented below in Table 2.

Table 2. Overview of the dissertation chapters, research objective, and design

	Chapter title	Research objective	Research design
Chapter 2	Variability drivers of treatment costs in hospitals: A systematic review	It provides an overview of studies focusing on variability in treatment costs, outlines their study characteristics and cost drivers, and suggests future research methodology.	Systematic literature review
Chapter 3	Variability in-hospital treatment costs: a time-driven activity-based costing approach for early-stage invasive Breast cancer patients	Measure the impact of several patient and disease characteristics on the overall treatment costs and generate insights into the drivers of cost variability within one medical domain.	Retrospective single-case
Chapter 4	Exploring Costs and Factors Influencing Variability in Psoriasis Care: A Single Centre Study	Empirically determine the drivers of costs in a dermatology setting to identify opportunities for process redesign.	Empirical analysis using retrospective data from a single hospital
Chapter 5	Cost Variability Drivers in the Treatment of Luminal B Early-Stage Breast Cancer	Empirically determine the drivers of costs for total treatment and surgical intervention for early-stage luminal B breast cancer to impact reimbursement initiatives.	Empirical analysis using retrospective data from a single hospital
Chapter 6	Comparing Theoretical Perspectives and Practical Applications of Bundled Payments: An Overview and Identification of Gaps	Provide a comparative overview and identify gaps between the theoretical perspective and the practical application of bundled payments in the literature.	Scoping literature review

While the sustainability of the sector has always been a topic of conversation, the impact of the global pandemic reiterated the importance of individuals' health and the importance of the healthcare sector on the international stage. Through the various chapters of this thesis outlined below, we seek to positively contribute to an industry that plays such a fundamental role in the lives of all the people in the world.

Chapter 2: Variability drivers of treatment costs in hospitals: A systematic review

Studies focusing on variability drivers of treatment costs can provide the necessary information for policymakers and healthcare providers seeking to redesign reimbursement schemes and improve the value obtained for patients [115, 116].

Considering this, Chapter 2, a systematic literature review, focuses on taking a hospital costing perspective to provide an exhaustive overview of the current literature on cost variability in treatment costs. Additionally, this review outlines the main study characteristics and cost drivers identified in the literature and suggests methodological considerations for future research.

To do this, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Cochrane Handbook for Systematic Reviews of Interventions [117, 118]. We searched several relevant academic databases to identify the necessary literature. Two investigators extracted and appraised data for citation until October 2020.

Through this research, we contribute to understanding the current literature on the topic: (1) we present an overview of the various patient, treatment, and disease characteristics that explain hospital cost variability, (2) show evidence of the limited transparency on the level of hospital costs regarding definitions, (3) we present recommendations for future studies regarding the relevant variables to investigate and how costs must be measured, and (4) we detail and suggest considerations for appropriate statistical methods to use moving forward.

Chapter 3: Variability in-hospital treatment costs: a time-driven activity-based costing approach for early-stage invasive Breast cancer patients

Given the cost challenge in healthcare, greater cost transparency has become imperative. Previous studies point to the fact that increased cost transparency results in a better understanding of costs and identifying relevant drivers of costs [41, 119–122].

Chapter 3 utilizes a standardized diagnostic and generic treatment path for measuring the costs of breast cancer. By taking the molecular subtype classification as a perspective, we aim to measure the impact of several patient and disease characteristics on the overall treatment cost for patients. Additionally, our analysis seeks to generate initial insights into the drivers of cost variability in early-stage breast cancer.

We conduct a retrospective case study at a breast clinic in Belgium and measure the costs over the complete cycle of care using TD-ABC. We use 14 anonymous patient files to study the impact of patient and disease factors on costs.

Through this investigation, we identify relevant patient and disease characteristics contributing to cost variation. We do this across the four main molecular subtypes identified in early-stage breast cancer patients.

Chapter 4: Exploring Costs and Factors Influencing Variability in Psoriasis Care: A Single Centre Study

To further expand on the discussion of costs and their implications in the sector, we focus on a disease domain where treatment is granted in a dermatology setting. We take a limited view and focus on costs relating to the consultation component of the treatment pathway for psoriasis.

Following the steps outlined for TD-ABC, we construct a generic pathway to determine the relevant activities relating to the consultation process. Using a retrospective study design, we measure costs for 127 patients seeking treatment during a limited period. We employ statistical analysis to determine the drivers of costs in the dermatology department. Through this analysis, we strive to identify opportunities to redesign the department for greater efficiency. This is done by investigating actual costs relating to the consultation of psoriasis and identifying the relevant patient and disease factors contributing to cost variability.

Chapter 5: Cost Variability Drivers in the Treatment of Luminal B Early-Stage Breast Cancer

Accurately measuring costs and their associated drivers is imperative as expenditure continues to rise. As VBHC gains prominence, many studies still use claims data to estimate costs within disease domains, particularly breast cancer [123–126]. While large quantities of data are available when using claims, within the VBHC framework, Porter argues that actual costs should be measured to move the sector toward achieving value [21].

In Chapter 5, we further emphasize the value of using actual costs; we take a narrower perspective and build on our previous work in breast cancer. We utilize one molecular subtype, historically offering variation in patient and treatment mix, to further understand the disease domain's costs.

We employ a retrospective analysis of a single centre treating early-stage breast cancer patients diagnosed with the molecular subtype luminal B. We use TD-ABC to measure the total treatment costs of 106 patients. We perform statistical analysis to identify which patient and disease factors (e.g., age, BMI, number of comorbidities, classical diagnostic parameters, etc.) drive cost variability for the complete care cycle and the surgical component of the treatment pathway.

Through this analysis, we highlight the importance of studying cost variability in the context of breast cancer. We identify relevant characteristics contributing to cost variations on multiple levels. Furthermore, through this analysis, we provide critical managerial considerations to deliver more efficient care through process recommendations and how cost insights can be used to discuss bundled payments.

Chapter 6: Comparing Theoretical Perspectives and Practical Applications of Bundled Payments: An Overview and Identification of Gaps

It has become increasingly apparent that the current fee-for-service system, which emphasizes volume [64, 127], is no longer sustainable for the sector. Therefore, to tackle this, one of the suggestions links to a fundamental change in the level of reimbursement, thus a realignment of provider incentives with patient outcomes [75, 128]. Bundled payments have been endorsed as the reimbursement approach within VBHC as a driver of reform [30]. While existing research has explored the impact of bundled payments across several factors, we see a discrepancy in the implementation compared to the outline provided by Porter and Kaplan in the 2016 Harvard Business Review paper entitled "How to Pay for Health Care" [24].

Chapter 6, therefore, provides an overview of the current state of bundled payment literature using the five components presented by Porter and Kaplan. We compare the implementation and design of bundled payments in the literature and how Porter and Kaplan initially conceptualized them. This analysis identifies the challenges faced in materializing bundled payments by focusing on what is missing between the theoretical concept and practice.

We use a scoping literature review to systematically search several relevant databases to identify academic studies and extract information pertaining to the five elements.

Through this investigation, we systematically compare existing literature to the core elements Porter and Kaplan suggest are needed to form the basis of bundles. We find a diverse range of approaches and a lack of standardization in the literature. Furthermore, some fundamental questions remain unclear and unanswered; these findings highlight the challenges we face regarding designing bundles that enhance quality, reduce costs, and promote better care coordination.

1.5. Publications

1.5.1. Articles from this dissertation that have been published in international peer-reviewed academic journals

Chapter 2

*Jacobs K, *Roman E, Lambert J, Moke L, Scheys L, Kesteloot K, Roodhooft F, Cardoen B. Variability drivers of treatment costs in hospitals: A systematic review. Health policy. 2022 Feb 1;126(2):75-86.

* Shared first author

Chapter 3

Roman E, Cardoen B, Decloedt J, et al. Variability in hospital treatment costs: a time-driven activity-based costing approach for early-stage invasive breast cancer patients BMJ Open 2020;10:e035389. doi: 10.1136/bmjopen-2019-035389

1.5.2. Related publications

Hilhorst NT, Deprez E, Roman E, Borzée J, De Beule D, Dullaers C, Hoorens I; Lambert. PsoPlus: an Integrated Practice Unit for Psoriasis. Dermatology. 2023 Feb 14. doi: 10.1159/000529398. Epub ahead of print. PMID: 36787697.

Hilhorst N, Roman E, Borzée J, Deprez E, Hoorens I, Cardoen B, Roodhooft F, Lambert J. Value in psoriasis (IRIS) trial: implementing value-based healthcare in psoriasis management - a 1-year prospective clinical study to evaluate feasibility and value creation. BMJ Open. 2023 May 23;13(5):e067504. doi: 10.1136/bmjopen-2022-067504. PMID: 37221023.

2. Variability drivers of treatment costs in hospitals: A systematic review

2.1. Introduction

Value-based healthcare, defined as the health outcome per dollar spent [129], is commonly used as a framework to improve outcomes while controlling spending in light of healthcare's growing economic burden on society. The concept has steadily altered care delivery by defining and measuring outcomes [130], introducing cost-reduction strategies [131] and moving towards value-based payments [132]. Cost variability studies can facilitate the transition towards value-based healthcare, both for policymakers and healthcare providers alike.

Studies on treatment cost variability can inspire the (re)design of reimbursement schemes, to incentivize providers to reduce spending and improve outcomes. A functional reimbursement scheme [30] should be case-mix adjusted to avoid cherry-picking and provide incentives for efficiency improvements (e.g., avoiding unnecessary spending). As such, cost variability studies indeed provide crucial insights into the drivers of treatment costs. Variability studies should focus on differences in real costs (i.e., the monetary value of the resources used to provide care) rather than on reimbursement. Reimbursements can be disconnected from the real costs incurred by healthcare providers to organize care [21, 133]. This confusion between real costs and reimbursement is a major barrier to reducing the cost of healthcare [30]. Furthermore, the payer's perspective only focuses on services that are reimbursed. Hence, services that are not reimbursed would be of zero value – although resources are required to provide them. Additionally, some services may receive a higher or lower reimbursement rate relative to the delivery cost, resulting in these services being overvalued or undervalued. Thus, focusing on the payer's perspective risks replacing the current (probably distorted) reimbursement system with a new distorted one. Therefore, the observed and justified differences in real costs (between different patient groups) should be used to set or adjust reimbursement rates (between these different groups) in line with these differences.

Additionally, after identifying sources of unwarranted cost variability, healthcare providers can redesign current care pathways of a subgroup of patients to decrease costs [27]. Moreover, providers can prevent expensive patient-treatment combinations on an individual patient level and promote lower-cost ones if this generates comparable outcomes.

To conclude, treatment cost variability studies from the healthcare provider's cost perspective play a crucial role for many stakeholders transitioning towards achieving greater value. Well-established guidelines have existed for some time, for economic evaluation studies out of the societal perspective, comparing the cost and consequences of different preventive, diagnostic or therapeutic interventions (e.g., comparing a new drug or device with the golden standard, comparing different care path variations, etc.) [134, 135]. However, such guidelines for cost variability studies where variability in costs is attributed to different independent variables such as treatment, disease or patient characteristics are not yet available. As these guidelines could increase the usability of cost variability studies for different stakeholders in achieving greater value, this systematic literature review sought to provide an overview of all cost variability studies regardless of medical specialty. To keep sufficient focus, this review focuses on studies including hospital costs, as these costs represent a major part of total healthcare costs [136, 137], without excluding articles from the provider's perspective that included more than only hospital costs. Moreover, this review sought to provide an overview of the identified study characteristics, an overview of which variables explain variability in hospital costs, and recommendations on the methodology for future cost variability studies.

2.2. Methodology

This systematic review was conducted in close adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [117] and Cochrane Handbook for Systematic Reviews of Interventions [118].

2.2.1. Data sources and search strategy

A comprehensive search strategy was formulated for the following eight databases: PubMED/MEDLINE, Web of Science, EMBASE, Scopus, CINAHL, Science direct, OvidSP and Cochrane library. Titles and abstracts were searched using the following keywords: "cost variability", "cost variation", "cost differences" and "cost drivers", in combination with "hospital costs". Variations of these keywords were used to maximize the search scope. Restrictions such as country, language or year of publication were not applied. The initial database search was conducted from March to May 2020. In October 2020, an updated search of all databases was conducted to include newly published articles that were not found in the initial search. In addition to this, snowballing was conducted to ensure all potentially relevant articles were identified and screened. A complete overview of the search strategy used for each database can be found in Appendix Chapter 2A.

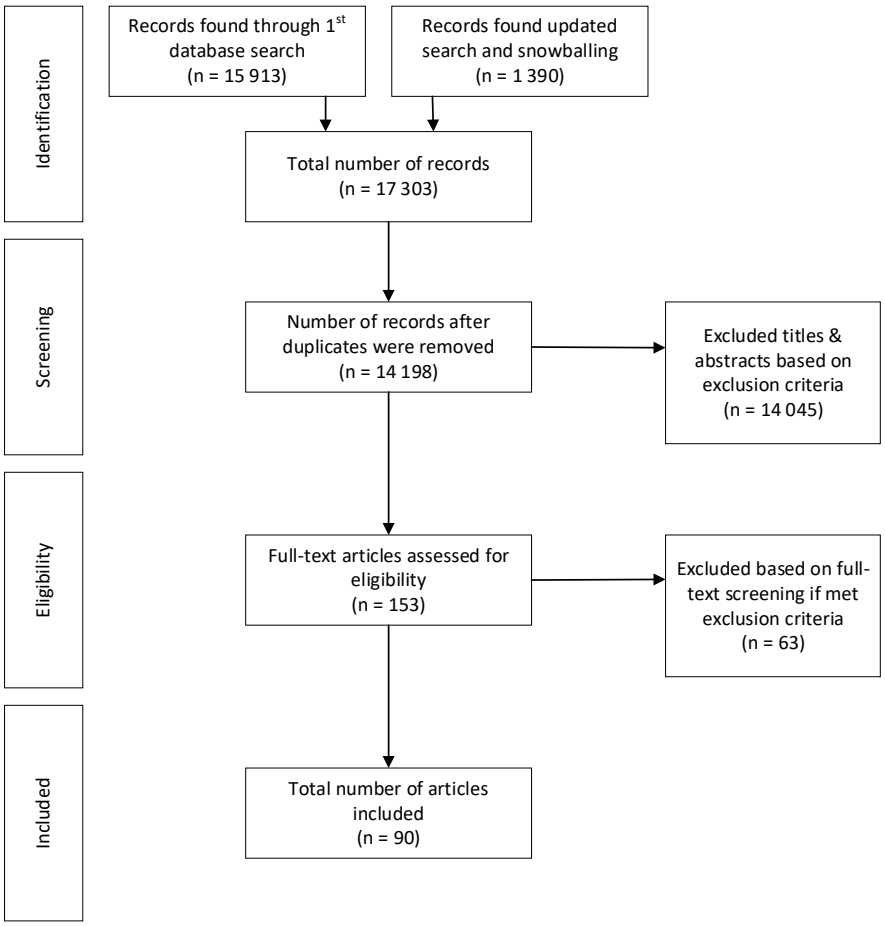
2.2.2. Study selection

All articles identified through the search strategy underwent two rounds of review. In the first round, duplications were removed, titles and abstracts were independently reviewed by two reviewers,

using the Rayyan QCRI application [138]. As the main focus of this review was to assess cost variability drivers, articles with average cost data were excluded as opposed to individual patient level cost data. Articles using patient-level cost data, which calculated costs from the payer's perspective (e.g., reimbursement or claims data, charges data) or the societal perspective (e.g., the opportunity cost of not being able to work because of sickness next to reimbursement costs) [134], instead of the perspective of resources used within the hospital, were also excluded. Articles from the societal perspective were excluded to narrow the scope to how cost variability studies, from the providers' perspective, could be useful in determining drivers of cost for reimbursement schemes and process improvement strategies. Papers that did not clearly state the cost perspective, used a mixed perspective (using hospital costs and reimbursements), or cost-to-charge ratios were also excluded. Furthermore, articles not written in English or not published in full texts (i.e., conference abstract only, editorial comment) were also excluded.

The second review round entailed an independent screening of the full text of the remaining articles by both reviewers, articles were excluded based on the first-round exclusion criteria. All disputes regarding the inclusion or exclusion of articles between the reviewers were discussed with a third reviewer until consensus was reached. The PRISMA flow diagram depicting the study selection process and number of eligible articles included in the review can be found in Figure 4.

Figure 4. PRISM and Meta-Analyses flow diagram of relevant article selection



2.2.3. Data extraction

Microsoft Excel was used to develop data extraction tables to record and structure the characteristics of eligible studies. General characteristics were extracted, including diagnosis/treatment group following the Clinical Classification System (CCS) [139], year of publication, journal type, a monocentric vs. multicentric study, the statistical methods used to identify cost drivers, etc. When a paper included different regression models on different costs components, for example, admission costs and full care cycle costs, the model with the largest cost scope (= the second) was used for the extraction.

To obtain a better understanding of treatment costs, information on the type of costs included and the costing method used were extracted. For the type of costs included, papers were divided into four categories. The first category, labeled "full patient costs", measured costs linked to the clinical services provided as well as to supporting services (=overhead, e.g., human resources department, administration and cleaning services). The second, labeled "patient care costs", only included costs linked to clinical services, excluding supporting services costs. However, sometimes overhead costs of the departments were included where the clinical services were provided. The third category, labeled "variable patient care costs", included variable costs only, linked to the patient's care. Variable costs

can be defined as those which increase proportionally with changes in activity levels of some variables [140], in this context, varying incrementally with the volume of care provided. The final category included all other articles which did not fit the above-mentioned groupings, given the limited insights provided within the studies, and were labeled under "not clearly defined".

To classify costing methods, papers were classified, if possible, as either "Activity-Based Costing (ABC)", "Time-Driven Activity-Based Costing (TD-ABC)" and "Other". If the reviewers could not make the appropriate classification, papers were classified under "not clearly defined". Papers were classified as ABC papers if the 2-stage allocation method was used where costs were pooled at the activity level and subsequently allocated to the patient via activity drivers (e.g., number of medical images, time in an OR). Papers that calculated a capacity cost rate for each involved resource and allocated costs to the patient via the time that that specific resource was used were classified under TD-ABC [141]. Papers which used a different costing approach to that of ABC and TD-ABC (e.g., Relative Value Units and Resource Intensity Weights), but clearly explained how costs were calculated were categorized under 'Other'. Papers that did not describe their cost allocation method but labelled their costing system explicitly as ABC or TD-ABC were also classified accordingly.

Additionally, information regarding the cost time scope was retrieved. A single care episode encompassed either an aspect of hospitalization (e.g., ICU), the entire hospitalization (e.g., from admission to discharge) or an outpatient episode. The multiple care episodes encompass inpatient care episodes (e.g., index hospitalization and possible readmissions), the inclusion of different outpatient care episodes, or a mix of inpatient and outpatient care episodes over a defined time period. Furthermore, the time period for which patients were included in the studies was extracted.

The independent variables used to explain cost variability in the included studies were divided into 5 categories during the data extraction process: (1) patient characteristics, broken down into general demographics (e.g., age, gender and race), socio-economic characteristics (i.e., marital status and type of insurance), behavioral variables (e.g., smoking or drinking) and comorbidities and their relevant scores, (2) disorder characteristics, including e.g. classifications/diagnoses, severity, phase/stage, (3) treatment characteristics, including procedure variations, treatment intensity, pathway variations, (4) outcome characteristics, such as complications, readmissions, mortality and patient-reported outcomes measures (PROMs) and (5) institutional characteristics, divided into hospital characteristics (i.e., size, facility type (e.g., surgery in ambulatory centre vs. main operating theatre), hospital type (e.g. tertiary care centre vs. community hospital)), environmental characteristics (e.g., geographical location and purchasing power differences) and resource characteristics (e.g., differences in treating physicians, physician specialty or physician experience). When certain variables, such as facility scores, severity of illness scores and DRG-groupings, did not conclusively lead to one of the defined categories, they were captured across multiple categories. Again, both reviewers extracted the information separately, results were subsequently merged, and differences were discussed until consensus was reached with the help of the third reviewer.

2.3. Results

2.3.1. Study selection

The initial search identified 17,303 citations. Once duplicates were removed, 14,198 studies remained to be screened based on title and abstract. After the initial review and the inclusion of the updated search for 2020, a total of 153 potentially relevant articles remained to be screened on full text. 90 articles [142–231] were included once the full-texts were screened and the exclusion criteria were applied.

2.3.2. General characteristics

The general characteristics included in the literature review can be found in Table 3. Publication year of the articles ranges from 1995 to 2020 with a large concentration published in the last decade, from 2011 to 2020. North America (56.7%) and Europe (26.7%) accounted for most of the articles, based on the location of data collection. The main objective of most articles (92.2%) was cost understanding and/or cost optimization. Most articles, except one [226], used a statistical technique, either bivariate analyses (correlation, regression, etc.), multivariate analyses or both, to identify relevant independent characteristics.

Table 3. General study characteristics

Characteristic	% (n)	References
Year of publication		
1995 - 2000	4.4% (4)	[181, 195, 204, 208]
2001 - 2005	10.0% (9)	[173, 184, 197, 207, 209, 212, 218, 220, 227]
2006 - 2010	10.0% (9)	[143, 159, 164, 176, 177, 190, 194, 198, 215]
2011 - 2015	15.6% (14)	[148, 152, 156, 163, 168, 172, 178, 182, 192, 199, 210, 219, 228, 231]
2016 - 2020	60.0% (54)	[142, 144–147, 149–151, 153–155, 157, 158, 160–162, 165–167, 169–171, 174, 175, 179, 180, 183, 185–189, 191, 193, 196, 200–203, 205, 206, 211, 213, 214, 216, 217, 221–226, 229, 230]
Type of journal		
Health disease or disorder specific journals	83.3% (75)	[142, 145, 146, 148–156, 158–165, 168–174, 176, 177, 179–184, 186, 187, 189, 191–193, 195–206, 208–225, 228–231]
Other healthcare journals	16.7% (15)	[143, 144, 147, 157, 166, 167, 175, 178, 185, 188, 190, 194, 207, 226, 227]
Location of data collection		
Asia	2.2% (2)	[167, 170]
Europe	26.7% (24)	[143, 144, 146, 149, 156, 162, 163, 165, 168, 172, 173, 175–177, 184, 194, 198–200, 211, 212, 215, 225, 226]
Middle East	1.1% (1)	[192]
North America	56.7% (51)	[145, 147, 150–155, 157–160, 164, 171, 174, 179–183, 186, 187, 189, 191, 193, 195–197, 201–205, 207–210, 213, 214, 216, 218, 220–224, 227–231]
Oceania	5.6% (5)	[148, 169, 178, 217, 219]
South America	4.4% (4)	[185, 188, 190, 206]
Multiple regional locations	1.1% (1)	[166]
Not clearly stated	2.2% (2)	[142, 161]

Clinical classification of paper topics*		
Mixed pathologies (ICU, palliative care, …)	16.7% (15)	[144, 149, 153, 158, 166, 173, 176–178, 184, 190, 209, 211, 212, 220]
Diagnoses category label		
Neoplasms	15.6% (14)	[155, 160, 163, 168, 171, 172, 180, 183, 185, 188, 202, 210, 226, 231]
Diseases of the circulatory system	13.3% (12)	[151, 157, 159, 164, 181, 191, 193, 195, 198, 207, 208, 215]
Diseases of the musculoskeletal system and connective tissue	10.0% (9)	[152, 154, 174, 196, 205, 213, 222, 223, 225]
Injury and poisoning	10.0% (9)	[142, 148, 170, 174, 182, 186, 197, 203, 219]
Other diagnoses category labels	15.6% (14)	[156, 165, 167, 175, 179, 189, 192, 194, 199, 204, 206, 214, 224, 227]
Procedures category label		
Operations on the nervous system	10.0% (9)	[155, 160, 163, 168, 171, 172, 180, 183, 202]
Operations on the cardiovascular system	11.1% (10)	[157, 164, 181, 186, 191, 195, 207, 208, 215, 218]
Operations on the musculoskeletal system	13.3% (12)	[147, 150, 152, 154, 174, 182, 187, 196, 213, 222, 223, 225]
Objective/rationale of paper*		
Cost optimization/understanding	92.2% (83)	[142–146, 148–165, 167–173, 175–177, 179–198, 200–210, 212, 214–231]
Insights for reimbursement	35.6% (32)	[142–144, 146–148, 159, 162, 165, 169, 172, 174, 175, 178, 180, 194, 199, 210, 211, 213–215, 219, 220, 223–226, 228–231]
Other	1.1% (1)	[218]
Sample size of data		
0 – 100	12.2%% (11)	[161–164, 168, 170, 177, 181, 192, 205, 226]
101 – 1000	60.0% (54)	[144, 146, 147, 150–152, 154–156, 159, 160, 165–167, 169, 171, 173, 175, 176, 179, 180, 182, 183, 185–188, 191, 193, 194, 196–200, 202, 204, 206, 208, 210, 213–215, 217, 220–225, 227, 229–231]
Greater than 1000	27.8% (25)	[142, 143, 145, 148, 149, 153, 157, 158, 172, 174, 178, 184, 189, 190, 195, 201, 203, 207, 209, 211, 212, 216, 218, 219, 228]
Type of hospital setting		
Monocentric	68.9% (62)	[142, 144, 147, 149–151, 153–155, 157–162, 164, 165, 168–171, 173–175, 177, 179–183, 185–190, 192–194, 196–200, 202, 204–206, 208–210, 213–215, 217, 218, 220–222, 224–226]
General hospital setting	7.8% (7)	[165, 168, 188, 190, 204, 222, 226]
University hospital setting	46.7% (42)	[142, 144, 149, 151, 153–155, 157–159, 161, 162, 164, 169, 174, 175, 177, 180–183, 186, 187, 189, 192, 194, 197–199, 202, 206, 208–210, 213, 214, 217, 218, 220, 221, 224, 225]
Unclear setting	14.4% (13)	[147, 150, 160, 170, 171, 173, 179, 185, 193, 196, 200, 205, 215]
Multicentric	30.0% (27)	[143, 145, 148, 152, 156, 163, 166, 167, 172, 176, 178, 184, 191, 195, 201, 203, 207, 211, 212, 216, 219, 223, 227–231]
General hospital setting	1.1% (1)	[178]
University hospital setting	3.3% (3)	[156, 191, 212]
Mixed hospital setting	10.0% (9)	[195, 201, 207, 211, 216, 227–230]
Unclear setting	15.6% (14)	[143, 145, 148, 152, 163, 166, 167, 172, 176, 184, 203, 219, 223, 231]
Not clearly stated	1.1% (1)	[146]
Data collection		
Retrospective	60.0% (54)	[142, 147, 150–152, 155–158, 160, 162–164, 166, 169–174, 178–180, 182, 183, 185–189, 192, 193, 196, 200, 201, 203–205, 208, 212–217, 220, 221, 224–228, 230, 231]
Prospective	11.1% (10)	[165, 168, 176, 177, 181, 198, 202, 206, 209, 210]
Retrospective use of prospectively collected data	13.3% (12)	[145, 146, 153, 159, 161, 167, 184, 191, 197, 222, 223, 229]
Not clearly stated	15.6% (14)	[143, 144, 148, 149, 154, 175, 190, 194, 195, 199, 207, 211, 218, 219]
Statistical methods used*		
Bivariate analyses (correlation, regression)	70.0% (63)	[143, 145, 148–151, 153, 155–164, 166–171, 175, 177, 179–187, 192, 193, 195, 197, 198, 200–202, 204, 208–210, 212–217, 219–222, 224, 225, 227, 229–231]

Multivariate analysis	81.1% (73)	[142, 144–159, 161, 162, 164–174, 177–181, 184, 186–191, 193–201, 203–209, 211–215, 218–220, 222–225, 227, 228, 231]
% of explained variation was provided*	37.8% (35)	[142, 143, 147, 148, 151, 153, 156, 159, 161, 164, 166, 169, 170, 177, 188, 190, 194, 195, 197, 198, 203, 204, 207–209, 213, 214, 218, 220, 222–225, 227]
0 – 0.25	7.8% (7)	[166, 195, 198, 207, 208, 213, 222]
0.26 – 0.50	12.2% (11)	[147, 153, 156, 159, 164, 190, 194, 203, 204, 207, 218]
0.51 – 0.75	14.4% (13)	[148, 151, 161, 188, 190, 197, 209, 214, 220, 223–225, 227]
0.76 – 1.00	6.7% (6)	[142, 143, 169, 170, 177, 223]
Type of multivariate regression		
Linear regression	92.2% (83)	[142–156, 159–176, 178–197, 199–201, 203–221, 223–225, 227–231]
Logistic regression	6.7% (6)	[157, 158, 177, 198, 202, 222]
No statistics methods used	1.1% (1)	[226]

* Represents categories which are not mutually exclusive, thus some articles are referenced across categories if applicable

2.3.3. Definition of treatment costs

The full overview of the characteristics which make up treatment costs, i.e., the dependent variable, can be found in Table 4. Regarding cost time scope, the majority of articles investigated the entire hospitalization costs (n=50). Some articles only looked at the costs of one aspect of the hospitalization, (n=22), for example, only at the costs of the ICU admission [177, 184, 191], an episode of specialist palliative care [144], preoperative [150] or postoperative care [205] or the first 24 hours of hospitalization [220]. Articles including the cost of multiple care episodes in a defined time period mainly included both inpatient and outpatient care episodes (n=13). Four of them included inpatient care episodes only. For both single and multiple care episodes, no articles pertaining to outpatient care only focused on cost variability.

44.4% of the articles used the full cost of care for their analysis, 30.0% of the articles only included patient care costs (excluding overhead) in their studies. Six articles (6.7%) used variable patient costs in their analysis. And finally, the remaining 20.0% of articles could not be classified as it was not clearly stated which cost categories were incorporated. In terms of costing methods, 48 articles were classified under ABC and six articles were classified under TD-ABC. An additional six articles were classified under “other”. For a considerable number of papers (n=30), the costing method could not be defined. 96.7% of the articles mentioned the years considered regarding the inclusion of patients. Of those studies, some considered a timeline of less than one year (n=14). Others did data collection over several years (n=73). Of those, 16 discounted costs.

Table 4. Definition of treatment costs in hospitals (dependent variable)

Characteristic	% (n)	References
Cost time scope		
A single care episode		
One aspect of hospitalization (e.g., ICU)	24.4% (22)	[148, 150, 152–155, 170, 173, 177, 182, 184, 186, 187, 191, 201, 205, 216, 218, 220, 221, 229, 230]
Entire hospitalization	55,6% (50)	[143, 146, 147, 151, 157–162, 165, 167–169, 171, 174–176, 178–181, 183, 189, 190, 192–195, 197–199, 202–204, 206–212, 214, 215, 219, 222, 224, 227, 228, 231]
Outpatient episode	0.0% (0)	
Multiple care episodes over a care cycle		
Inclusion of only inpatient care episodes (e.g. index hospitalization and possible readmissions)	5.6% (5)	[144, 149, 196, 213, 217]
Inclusion of different outpatient care episodes	0.0% (0)	
Inclusion of all care episodes; both Inpatient and outpatient care episodes	14.4% (13)	[142, 145, 156, 163, 164, 166, 172, 185, 188, 200, 223, 225, 226]
Cost scope		
Full patient costs	44.4% (40)	[142–144, 146, 148, 149, 157, 159, 164, 165, 167–169, 172, 175–177, 179–181, 184, 189–191, 194, 198, 199, 206, 208, 210–212, 214, 215, 217–220, 224, 226]
Patient care costs only	30.0% (27)	[147, 150–155, 158, 163, 166, 171, 173, 174, 178, 183, 185–188, 196, 202, 204, 214, 221–223, 225]
Variable patient care costs	6.7% (6)	[195, 203, 207, 209, 213, 216]
Not clearly defined	20.0% (18)	[145, 156, 160–162, 170, 182, 192, 193, 197, 200, 201, 205, 227–231]
Costing methods		
Activity-based costing	53.3% (48)	[143, 144, 146, 148–151, 153–158, 164, 167–169, 173, 175, 180–187, 189–191, 195, 196, 198, 199, 202–204, 206, 211, 212, 215–218, 220, 221, 225, 230]
Time-driven Activity-based costing	6.7% (6)	[165, 172, 176, 194, 222, 226]
Other (e.g., relative value units, resource intensity weights)	6.7% (6)	[145, 159, 162, 178, 208, 210]
Not clearly defined	33.3% (30)	[142, 147, 152, 160, 161, 163, 166, 170, 171, 174, 177, 179, 188, 192, 193, 197, 200, 201, 205, 207, 209, 213, 214, 219, 223, 224, 227–229, 231]
Other aspects of cost		
Inclusion time scope*	96.7% (88)	[142–146, 148, 150–225, 227–231]
Less than one year	15.6% (14)	[143, 144, 167, 175–177, 185, 188, 194, 195, 204, 215, 219, 220]
Multiple years	81.1% (73)	[142, 145, 146, 148, 150–166, 168–174, 178–184, 186, 187, 189–193, 196–203, 205–214, 216–218, 221–225, 227–231]
Discounted costs	17.8% (16)	[144, 156, 157, 163, 165, 174, 184, 187, 188, 194, 197, 201, 210, 217, 223, 228]

* Represents categories that are not mutually exclusive, thus some articles are referenced across categories if applicable.

2.3.4. Variability drivers of treatment costs in hospitals

For studies that studied patient characteristics as possible drivers, the most common variables considered were age and gender of patients. Of the articles investigating age, more than half (n=37) found it to be significant. In turn, only 39.3% of articles that investigated the impact of gender identified it as a statistically significant cost driver. In addition to general demographics, a range of comorbidities was analyzed. Of the articles considering comorbidities (i.e., hypertension, diabetes, history of stroke etc.), 71.4% found that they significantly impact costs. Articles looking into the impact of disease

characteristics on costs, primarily analyzed the impact of severity of the respective disease. 78.3% of the articles found it significant in explaining costs.

For treatment characteristics, procedure variations such as surgical vs. non-surgical treatment, number of treatments, and initial vs. reintervention, were the main components under investigation. All (n=31) but three articles [143, 170, 206] analyzing length of stay (LOS) found a significant relationship.

For studies including outcome characteristics, the majority looked into the impact of complications on costs. 87.0% of these articles identified complications as a significant cost driver. Only 4 articles used PROMS as an independent variable for consideration [168, 202, 206, 223].

Articles evaluating hospital characteristics typically focused on whether different "facilities" played a role in driving costs. 84.6% of included studies found that the facility (i.e., ambulatory surgical facility vs. inpatient facility) in which treatment took place impacted the overall treatment costs. A limited number of studies (n=4) investigated how the geographical location impacted costs. Articles focusing on resource characteristics predominately considered the impact of medical staff on costs. An overview of the full results of all independent variables and their significance can be found in Table 5.

Table 5. Drivers of variability of treatment costs in hospitals (independent variables)

Characteristic	**% (n)**	**References**
Patient Characteristics		
Demographics		
Age	81.1% (73)	[144–146, 148, 154, 155, 159, 160, 163–166, 168, 169, 171, 173, 175, 177, 180, 182, 186, 188, 194, 197, 199, 201, 202, 205, 206, 210, 211, 222, 226–228, 231]; [147, 149, 150, 152, 153, 156–158, 161, 162, 170, 172, 174, 176, 181, 183–185, 189, 191, 192, 195, 196, 198, 200, 203, 204, 207, 208, 212–215, 218, 219, 224, 225]*
Gender	67.8% (61)	[144–146, 149–152, 155, 157, 159, 162–166, 169, 170, 173, 174, 180–182, 184–186, 188, 194, 198, 199, 201–205, 210, 218, 219, 225]; [142, 144, 147, 148, 153, 154, 158, 167, 168, 171, 172, 190, 192, 195, 200, 207, 208, 211–213, 222, 224, 228, 231]*
Race	11.1% (10)	[185, 186, 188, 208, 213, 232]; [174, 180, 207, 228]*
BMI	22.2% (20)	[146, 177, 180, 187, 194, 199, 202, 205, 206, 208, 213, 225, 226]; [156, 172, 200, 215, 222, 224, 231]*
Socio-economic characteristics (e.g., insurance type, education level, marital status)	16.7% (15)	[152, 169, 180, 185, 203, 205, 208, 212]; *
Behavorial variables (e.g., alcohol use, tobacco use, sedentary lifestyle)	14.4% (13)	[185, 188, 192, 205, 208, 222, 225, 231],[157, 164, 180, 195, 210]*
Other demographics	8.9% (8)	[208]; [142, 156, 167, 199, 200, 205, 225]*
Comorbidities		
General comorbidities	31.1% (28)	[146, 164, 165, 177, 184, 188, 218, 226], [145, 147, 157, 158, 161, 171, 185, 193, 199, 200, 204, 205, 207, 208, 215, 222–225, 231]*
Number of comorbidities	3.3% (3)	[171], [203, 211]*
Comorbidity indices		
Charlson comorbidity index	11.1% (10)	[146, 180], [149, 159, 166, 172, 174, 179, 190, 212]*
Elixhauser comorbidity index	5.6% (5)	[157, 158, 189, 191, 212]*
ASA score	22.2% (20)	[146, 154, 155, 168, 182, 202, 213, 231], [150, 151, 153, 161, 172, 174, 187, 191, 208, 214, 222, 224]*

Other comorbidity indices	6.7% (6)	[179, 231], [144, 149, 210, 225]*
Other comorbidity characteristics	18.9% (17)	[175, 177, 182, 192, 198, 210, 213], [147, 157, 174, 176, 189, 191, 205, 208, 209, 214]*
Disease Characteristics		
Disease classifications/diagnoses	27.8% (25)	[168, 171, 177, 178, 206, 226], [147, 149, 152, 158, 163–165, 169, 175, 198, 199, 203, 207, 211, 212, 215, 219, 220, 225]*
Disease severity	51.1% (46)	[165, 167–169, 180, 182, 205, 210, 226, 231], [146, 148, 149, 151, 155, 159, 160, 164, 166, 170–173, 176, 177, 179, 181, 191, 192, 194, 196–198, 200–203, 208, 212, 215, 218, 220, 222, 224, 227, 228]*
Disease phase/stage	10.0% (9)	[188, 210, 226]; [144, 172, 202, 212, 219, 231]*
Other disease characteristics	25.6% (23)	[148, 171, 205, 208]; [147, 149, 155, 156, 159, 164, 166, 168, 172, 176, 186, 189, 192, 198, 200, 204, 207, 212, 223]*
Treatment Characteristics		
Procedure variations	45.6% (41)	[146, 160, 162, 165, 170, 174, 181, 182, 222, 229, 231],[142, 143, 145, 147, 151, 153, 154, 157, 161, 164, 171, 172, 177, 187, 191, 195–197, 200, 201, 205, 208, 209, 212, 215, 217, 218, 223, 224, 230]*
Treatment intensity	15.6% (14)	[162, 164, 168]; [154, 171, 186, 190, 205, 208, 211, 214, 217, 224, 225]*
Initial treatment vs. reintervention	13.3% (12)	[162, 187, 201, 202, 205, 222, 231]; [150, 196, 208, 223, 224]*
Elective vs. emergency procedure	12.2% (11)	[157, 166, 172, 173, 184, 190, 195, 207, 208, 212, 224]*
Pathway variations		
ICU admission	12.2% (11)	[160, 170]; [148, 169, 179, 184, 189, 198, 219, 220, 227]*;
Discharge disposition	15.6% (14)	[170, 189, 202, 205]; [144, 150, 151, 154, 155, 157, 158, 203, 211, 212]*
Other pathway variations	11.1% (10)	[203, 214]; [142, 147, 157, 163, 175, 198, 209, 224]*
Process variables		
Length of stay (of the entire hospitalization or the ICU)	34.4% (31)	[143, 170, 206]; [145, 148, 150, 152–155, 157, 158, 160, 167, 169, 171, 173, 175, 177, 179, 183, 193, 196, 198, 200, 202, 205, 211, 219, 223, 225]*
Operating theatre time	12.2% (11)	[179]; [150, 162, 169, 174, 186, 223, 224, 229–231]*
Year of treatment	8.9% (8)	[164, 199]; [145, 151, 152, 159, 179, 203]*
Other treatment characteristics	33.3% (30)	[160, 162, 167, 170, 179, 204, 205, 227]; [142, 160, 166, 169, 173, 176, 185, 188, 190, 191, 195, 206, 207, 211, 212, 214, 218, 222, 224, 225, 229–231]*
Outcome characteristics		
Complications	25.6% (23)	[154, 168, 173]; [145, 147, 150, 155, 157, 161, 162, 169–171, 179, 180, 197, 202, 205, 206, 209, 214, 217, 231]*
Readmission	4.4% (4)	[145, 158, 200, 225]*
Mortality	18.9% (17)	[144, 166, 177, 192, 206]; [156, 159, 173, 179, 184, 188–190, 195, 198, 209, 231]*
Patient reported outcomes measures (PROMs)	4.4% (4)	[168, 202]; [222, 223]*
Institutional characteristics		
Hospital characteristics		
Different hospital/facility	14.4% (13)	[167, 178], [145, 163, 182, 186, 187, 212, 216, 221, 224, 228, 229]*
Hospital size	2.2% (2)	[143, 195]*
Other hospital characteristics	4.4% (4)	[145, 201, 203, 211]*
Environmental characteristics		
Location	4.4% (4)	[166, 195, 201, 229]*
Other environmental characteristics	1.1% (1)	[143]*
Resource characteristics		
Medical staff	13.3% (12)	[182]; [147, 169, 179, 186, 187, 191, 216, 221, 223, 228, 229]*
Other resource characteristics	1.1% (1)	[186]*

* At least one significant relationship was found between costs and a variable(s) that could be listed in the particular category where the reference is listed.

2.4. Discussion

Given the global rise in health care expenditure, cost variability studies have become increasingly important when shifting our focus to understanding/investigating costs. The growing importance of these studies is evident when one looks at the number of published papers in the last five years (n=54). The main objective of cost variability studies is to create greater cost transparency/understanding and provide insights (i.e., factors influencing costs) relevant for reimbursement schemes – the two main aims of all papers included in the review. Through its influence on costs, these studies can lead to more informed decision-making, which can alleviate the pressure faced by the sector.

By investigating existing literature, this review resulted in a structured overview of the published articles on treatment cost variability in hospitals, coupled with their general study characteristics, the definition of those costs and variability drivers. By comparing the different studies, best practices are identified, and methodological recommendations for the research community looking to perform future cost variability studies can be made. Furthermore, suggestions have been made to support providers seeking to investigate possible process improvement strategies which could impact policy at an institutional level, and finally, relevant considerations have been highlighted for policy makers/governmental agencies mainly focused on impacting the current financial structure and reimbursement system within the sector. Because the quality of cost variability studies depends on how costs were calculated, focus went into assessing the different dimensions of the costing systems used. It was difficult to assess the quality of one-third of the papers that did not clearly describe the costing method. This could be related to the type of journals these papers were published in, namely health disease or disorder specific clinical journals where the methodological focus is mainly on clinical content and to a lesser extent on how costs are calculated. From the perspective of reproducible science, with the focus of increasing the credibility of research output [233], we encourage future research focusing on cost variability to report their methods, particularly how costs were measured more transparent and clear. As a suggestion, scholars could use the Transparency and Openness Promotion (TOP) guidelines that incentivizes greater reporting of research [234], or alternatively, refer to the costing models used in prior publications with a more detailed costing method description. From a policy perspective, government could consider implementing standardized costing method systems across providers, these are typically used for costing studies conducting economic evaluations. Two examples of this are Dutch Costing Guidelines [235] and the Ontario Case Costing Initiative [236], both aim to standardize costing methodologies which support the implementation and assessment of cost research.

In addition to fostering more transparency and stimulating cost research output, standardized costing methods will also have an impact at an institutional level. If providers have a better understanding of costs, it will allow for better management of care and optimization of existing

processes to reduce waste [30]. Research focusing on policy shows that better care coordination has been identified as a highly effective way to contain costs [237]. Thus, highlighting the importance cost transparency can have for multiple stakeholders. Therefore, by introducing guidelines centred around standardized costing methods, greater efforts can be made to move closer to eliminating unnecessary financial leakages and create better alignment in how care is provided across health providers. It should be noted that these attempts are hampered when the reporting of how costs are calculated and the variables included to calculate costs, is not done sufficiently [41]. Looking at the results of the included studies pertaining to the dependent variable (e.g., costing method used, and how costs were calculated), it is evident that room for improvement exists.

When considering the data used within the studies, as costs are calculated from the provider's perspective, they reflect the costs to provide care. Thus, most data sources were internal, meaning data originated from the organizations themselves. However, in certain instances external data was utilized in some costing models. For example, one article calculated costs of three sites located in different countries with the same unit costs originating from one country [166]. By using this approach, variation in costs could be attributed to differences in the provided care between the sites. Another article used the same approach to level for differences in costs between geographic location within a country [207]. Other basic aspects regarding data collection were well reported. 100% of the authors were clear on the sample size and 84.4% of the papers stated if data was collected retrospectively, prospectively or entailed the retrospective use of prospectively gathered data. However, details on patient identification/inclusion, duration of data collection, and use of clinical vs. administrative data were not mentioned by all papers.

Given the rise of big data and the increased use of real-world evidence it is imperative that from a research integrity perspective we disclose how data is collected. Thus, we echo our previous recommendation of providing transparency, not only on how data for the costing model was obtained but the way the independent variables are collected. In doing so, this would allow for better assessment of the quality of the research provided.

Regarding cost scope, most papers clearly stated whether they included full patient costs (including overheads), only patient care costs (excluding overheads) or only variable costs. The choice of which costs to use is dependent on the objective of the researcher, policy maker or provider. For policy makers who are focused on developing or modifying reimbursement schemes, we suggest using full patient costs when looking to set full reimbursement rates, as these costs capture both the clinical and supporting services, which should also be covered [76, 238]. Furthermore, these costs can be used by providers if the objective is identifying variability for process improvement.

When considering patient care costs, papers that used these costs argued that care delivery had limited or no effect on the use of supporting services, thus justifying their exclusion. When these overhead costs are included by applying a flat-rate percentage, referred to as the peanut-butter approach [27], patient care costs would be equally proportional to full patient costs (including the overhead cost).

Therefore, the ability for independent variables to explain variability in treatment costs remains the same. One paper that allocated overhead costs more elaborately built two models, one to explain only variability in patient care costs and another one to explain variability in full patient costs. Interestingly, both models identified the same variables to explain variability [214]. Thus, the above suggests that only including costs linked to providing clinical services in cost calculations can be justified. However, the costs cannot be used to set full reimbursement rates. They can however be used to determine the variables for risk adjustment as well as identifying process improvement opportunities.

When looking at variable costs only, we believe this view on costs are too limiting for policy makers and researchers. Authors who included variable costs reasoned that these costs are the only ones affected by patient care management changes, as often observed in healthcare costs studies [30]. Indeed, in the short run, the care delivery changes do not affect the fixed costs such as equipment or staff. However, care delivery changes can affect future budgeting decisions and thus alter fixed costs on the long run. To fuel those decisions, we argue that physicians and management need insights in these costs as well.

Considering the time horizon of costs when patients over multiple years are included, the general recommendation is to discount costs [134]. Other approaches used the same capacity cost for resources to level out variation due to inflation and included 'year of admission/treatment' as an independent variable in the regression model. Studies which included 'year of admission/treatment' found this to be a significant independent variable impacting costs, which could be explained by price evolutions over time. We recommend future studies to combine these two approaches of discounting costs and including 'year of admission/treatment' as an independent variable. As such, possible changes in the process over time and/or price evolutions can be assessed independently from inflation.

For studies performing statistical analysis we recommend that scholars should first consider running a bivariate analysis to identify significant variables and then include those variables in a multivariate model, an approach which was taken in 49 papers. By following this sequence, researchers have a better view of the relationship between different independent variables and costs separately that might have remained hidden when only a multivariate analysis is performed [239]. This would for example leave options open to use a variable that is as good in explaining cost variability compared to another variable but is easier to collect for risk-adjust the bundled payment scheme. This information is lost, an approach taken by 25 papers, when only carrying out a multivariate analysis without correlation analyses.

Like other healthcare costing studies [7], included studies reported a right-skewed distribution of the dependent variable. Three approaches were identified from the studies; logistic regression, generalized linear models and linear regression with logarithmic transformations. It should be noted that a logistic regression was used to model the probability of an episode of care/patient being part of the most expensive group. This approach and resulting insights seem valuable, because the small number of relatively expensive patients/episodes of care can greatly impact costs. However, when few

study objects are combined with many variables in an analysis, we recommend using linear regression analyses instead of a logistic regression as the required Events Per Variable (EPV) for the former are lower [240].

The limited number of multicentre studies reflects the barriers around setting up identical costing systems in multiple centres to make cost comparisons. Multicentre studies are preferred as they provide a more solid base for generalizations of the results [241]. These types of studies could benefit from standardized costing frameworks, a set of guidelines for standardizing cost calculations which can be used by researchers across different providers to come to comparable costs. With these frameworks, more cost variability studies across multiple centres could be performed, allowing for more benchmarking and improvement opportunities to be investigated. When scholars are limited to a monocentric study design, if possible, we suggest comparing the costs between different facilities/wards within that centre. By doing this, process differences can also be assessed, which could lead to further optimizations.

In addition to the study characteristics and dependent variable this systematic review looked into the different independent variables. Overall, most papers included patient, treatment and disease/disorder characteristics, as these are both clinically relevant and data is readily available. Policymakers can use these preoperative factors for developing or adjusting reimbursements schemes at a patient level. If schemes are implemented correctly on a case-by-case basis, determined by the risk profile of individual patients, it will protect against cherry-picking [213]. Moreover, some papers included institutional variables (hospital, environmental and resource characteristics) which, on their own, can lead to the identification of process improvement opportunities. Differences in costs due to facility type (stand-alone ambulatory surgery facility vs. inpatient operating theatre) for example led to revisiting the task assignment of different professions in the operating room [182, 186]. Subspeciality training resulted in more effective care and decreased cost through less resource consumption [191]. Finally, the surgical team learning curve was linked to decreasing costs, revealing the opportunity to reduce care costs by accumulating volume over time [169]. From these examples, we can conclude that if institutional variables impact costs significantly, it may be worthwhile investigating them further, looking into the underlying reasons of cost differences as signaled by these institutional variables, to identify process improvement initiatives by reducing practice variation [242]. Therefore, we suggest including these types of variables as well in future research.

Policy makers, providers, and researchers are advised to use patient, treatment, and hospital characteristics in conjunction with institutional characteristics and vice versa. By doing this, one can set the impact of these different variables apart. For example, researchers can assess if differences in costs between hospital facilities are caused by differences in patient case-mix or differences in costs between treatment options are caused by variability in the skill's level of the treating physician.

Outcome variables included mortality, readmission and complications, which are all "to be avoided" outcomes. As to be expected, very often, significant relationships with costs were found.

Identifying the impact of complications on costs can improve the health provider's strategy to avoid complications and improve outcomes. Complications that can be prevented should not be incorporated in the reimbursement fee so that providers are held financially accountable for them [21]. Few papers [168, 202, 222, 223] attempted to link (progress in) outcomes measured by PROMs to costs. Two of them [222, 223] revealed a significant relationship with costs. As more PROMs data becomes available [243], the potential to link outcomes with costs can further be evaluated.

The included papers clearly use different approaches towards (treatment) variables that indicate resource consumption, including LOS, LOS in the ICU and OR time. Some authors for example deliberately excluded these variables from the models because of the potential causal relationship with several other variables, including complications, comorbidity (scores) and disease severity [202]. Others considered them too closely related to the dependent variable [144, 194]. Of the papers which included LOS and OR time, 90.3% and 90.9% respectively found a significant relation. As LOS and other variables that indicate resource consumption are driven by patient and treatment characteristics and (bad) quality, ideally, patient and treatment characteristics, rather than LOS should be used to adjust the reimbursement schemes [76]. If analyses show that costs differ significantly between patients due to differences in patient, disease or treatment characteristics, policymakers can agree upon different reimbursement rates between these groups. However, these differences should not be based on parameters that can very easily be influenced by care providers themselves, for example LOS in the ward or ICU. Ideally, only characteristics that cannot be influenced should be considered. By including LOS and similar variables in a multivariate regression model next to the patient and treatment factors, the regression coefficients of the latter variables, used to adjust the reimbursement fee, will be affected due to correlation. We, therefore, suggest leaving out variables indicating resource consumption from the multivariate regression model, when aiming to use the model as a foundation for building risk-adjusted bundled payment schemes. If this approach is followed, then one can quantify how much the patient/treatment factors impact costs. Additional correlation analyses between the patient/treatment factors and OR time, LOS or similar might show how the patient/treatment factors cause additional costs (e.g., by prolonging the LOS with x days or increasing OR time with x %).

In addition to knowing which variables explain variability, the percentage of explained variability by the included variables provides interesting insights. Policymakers can use this information to arrive at optimal reimbursement strategies. Only 37.5% of the papers mentioned how much variability could be explained by the different variables in their analysis. Policymakers can use this information to decide upon the optimal reimbursement strategy. When patient, disease, and treatment characteristics explain a high % of cost variability, bundled payments can be risk-adjusted so that risk can be shared properly between payer and provider. If, on the other hand, these factors cannot explain the variability, it is difficult to risk-adjust bundled payments.

To distinguish more precisely the variability explaining ability of patient, treatment and disease characteristics between each other, multiple "nested" multivariable regression models can be used. In

this approach used by de Barros Reis et al. [188], a set of variables from a different category is added to every subsequent regression model to explain the additional variation and tamp out significant predictors of previous models.

The results of this literature review should be interpreted within the context of its design and limitations. Firstly, as argued in the introduction, only cost studies from the hospital perspective were included. Therefore, potential papers that did not clearly describe the cost perspective were excluded from this analysis. In addition, we acknowledge that articles that included costs from the provider's perspective but did not have a hospital cost component, could have been missed. Additionally, cost variability studies with societal costs as a focus were excluded to narrow the focus on hospital costs and their methodology, reflecting the quality of these papers. A systematic review focusing on cost variability studies where costs are calculated from the societal perspective examining which cost buckets were considered and which policy recommendations could be impacted serves as interesting future academic work. Furthermore, an additional avenue for future research could focus on studies which take the costs of care of all providers over the entire care trajectory into consideration. Secondly, bias could arise due to the reviewer's subjective interpretation. To reduce this to a minimum, all steps of the systematic review, including abstract screening and data extraction, were done by two independent reviewers, following the state-of-the-art guidelines [117, 118].

2.5. Conclusion

Both healthcare providers and policymakers can benefit significantly from better understanding the drivers of rising health care costs as more effective and more efficient health care delivery is required. This review aimed to summarize the main drivers of hospital cost variability documented in the literature and provide methodological recommendations for future hospital cost research to support the development/adjustment of reimbursement systems and/or cost reduction initiatives. A total of 90 costing studies investigating the impact of a range of independent variables on hospital costs were included. Many of the articles identified variables that significantly impact costs, allowing for the formulation of a concise overview of relevant characteristics. It is highly recommended for both policymakers and healthcare providers that an array of variables across all the different categories; patient, disease, treatment and also outcome, hospital, resource and environmental factors, should be considered. Based on the studies' results, suggestions for methodological improvements in hospital cost variability studies have been provided. We hence seek to positively contribute to future research to uncover and shed light on the drivers of hospital treatment costs.

3. Variability in-hospital treatment costs: a time-driven activity-based costing approach for early-stage invasive breast cancer patients

3.1. Introduction

The aim of this study is to analyse the variability in treatment costs for a single disease using the perspective of molecular subtypes and several patient-specific and disease-specific characteristics. Worldwide, it has been documented that healthcare costs are on the rise [21]. This increase is driven by a number of factors related to ageing population, technological advancements and the current reimbursement system [30, 72]. However, in conjunction with these factors it has been noted that significant cost variation exists across hospitals in providing care [244]. To curb higher expenditure and reduce cost variability, greater understanding of the drivers of variation is warranted [245]. Using Time-Driven Activity-Based Costing (TD-ABC), we aim to quantify the impact of multiple characteristics on the overall cost of treatment. Previous academic studies have drawn attention to identifying particular variables that lead to differences in costs for hospitals [119–122, 246]. These studies provide evidence that costs can vary based on a number of factors such as hospital structure and physician variables.

We focus on breast cancer as the medical disease to examine the impact of patient and disease factors on the variability of costs. Globally, breast cancer remains the most commonly diagnosed cancer and it is the leading cause of death in women [247]. Breast cancer is considered a heterogeneous disease, and evidence shows that clinically similar tumours often translate into different prognoses and react differently to therapy [248]. From existing medical literature, we see that patient and disease characteristics play a significant role in the treatment path followed by patients [249]. The classification of the disease is based on severity, and patients' overall health status impacts the medical decisions taken [250]. Using the four main molecular subtypes of breast cancer, we aim to quantify the impact of these characteristics on the variability of costs. Our academic study takes place in the breast clinic of a hospital where all patients are treated by a multidisciplinary team (MDT). The MDT is responsible for all medical decisions, and patients are surgically treated by the same oncoplastic surgeon, therefore controlling for hospital and physician variability. To accurately measure costs we use TD-ABC as the costing technique, which has been proposed by Kaplan and Anderson [28] and has been used in a growing body of research [59, 91].

3.2. Methods

3.2.1. Overall TD-ABC Model

Our research was conducted at a breast clinic located in Belgium. All relevant patient and financial data were collected through a research collaboration with a general hospital. Through face-to-face interviews with the physician and medical staff, generic process maps for each step in the intervention path were developed [27]. A full overview of the treatment steps can be found in the supplementary Appendix Chapter 3A. Through designing the process maps, the relevant activities were identified with the corresponding medical personnel, medical equipment and facilities used. Time estimates were based on the average time spent per activity, and the full duration of the activity was covered. The estimates used are based on subjective estimates provided by the medical personnel. All data were collected through interviews with medical staff and through direct observations.

Annual costs for medical equipment and hospital facilities were retrieved from the financial database of the hospital in collaboration with the finance department. All costs used in our analysis are taken from the perspective of the hospital. Salaries include all additional remuneration benefits paid to employees. Given the sensitivity surrounding remuneration, the cost for medical personnel was calculated using figures from a Belgian study published by the Belgian Health Care Knowledge Centre in 2012 [251], which is a federal research institution focusing on healthcare research. To provide a more accurate salary figure, an index of 7.2% was added to account for inflation.

Costs relating to the surgical intervention were made up of medical personnel's salaries, direct medical materials, medical machines and equipment and indirect costs. For our study, we worked with one breast surgeon who works in a standardised way. We had one dedicated operating team made up of one nurse, a surgical trainee and anaesthetist for all surgical interventions, thus we limit any potential variability that may arise from the use of different surgical techniques. Through direct observation of the surgical procedures, full lists were made regarding all the medical instruments used in each type of surgical intervention. The per unit cost of the direct medical materials was provided by the pharmaceutical department of the hospital. These costs represent the direct cost the hospital pays to their suppliers for these materials.

For all medical machines and equipment, the annual cost was made up of the maintenance and depreciation costs for a year. Facilities costs were incorporated into the indirect costs of the departments. The full indirect costs covered depreciation and maintenance costs, financial and general costs, heating, administrations, linen, food, personnel accommodation and other medical costs.

The annual practical capacity was calculated for all resources. The practical capacity used within the hospital for in-house medical staff amounts to 1620 hours/year/ person. This amount takes into account all potential vacation days, clinical days and other administrative breaks. The practical capacity for the medical machines is based on the same available number of hours as in-house medical staff. The more senior medical staff employed as independents have a practical capacity of 2400 hours/

year/person. The cost per unit of resources used is displayed in the supplementary Appendix Chapter 3B.

3.2.2. Patient and disease characteristics

Using the general treatment framework, we consulted medical literature and identified several relevant patient and disease characteristics to analyse how these factors impact the costs through their impact on the treatment path. A full overview of the selected patient and disease factors for this analysis is displayed in Table 6 [252–254]. Each treatment step was impacted by the presence of one or more of the listed characteristics. Our analysis focuses on how these factors drive cost differences for patients within and between molecular classifications.

Based on medical guidelines, the starting point for all breast cancer patients is the standard diagnostic process made up of the triple assessment [82]. This allows physicians to confirm the diagnosis and to assess the tumour biology to define the molecular subtype. Historically, clinicopathological parameters such as tumour size, lymph node involvement and histological grade were used to diagnose breast cancer patients [255]. However, the advancement of technology has allowed for greater understanding of the molecular biology of the disease. Biomarkers such as Ki-67 proliferation index, estrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor 2 (HER2) are used to classify patients into molecular subtypes [256]. Several molecular subtypes have been developed using these biomarkers. We focused on the four main subtypes, namely luminal A and B, triple negative and HER2-enriched and use these groupings to stage patients.

Patients classified as luminal A display positive expressions for ER and PR, with the absence of HER2, and have low proliferation and histological grades [252]. In comparison, luminal B subtypes express lower levels for hormonal receptors (ER and PR) but could express positive levels for HER2.

Luminal B classifications are more aggressive due to their higher histological grade and proliferation levels [252, 257]. HER2-enriched cancer displays an overexpression for the HER2 gene pathway [248], and the majority of cases express low levels of hormonal genes [258]. HER2-enriched cancers have high proliferation levels and grade [257]. The triple negative subtype displays low expressions for all three important receptors, namely ER, PR and HER2, and high grade and proliferation are associated with triple negative tumours [259].

Based on the molecular subtype and other classical disease parameters, the MDT determines the possible need for neoadjuvant therapy before surgery. Having completed the diagnostic workout and any necessary neoadjuvant therapy, patients are then expected to undergo a surgery intervention compromising of either breast conservative surgery (BCS) or mastectomy (MX). This decision is largely driven by the severity of the disease and in some cases by patient characteristics pertaining to the presence of oncogenetics. Additional interventions are conducted during the surgery such as the sentinel node procedure and the axillary dissection. Inclusion of these measures are driven by positive results of the biopsy testing during surgery. Following surgery, local adjuvant therapy is then

administered in the form of radiation therapy. The MDT determines the systemic treatment such as adjuvant chemotherapy, adjuvant hormonal therapy and adjuvant Herceptin. The combination of adjuvant therapy is driven by the molecular subtype of the disease as well as the patient and disease characteristics, such as age of patient at diagnosis and higher tumour grade and size.

Table 6. Overview of the patient and disease characteristics based on medical literature

Triple assessment	Further imaging	Prepping	Surgery intervention	Post-surgery intervention	Adjuvant therapy
Patients follow a standardised initial assessment to diagnose patients — triple assessment includes clinical exam, standard imaging and biopsy procedure.	MRI Scan: younger than 40, and/or dense breast tissue, lobular subtype, neo-adjuvant setting, oncogenetic mutation, high proliferation index. Classical imaging (ultrasound of liver, chest X-ray & bone scan): if positive result from triple assessment. Targeted imaging (CT of thorax and abdomen, bone scan, positron emission tomography (PET)/CT—not routinely used): if lymph node positive.	Neoadjuvant setting (chemotherapy +target therapy): triple negative molecular subtype, HER2-enriched molecular subtype, tumour size T4, MDT decision. Tumor localisation: clipping of the tumor.	BCS: T1 or T2, limited ductal carcinoma in situ (DCIS), possibility to obtain free margins with BCS, possibility to give neoadjuvant therapy, good response on neoadjuvant therapy imaging. Mastectomy: No BCS possible, no radiotherapy possible, BMI range impacts operating time, positive oncogenetic testing, positive surgical margins with BCS. Additional surgery interventions: dependent on sentinel node status or histological findings at pathology.	Patients follow a standardised hospitalisation stay after surgery—this includes all postsurgery checks, any psychologist consultations and postsurgery check-ups by the doctor and the nurse.	Adjuvant hormonal therapy: included if hormonal receptor status (ER and PR) is positive. Adjuvant target therapy: HER2-enriched molecular subtype only. Adjuvant chemotherapy: younger than 80 years, MDT decision, triple negative molecular subtype, HER2-enriched molecular subtype, high proliferation index Adjuvant radiation therapy. BCS surgery intervention was incorporated. ME: in selected cases (refer to MDT decision). Additional surgery intervention: MDT decision based on surgical biopsy results.

The time frame used in our generic treatment pathways varied depending on the inclusion of neoadjuvant therapy, the inclusion of local adjuvant radiation therapy and the type of systemic therapy chosen for the patient. On average the diagnostic workup was performed over a maximum of 2 weeks, including the MRI scan. The surgical intervention was performed 1 week after the full diagnostic workup was complete, unless neoadjuvant treatment was required. For neoadjuvant and adjuvant Herceptin therapy, the costs represent the 18 sessions required resulting in an administration timeline of 12 months. For neoadjuvant and adjuvant chemotherapy, the full costing was used for all required sessions which typically lasts 6 months. The costs for local adjuvant radiation therapy represent the 4–5 weeks standard time period. Based on medical guidelines, regarding the administration of adjuvant hormonal therapy, costs were calculated on either 5–10 years, and this information was provided in the patient files. The cost for endocrine therapy has been included in the adjuvant hormonal therapy amount. For the purpose of our analysis we excluded ovarian suppression costs, and we acknowledge that the inclusion of this activity for premenopausal patients will increase treatment costs as this can either be achieved through a surgical intervention or the administration of GnRH analogues. However, this intervention is required only for a subpopulation of patients; therefore, they were not included in our study.

For our analysis, we used a total of 14 patient files to illustrate the effect of several characteristics identified on the generic treatment path and how those subsequently impacted the overall treatment costs for patients. Our reasoning for selecting these 14 patients was to capture a diverse number of characteristics. The selected patients not only had different characteristics across the four molecular subgroups but they also had differences within the molecular classifications. We excluded patients with extreme comorbidities from our analysis. The presence of comorbidities impacts the decision-making regarding the treatment pathway patients follow and subsequently impacts costs. However, the intersection between severe comorbidities and breast cancer fell beyond the scope of our research. The full treatment cost for each patient was calculated based on the medical interventions and the per unit cost calculated using the TD-ABC technique. An overview of the patient files and the relevant characteristics of the patients can be found in Table 7.

Table 7. Overview of patient and disease characteristics of the 14 patient files used

Disease characteristics	Luminal A					Luminal B					Triple Negative	HER2 - enriched		
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**
Molecular receptors*														
ER+	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
PR+	Yes	Yes	Slightly	Yes	Slightly	No	No	Yes	Yes	Yes	No	Slightly	No	No
HER2+	No	No	No	No	No	Yes	No	No	Weak	No	No	Yes	Yes	Yes
Proliferation index (ki67)	5-10%	5-10%	10%	10%	33-50%	15%	25-33%	5-10%	60%	33-50%	90%	75%	50-75%	50%
Classical staging parameters														
Diameter of tumor														
T1: </= 20mm	X	X	X			X	X					X		
T2: 20mm – 50mm					X					X	X		X	X
T3: > 50mm				X										
T4: Inflammatory breast cancer								X	X					
Nodal status														
N0: less than 0.2mm impacted	X	X	X		X	X	X			X		X	X	X
N1: 1 to 3 nodes positive											X			
N2: 4 to 9 nodes positive								X	X					
N3: 10 nodes or more positive				X										
Grade of tumor														
G1: low														
G2: intermediate	X	X	X		X			X	X					
G3: high				X		X	X			X	X	X	X	X
Patient related factors														
Age at diagnosis														
</= 40	X								X	X		X		
40 – 65		X	X	X		X	X				X			X
> 65					X			X					X	
BMI if needed (for Mastectomy)														
< 18.5 (underweight)														
18.5 – 24.9 (normal)		X		X				X		X		X		
25 – 29.9 (overweight)									X					
> 30 (obese)														
Comorbidities present					X	X		X					X	
Oncogenetics present							X		X			X		

**Classification of patients is made on classical histological findings; gene profiling does not take place at this hospital. BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor*

3.2.3. Patient and public involvement

Patients had no influence on the research questions or outcomes of this research. No patients were involved in the design of this study. We used blind patient files; therefore, no patient recruitment took place. We included only certain patient and disease characteristics which were made available to us by the physician, and no personal information of patients was used in this study. Given the nature of removing all personal information, there is no requirement to disseminate the information to patients.

3.3. Results

From the costing results, we identified that a significant variation in treatment costs exists between patients within each molecular subtype as well as across molecular subtypes. Typically for luminal A the cost differential amounts to roughly 166%, and the greatest treatment cost amounts to US$29 780 relative to US$11 208 for a patient requiring fewer medical activities. The major driver of cost is due to disease-specific characteristics such as the higher tumour grade, tumour size and the presence of extensive lymph node involvement. These characteristics may lead to the inclusion of adjuvant chemotherapy as part of the treatment. When focusing our attention on luminal B, we noticed that patients with identical disease characteristics, such as tumour size and grade, resulted in the same overall treatment costs, amounting to US$16 335. However, the treatment costs tend to increase exponentially when the disease characteristics are higher or considered to be more aggressive. Additionally, patient-related factors lead to cost variations for luminal B. We noted that age at diagnosis, particularly patients aged 40 and below, and the presence of oncogenetic factors tend to have higher overall treatment costs due to more aggressive treatment schemes that include neoadjuvant therapy and a combination of surgery interventions and adjuvant therapy. These disease and patient characteristics resulted in a 242% cost difference whereby treatment costs ranged from US$13 435 to US$45 908.

Historically, the triple negative subtype is considered to be a highly aggressive form of cancer. Therefore, costs for this particular subtype are driven by disease characteristics. Based on medical guidelines, neoadjuvant therapy is recommended for this subtype before surgery. Taking this into consideration, the average treatment cost amounts to US$26 923. The final subtype, HER2-enriched, on average has the highest overall treatment cost due to the inclusion of Herceptin as part of the treatment intervention. Therefore, the characteristics of the disease pertaining to receptor status play an important driver of cost for this subtype. HER2-enriched cancer requires treatment against the HER2 receptor. Additionally, like luminal B, the positive presence of oncogenetics and the age below 40 years impact the cost through the inclusion of neoadjuvant therapy and more aggressive adjuvant therapy schemes.

When considering the costs variability across the molecular subtypes, we notice that the more aggressive classifications like triple negative and HER2-enriched are driven by the disease

characteristics. The medical decision-making is heavily influenced by the need to contain the growth of the cancer in the patient. Consequently, the medical interventions needed to treat these types of cancers are more detailed, such as incorporating neoadjuvant therapy into the treatment path, thus by definition leading to cost differences across the classifications. A similar remark can be made about luminal A type cancers that are impacted by the disease characteristics. However, the major motive for costs differences between luminal A, triple negative and HER2-enriched relate to the fact that luminal A type cancer is often considered to be less aggressive. The number of medical interventions required is considerably fewer for luminal A. From our analysis, most luminal A patients did not require extensive adjuvant therapy that generally impacts overall cost. We noted that luminal B is the most complex classification in that the medical decisions taken for this group can be impacted by both patient and disease-related variables. These equally serve as drivers of cost unlike the other three classifications that are largely impacted by disease characteristics only. The full treatment costs covering all the relevant activities for the 14 patients can be found in Table 8.

Table 8. Full cost breakdown calculated based on financial data from the hospital database

Cost breakdown per patient	Luminal A					Luminal B					Triple Negative	HER2 - enriched		
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Classical diagnosing -triple assessment	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**	**$1,005**
Prepping														
Sentinel node scan	$115	$115	$115	$115	$115	$115	$115	-	-	$115	$115	-	$115	$115
Tumor localisation	$425	$425	$425	-	$425	$425	$425	-	-	$425	$425	-	$425	$425
Prepping cost	**$540**	**$540**	**$540**	**$540**	**$540**	**$540**	**$540**	**-**	**-**	**$540**	**$540**	**-**	**$540**	**$540**
Intervention														
Surgery	$1,698	$1,698	$1,698	$611	$1,698	$1,698	$1,698	$611	$611	$2,661	$1,344	$713	$2,661	$1,698
Frozen section testing	$63	$63	$63	$63	$63	$63	$63	$63	$63	$63	$63	$63	$63	$63
Pathology testing	$495	$495	$495	$495	$495	$495	$495	$495	$495	$495	$495	$495	$495	$495
Adj. Chemotherapy	-	-	-	$16,118	-	-	-	-	-	$16,118	-	-	$16,712	$16,712
Adj. Hormonal therapy	$1,095	$2,178	$2,178	$2,178	$2,178	$2,178	$2,178	$2,178	$547	$547	-	$2,178	$2,178	-
Adj. Radiation therapy	$6,934	-	$6,934	$5,662	$4,159	$6,934	$6,934	$5,662	$5,662	$5,662	$6,111	$5,662	-	$6,111
Adj. Herceptin	-	-	-	-	-	-	-	-	$14,587	-	-	$14,587	$16,403	$14,587
Intervention costs	**$10,286**	**$4,434**	**$11,368**	**$25,127**	**$8,593**	**$11,368**	**$11,368**	**$9,009**	**$21,965**	**$25,546**	**$8,013**	**$23,697**	**$38,512**	**$39,667**
Add. hospital expenses														
Consultations	$311	$350	$311	$311	$311	$311	$311	$311	$350	$350	$311	$350	$311	$311
Multi-disciplinary team meetings	$201	$201	$201	$201	$201	$201	$201	$201	$201	$201	$201	$201	$201	$201
1 day ward stay	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161	$1,161
Add. hospital related costs	**$1,673**	**$1,712**	**$1,673**	**$1,673**	**$1,673**	**$1,673**	**$1,673**	**$1,673**	**$1,712**	**$1,712**	**$1,673**	**$1,712**	**$1,673**	**$1,673**
Optional activities														
Further imaging	$566	$678	$566	$678	$566	$566	$566	$566	$678	$566	$566	$566	$566	$566
Additional CT scan	-	-	-	$510	-	$510	$510	$510	-	$510	-	-	-	-
MRI Scan	$674	$674	$674	$674	-	$674	$674	$674	$674	$674	$674	-	-	-
Optional activities costs	**$1,240**	**$1,352**	**$1,240**	**$1,861**	**$566**	**$1,749**	**$1,749**	**$1,749**	**$1,352**	**$1,749**	**$1,240**	**$566**	**$566**	**$566**
Prepping - Neoadjuvant therapy														
Neoadj. Chemotherapy	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	$16,712	**-**	$13,106	$16,712	**-**	**-**
Neoadj. Hormonal therapy	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neoadj. Herceptin	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	$1,816	**-**	**-**	$1,816	**-**	**-**
Additional MRI scans	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	$1,347	-	$1,347	$1,347	**-**	**-**
Cost of Neoadjuvant therapy	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**$19,875**	**-**	$14,453	$19,875	**-**	**-**
Surgery intervention														
Axillary dissection	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Additional surgery	-	$2,165	-	-	-	-	-	-	-	$2,165	-	-	-	-
Total cost	**$14,743**	**$11,208**	**$15,825**	**$29,780**	**$12,376**	**$16,335**	**$16,335**	**$13,435**	**$45,908**	**$32,717**	**$26,923**	**$46,855**	**$42,296**	**$43,450**

**These numbers can also be translated into euros at the currency rate of $1/€0.88*

3.4. Discussion

Given the consistent global rise in healthcare costs, an increased need for understanding cost variability and greater cost transparency has been initiated [30]. Significant value exists when a higher knowledge of cost variability is obtained. Hospitals and management are in a better position to anticipate future spending, make more accurate spending forecasts and make adjustments to their planning and processes [260]. Additionally, understanding cost fluctuations allows for better measurement of inefficiencies and potentially provides solutions for the current reimbursement system [244]. In the current state of the sector, little is known about the true cost of treatment for most diseases. Consequently, this lack of knowledge hampers the efforts positioned towards cost reduction and reimbursement changes. Through our analysis, we focus on understanding how treatment costs vary as a result of several patient and disease characteristics. This perspective enables medical providers and physicians to predict the potential costs of treatment upfront, which is not currently being done [115].

When shifting our focus onto the particular molecular subtypes, we are able to identify specific characteristics contributing to the fluctuations in treatment costs. When looking at the luminal A subgroup, we noticed that disease characteristics impacted the treatment path decision. Luminal A breast cancer is considered to have a less aggressive tumour biology, in comparison with the other molecular subtypes, and has a better prognosis. However, when looking at the patient files we noticed that even within luminal A some patients may have more aggressive cancers. For this particular subgroup, the major driver for decision-making boils down to the characteristics of the disease. Two patients with similar age and patient-related factors have major cost variability. We noted that higher tumour grade, a larger tumour size and the presence of extensive nodal involvement may require the inclusion of adjuvant chemotherapy for treatment, as higher levels of these factors imply that patients are at greater risk [84].

For the luminal B subtype, both patient and diseaserelated factors could potentially play a role on cost variation. In the one instance, patients F and G had vastly similar disease-specific characteristics such as tumour grade, tumour size and nodal status, thus requiring identical treatment interventions resulting in treatment costs totalling roughly US$16 335. Patients H and I had comparable disease characteristics but major differences related to patient characteristics. Patient I was below the age of 40 at the time of diagnosis and tested positive for both the HER2 receptor and the BRC2 mutation gene. The presence of BRC2 potentially translates into an increased chance of locoregional relapse and/or an increase of contralateral breast cancer. These specific patient factors may lead to the inclusion of neoadjuvant therapy (chemotherapy and Herceptin) and may influence the type of surgery, in some cases, with or without prophylactic MX instead of BCS. The inclusion of neoadjuvant and adjuvant therapy potentially increases the overall treatment price by approximately US$34 000.

Both HER2-enriched and triple negative are classified as more aggressive types of cancer. The total costs are largely driven by the increased combination of interventions needed. The tumour grade

and proliferation index for these subtypes are generally higher. Given the name, HER2-enriched patients test positive for the HER2 receptor, requiring either neoadjuvant Herceptin therapy or adjuvant Herceptin therapy. The inclusion of Herceptin into the proposed treatment plan has a dramatic increase in the total costing. The full administration of Herceptin increases the treatment cost by approximately US$16 403 per patient. Therefore, this particular molecular subtype carries an enormous cost burden.

In comparison, triple negative subtypes display negative expression for all receptors. However, both patient characteristics like age and disease characteristics impact the cost based on the treatment decision. High tumour grades and high proliferation grades require more aggressive interventions increasing the cost through the need for treatment regimens which include chemotherapy. The full costing for chemotherapy per patient averages around US$16 415. For the triple negative patient, the inclusion of adjuvant chemotherapy is driven by the high proliferation levels and the grade of the tumour requiring more aggressive treatment.

When shifting our focus to other academic studies, we find one study within breast cancer which has calculated and analysed costs of a particular treatment step, like the radiation therapy, in the entire treatment process [91]. Some studies have used conventional breast cancer staging to calculate costs for each stage using the average cost in hospitals [123]. Additionally, specific medical studies have looked at linking molecular classifications to the prognosis of cancer [261]. Other studies focusing on cost variability have focused mainly on hospital-related characteristics and the impact on average costs. These studies found that characteristics such as the type of hospital structure (public vs private), the level of innovation and medical technology in the institution, the case load of surgeons and discharge dispositions influence costs [119–122].

As part of the value era one of the key reform initiatives to depart from the current fee-for-service reimbursement system is the introduction of bundled payments, whereby the full episode of care is financed. The initiation of bundled payments highlights the need for healthcare providers to predict which patients are at risk of higher treatment costs for a disease [231]. To achieve this, we have to turn our attention to the factors that drive variability. We provide initial insights into the average treatment costs for the molecular subtypes highlighting the cost impact of several disease and patient characteristics on the treatment pathway. By shifting the focus to analysing costs through the perspective of molecular subtypes and identifying the impact of several characteristics on cost, we aim to provide an alternative perspective into the way bundled payments could potentially be introduced.

In addition to generating an alternative approach for dealing with the change in the reimbursement system, we believe that this method could form the basis for other medical domains for future academic research. We chose to analyse patient and disease characteristics within early-stage breast cancer because of the disease's standardised nature. All patients undergo triple assessments for diagnosing, followed by a generic neoadjuvant and adjuvant treatment pathway. However, we recognise that the perspective of understanding cost variability could be applied to other disease domains. Insights could be generated in disease areas which follow a standard diagnosing path, ones with minor surgical

intervention and a generic treatment path postsurgery. An alternative oncological domain that could potentially be interesting to explore would be colon cancer that has standardised biopsy interventions. The field of dermatology serves as an interesting non-oncological domain as the treatment pathology is highly standardised for patients. Additionally, other medical domains that follow a similar disease classification like the molecular subtypes found in breast cancer serve as another interesting medical disease to which this approach could potentially be applied.

Using the generic treatment pathway developed, we provide evidence that significant cost variability exists across molecular subtypes and within molecular subtypes. We provide evidence that patient and diseaserelated factors impact the treatment path and highlight the impact on costs. However, one limitation of our study relates to the fact that limited generalisations can be made given the limited patient data used. For the purpose of our analysis, we selected 14 patient files to provide initial results that cost variability does exist as a result of patient and disease characteristics within the molecular subtypes. We believe that an extension to our research could focus on understanding how and to what extent these characteristics drive or impact cost variability through an empirical analysis using a larger sample size. Furthermore, a larger sample size allows one to explore the statistical impact of several characteristics on driving cost differences. This serves as an interesting avenue for research focusing on understanding cost variability in disease settings.

Another potential extension of this research is to link costs to the quality of care provided to generate insights into cost-effectiveness. With the push towards a value system, studies that focus on both costs and outcomes have become imperative. With the limitation surrounding the availability of quality data, we were unable to provide relevant academic findings for how this alternative perspective could impact the outcomes achieved for treating patients with breast cancer. Therefore, we recognise a need for future research that focuses on costs and their link to quality. By looking at costs and the impact costs have on quality, we move into a realm of being able to provide insights into costeffectiveness strategies. In conclusion, specific patient and disease characteristics play a major role in the treatment interventions and pathway for patients. Each molecular subtype is impacted by the range of patient and disease-related factors. These factors impact the overall cost of treatment within the four major molecular subtypes as well as across the molecular subtypes. Significant cost differences exist across the subtypes due to the severity of the disease, more aggressive forms such as HER2-enriched and triple negative require increased medical interventions leading to higher overall costs. Cost differences within molecular subtypes are driven in part by disease characteristics, but also heavily influenced by patient factors. By using the medical focus of the disease and linking it to costs and understanding the drivers of cost, we move one step closer to making more sound cost reduction decisions.

4. Exploring Costs and Factors Influencing Variability in Psoriasis Care: A Single Centre Study

4.1. Introduction

We have seen tremendous changes in the healthcare system over the past few years, thanks mainly to the growing demand for a value-based system [18]. More specifically, Value-Based Health Care (VBHC) has resulted in a paradigm shift from the classic volume-driven approach, which emphasizes the increased number of services, to one centred around achieving the greatest value for the patient [19, 20].

To achieve value, an essential feature of VBHC links to measuring costs more accurately. Doing so can profoundly affect decision-making and care delivery [21]. Considering what's been done regarding measuring and understanding costs, we see many academic studies across disease domains [262]. However, limited studies look specifically at costs linked to chronic diseases and how, through better cost understanding, we can identify opportunities to modify existing processes to deliver better patient care. Chronic diseases are particularly relevant to investigate, given that patients typically require treatment for extended periods; furthermore, population characteristics are constantly changing, leading to tremendous complexity.

To explore the value of studying costs and how this knowledge can assist in finding ways to modify processes, we select psoriasis, a well-known inflammatory chronic skin disease that impacts the skin and joints and affects roughly 2-3% of the world's population [93]. Additionally, over and above the common symptoms, such as irritated skin, the disease is associated with many coexisting comorbidities, such as psoriatic arthritis (PsA) and obesity [263]. Given its chronic classification, patients carry the disease for life and often experience severity fluctuations over time [264, 265]. From an economic perspective, the disease represents a significant societal burden. Academic studies typically conclude that the condition has resounding effects on patients' work productivity and household income [111, 266, 267], important factors driving the economic burden of the disease. Additionally, the direct medications used for treating psoriasis are tremendous [268], highlighting the load of the disease.

We focus on measuring costs to identify potential redesign opportunities for this disease. Building on our experience in breast cancer [226], we apply Time-Driven Activity-Based Costing (TD-ABC) to measure all the steps linked to the consultation for this dermatological disease. This costing

method was introduced within the VBHC framework to measure costs more accurately and to push for greater cost transparency [26, 30]. TD-ABC has extensively been applied within healthcare for different diseases [27]. From an academic perspective, however, very little is known about the actual costs linked to psoriasis [112]. As a result of this lack of cost transparency, little has been said about potential cost drivers or factors contributing to cost variability for treating psoriasis. Without this narrow view of costs and the respective drivers, we are limited in our ability to make cost-saving improvements that can positively affect the value achieved.

Thus, this academic paper focuses on how having a better view of costs can facilitate potential opportunities to modify how care is delivered. We do this specifically through our measurement and investigation of one component within the treatment pathway of this disease. We specifically focus on the consultations, covering those related to the nurse and physician. Within this setting, patients attending the dermatology department seeking psoriasis treatment have a consultation with a dedicated nurse followed by a consult with the physician. By using TD-ABC to measure the costs of the consultations, this paper aims to do the following: (1) measure costs linked to the consultation component of the treatment pathway (i.e., the dependent variables being the nurse, the doctor, and the total consultation), (2) compare costs of the different dependent variables along the lines of the two types of patient (i.e., known vs. new patients) seeking medical assistance, (3) empirically investigate the cost drivers of the above-mentioned dependent variables against several independent variables linked to the patient (e.g., patient-reported outcomes) and the disease factors (e.g., the severity of the disease), (4) measure the cost of treatment for one year and provide suggestions regarding future reimbursement change (5) and finally, through the investigation of costs and the drivers, we aim to identify opportunities for process improvements within the department to reduce costs linked to the disease. In doing so, we seek to help providers and policymakers make initial adjustments to improve cost-effectiveness while providing high-quality care for dermatology patients.

This study contributes to the continuous discussion centred on healthcare costs and VBHC. By focusing on a specific component of the treatment pathway and identifying particular areas for improvement, we aim to generate cost transparency and identify how more efficiency can be achieved for all stakeholders in the dermatology field. This paper covers the following components: our methodology regarding TD-ABC application, data collection, and analysis. We present the results of measuring consultation costs, yearly treatment expenses, and regression analysis. Finally, we discuss potential avenues for process changes and conclude on future research opportunities.

4.2. Methods

4.2.1. Data collection

Through collaboration with the dermatology department of UZ Ghent, we retrospectively collected patient, disease, and cost data. Initially, we collected data for all patients who attended

consultations at the outpatient clinic, PsoPlus, between May 2019 and March 2020. We excluded patients diagnosed with unrelated dermatological diseases (e.g., eczema); thus, only patients with psoriasis made up our dataset. We employed a data-cleaning strategy to remove all patients with missing data for our independent variables. The ethical committee of the hospital approved this study **(ONZ-2022-0518).** Informed consent was not required as we used anonymized data from patients. We extracted patient and disease-related information in two phases. Initially, the nurse and physician documented several independent variables during the consultation. Secondly, all additional and missing variables were collected using patient medical files.

4.2.2. Patient factors

We collected the patients' ages during the consultation, representing a continuous variable. Furthermore, we collected the gender of the patients as a dummy variable. During the consultation, the nurse calculated the Body Mass Index (BMI); BMI represents an aggravating risk factor for psoriasis [269]. Additionally, we collected information about the personality types of patients. We broke this up into two distinct parts. Firstly, disease burden relates to how psoriasis impacts patients' lives. Secondly, engagement with treatment, how happy patients are with their treatments, whether the treatment has a positive impact, etc. Both variables are composed of eight questions, with scores ranging from 0 to 3, with three being the highest level of satisfaction.

4.2.3. Patient-reported outcomes

The patient-reported outcome collected was the Dermatology Life Quality Index (DLQI). The DLQI is a simple questionnaire comprising ten questions scored between 0 and 3. The questions cover a broad range of topics such as treatment, feelings and symptoms, daily routine, work or school environment, and factors about personal relationships [103]. Scores above ten indicate that the disease severely impacts the patient's life. Like the patient factors, all patient-reported outcomes were collected during the consultation and verified by consulting the medical files at a later point.

4.2.4. Disease-related factors

Disease-specific characteristics collected represent medically reported outcomes as well as patient-reported outcomes. Medically documented outcomes were captured by the Psoriasis Area and Severity Index (PASI) score, which the physician measures. The body is divided into four regions to obtain the PASI score: the head, the trunk, and the lower and upper extremities [99]. A score between 0 and 6 is given for each region, resulting in a final score between 0 and 24. The higher the score, the higher the severity of the disease [101]. Again, these were collected during the consultation and verified by consulting the medical files later.

4.2.5. Comorbidities

Given the chronic nature of the disease and the importance comorbidities play in treating psoriasis, we extracted several data points. Firstly, we noted the existence of PsA; in medical literature, a strong correlation exists between psoriasis patients and the development of PsA [17]. Furthermore, psoriasis impacts patients' mental health [270]; thus, we collected scores relating to the Hospital Anxiety and Depression Scales (HADS). The HADS questionnaire has seven items for depression and anxiety. The scoring ranges from 0 to 3 per question, with 3 denoting the highest level of depression or anxiety. A score greater than eight indicates more significant symptoms of anxiety and depression.

4.2.6. Additional factors

We noted the type of medication prescribed to patients to determine the average treatment costs for a year (i.e., all consultation costs and the cost of direct medicines). While patients could be on combinations of drugs, we only considered the primary medications prescribed for this analysis. Therefore, all patients only had one medication they were on during data collection. There are four main categories of medicine: topical, light therapy, systemic, and biological. The information regarding medication types was used to calculate the average cost of one year of treatment and was not included in our regression analysis as an independent variable.

Moreover, we collected additional information relating to which nurses performed the consultation. The number of years of experience a nurse has typically played a part in the duration of the consultations. We noted whether the physician changed the treatment of a patient during the consultation. When this occurs, the consultation with the doctor takes longer as a medical explanation of the new medication is needed.

Additionally, we noted whether the patient was new to PsoPlus or an existing patient. New patients typically need longer consultations with both the nurse and the doctor, translating into longer times and, thus, higher costs. All data collected was deemed relevant based on existing academic studies and by medical personnel. See Table 9 for a complete overview of the collected data and its descriptions.

Table 9. Overview of the patient and disease characteristics

Patient characteristics	**Description**	**Variable type**
Age	Age of the patient at the time of consultation	Continuous
Gender	Male vs. female patients	Binary (coded as 0 or 1)
BMI	BMI = weight (kg) / height^2 (m^2)	Continuous
Personality type *Burden of disease* *Engagement with the disease*	A questionnaire consisting of 8 questions with scores from 0-3. A score of 3 corresponds to the highest level of satisfaction. Scores ranging from 0-24 Scores ranging from 0-24	Continuous
Patient-reported outcome	**Description**	**Variable type**
DLQI Score	Based on a score between 0 and 30. A higher score corresponds to a more negative impact.	Continuous
Disease-specific characteristics	**Description**	**Variable type**
PASI score	A score between 0 and 6 is given for each body region (divided into 4 parts), thus resulting in a final score between 0 and 24.	Continuous
Comorbidities	**Description**	**Variable type**
PsA	The presence of Psoriatic arthritis	Binary (coded as 0 or 1)
HADS *HADS – A* *HADS - D*	A questionnaire consisting of 7 questions with scores from 0-3. A score of 3 corresponds to the highest level of satisfaction. Scores ranging from 0-21 Scores ranging from 0-21	Continuous
Additional factors	**Description**	**Variable type**
Nurse	Indication of which nurse performed the consult	Binary (coded as 0 or 1)
Switch of treatment	Whether the physician changed the treatment during the consult	Binary (coded as 0 or 1)
Patient status	Whether the patient is new to PsoPlus or existing	Binary (coded as 0 or 1)

4.2.7. Costing data

We collected all cost data in collaboration with the hospital's financial department. Through direct observation of the consultations, we constructed a generic pathway followed by patients. This allowed us to identify all the necessary activities performed (e.g., nurse consultations, doctor consultations, etc.) and the corresponding personnel and facilities. Given the outpatient nature of the disease, no medical machines are used during the consultations.

A critical step in applying TD-ABC relates to the time measurements of the activities. Typically, we use average time stamps for the various activities performed. However, for this analysis, the medical staff used a stopwatch for the time estimates of the consultation; thus, we collected the direct time for all patients (i.e., nurse and doctor consultation). We added an average time of 5 minutes for the interaction with the secretary.

Given the sensitive nature of remuneration data, we used salary scales provided by the financial department for the nurses and the secretary. In contrast, for the physician, we used the exact salary amount. For the costs relating to the consultation room, the facilities department provided a day rate of €111,32, covering all the necessary expenses of the department. We based the practical capacity on the total clinical time available for PsoPlus patients. Thus, we accounted for medical personnel's vacation, clinical, and other administrative breaks. We calculated each resource's capacity cost rates using the salary and facility data and practical capacity cost rates (CCR). Doing so can provide a cost estimate for the nurses, doctors, and total consultations.

We make the following assumptions to measure the costs of one year of treatment (i.e., all consultations and direct medication). We calculate the average consultation cost using the data of returning patients, which amounts to €53.14; this value represents the cost of all future consultations a patient may have. To obtain the exact number of additional consultations, we look at the severity of the disease, the presence of comorbidities, and the type of medication prescribed; thus, patients could have two or three additional consultations in a year. To obtain the cost of the direct medication, we consulted BCFi (https://www.bcfi.be/nl/start), a drug-costing website used by physicians. To calculate the treatment costs for one year, we sum up the costs relating to the consultation we observed, the cost of future consultations, and the costs of the direct medication the patient is on.

4.2.8. Data analysis

The starting point of identifying effective process changes links to a good understanding of costs and the associated drivers; thus, different data analyses were conducted. We calculated the mean, standard deviation, minimum, and maximum costs for the different consultation stages and the costs of one year of treatment. We divide the consultation information according to whether the patient is known or new to the department. We reported the continuous variables' mean, standard deviation, and range of values for the collected characteristics. Additionally, we present the frequency and percentage of occurrence for the categorical variables across each independent variable.

We conducted several tests to understand the relationship between the dependent and independent variables. Firstly, we assessed the relationship using bivariate regressions for the continuous independent variables. Given the use of binary variables for the different categories, we only used the Mann-Whitney U test to understand the relationship with the dependent variables. We found that the distribution of the three dependent variables, the nurse, the doctoral, and the total consultation costs, was normal.

Furthermore, correlations were tested between all the dependent and independent variables to understand the underlying relations. The DLQI score, the variable measuring the impact of disease on quality of life, had a strong positive correlation with the burden of disease personality type ($r = 0.7975$). Additionally, we found a strong positive correlation between the variables HADS-A and HADS-D ($r = 0.7164$), indicating a strong relationship between the anxiety and depression levels of patients. To

account for these strong correlations, we generated interaction terms included as independent variables in the stepwise regression models. However, these interaction terms were insignificant in determining variation in the final regression models; thus, they were not part of the final model. The total correlation matrix is presented in Appendix 4A. We employed a stepwise regression technique with forward elimination to determine the appropriate regression model.

We used a significance level of 0.05 to retain variables in the final model. We performed a diagnostic of the results by assessing the normality of residuals using the Jarque-Bera test; additionally, we examined histograms and Q-Q plots of the data. The residuals' normality was respected for all the doctor and total consultation regression models ($p > 0.063$ and $p > 0.064$); however, it was violated for the nurse consultation. To account for this, we use a natural logarithm (ln) transformation to address this and achieve normality ($p > 0.385$). For the nurse regression, we reported exponential coefficients given the ln transformation. The regression models were checked for multicollinearity using the tolerance and variance inflation factor (VIF). No evidence was found in any of the three regression models. We consolidated all sample data in Microsoft Excel and used the Software Tool for Data Analysis and Statistics, STATA 13 (StataCorp LP, College Station, TX).

4.3. Results

4.3.1. Patient, disease, and other characteristics

82.7% of the patients were aged between 25 and 64, followed by seniors classified as 65 and above (8.6%) and youth (7.9%). The average age of the included patients was 43 years, with a minimum age of 17 and a maximum age of 71. Regarding the gender of patients, males made up approximately 63.8% of the patient population. For BMI, the highest categories corresponded to the normal weight and overweight ranges, with 33.1% of patients, respectively, followed by 32.2% of patients classified as obese. The mean BMI score was roughly 28, with the lowest score of 17.4 and an exceptionally high score of 45.5.

Regarding personality types, approximately 96.9% of patients reported a high level of engagement with the medical disease, while 89.8% of patients found that the disease burden for them was low; the average scores for the personality types were 20 and 5, respectively. For the patient-reported outcome, the DLQI, 57.5% of patients reported a score between 0 and 1, concluding that the disease has no impact on their lives, followed by 18.9% who said the condition has a small impact on their lives. The average score for the DLQI was 3.7.

For the disease-specific factor, 81.1% of the included patients had a PASI score between 0 and 5, thus corresponding to having mild psoriasis. The mean PASI score was roughly 2.5 across all patients.

For the variabilities linked to comorbidities, we noted that only 15% of patients reportedly had PSA. When considering the outcomes relating to HADS-A, 79.5% of patients displayed low anxiety

levels; the average score for this variable was 5. For HADS-D, roughly 91.3% of patients showed low levels of depression, with an average score of 3.

Regarding the additional variables collected, 43.3% of patients had their medication changed during the consultation with the physician. Of the patients included in the dataset, 92.9% were known patients (i.e., having already had treatment previously at the department). Finally, the division of labour between the nurses was unequal; the second nurse conducted 59.0% of all the consultations. Table 10 shows the patient and disease characteristics with their corresponding descriptive statistics.

Table 10. Overview of the patient and disease characteristics

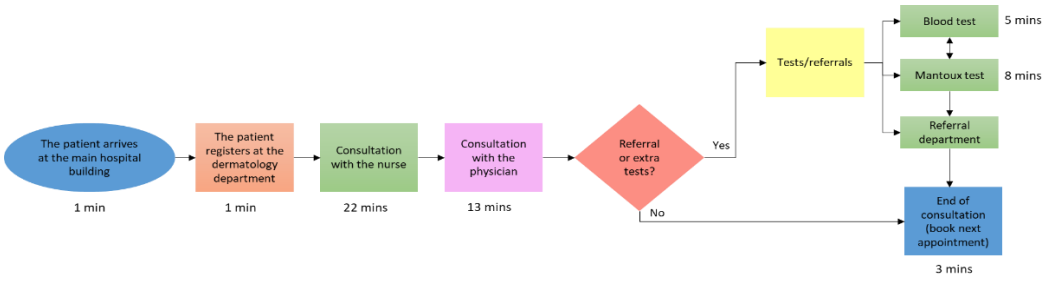
Patient Factors	**All included patients (n = 127) N (%)**	**Mean (SD)**	**Min**	**Max**	**P-value nurse costs**	**P-value doctors costs**	**P-value total consultation costs**
Age		43.4 (14.2)	12	71	0.742	0.474	0.599
Children = 0 to 14 years	1 (0.8%)						
Youth = 15 to 24 years	10 (7.9%)						
Adults = 25 to 64 years	105 (82.7%)						
Seniors = 65 years and over	11 (8.6%)						
Gender		-	-	-	0.168	0.744	0.495
Female	46 (36.2%)						
Male	81 (63.8%)						
BMI		27.8 (5.1)	17.4	45.5	0.487	0.812	0.993
< 18.5 (underweight)	2 (1.6%)						
18.5 – 24.9 (normal)	42 (33.1%)						
25 – 29.9 (overweight)	42 (33.1%)						
> 30 (obese)	41 (32.2%)						
Personality type							
Engagement with disease		20.7 (3.8)	5	24	**<0.001**	**<0.000**	**<0.000**
Low engagement: 0 to 12	4 (3.1%)						
High engagement: 13 to 24	123 (96.9%)						
Burden of disease		5.4 (5.1)	0	24	**<0.000**	**<0.019**	**<0.001**
Low burden of disease: 0 to 12	114 (89.8%)						
High burden of disease: 13 to 24	13 (10.2%)						
Patient-reported outcomes							
DLQI Score		3.7 (5.6)	0	22	**<0.000**	**<0.007**	**<0.000**
No effect on patients' life = 0 to 1	73 (57.5%)						
Small effect on patient's life = 2 to 5	24 (18.9%)						
Moderate effect on patient's life = 6 to 10	13 (10.2%)						
Very large effect on patient's life = 11 to 20	14 (11.0%)						
Extremely large effect on patient's life = 21 to 30	3 (2.4%)						
Disease-specific characteristics							
PASI Score		2.5 (3.7)	0	20.7	**<0.005**	**<0.002**	**<0.000**
Mild = ≤ 0 and < 5	103 (81.1%)						
Moderate = ≤ 5 and < 10	18 (14.2%)						
Severe = ≥ 10	6 (4.7%)						
Comorbidities							

PSA		-	-	-	0.452	0.562	0.514
No	108 (85.0%)						
Yes	19 (15%)						
HADS*							
Presence of HADS-A		4.9 (4.1)	0	17	0.164	**0.077†**	**0.053†**
Low levels of anxiety: 0 to 8	101 (79.5%)						
High levels of anxiety: >8	26 (20.5%)						
Presence of HADS-D		3.1 (3.4)	0	14	**0.071†**	0.188	**0.098†**
Low levels of depression: 0 to 8	116 (91.3%)						
High levels of depression: >8	11 (8.7%)						
Additional variables							
Therapy switch		-	-	-	0.030	**<0.000**	**<0.000**
No	72 (56.7%)						
Yes	55 (43.3%)						
Patient status		-	-	-	**<0.000**	**<0.024**	**<0.007**
Known	118 (92.9%)						
New	9 (7.1%)						
Nurse		-	-	-	0.214	0.848	0.895
Nurse 1	52 (40.1%)						
Nurse 2	75 (59.0%)						
†: significant at 10%							

4.3.2. Patient pathway

Based on the observations of the consultations, we constructed the generic pathway followed by patients (Figure 5). The PsoPlus consultations operate differently from other dermatology departments treating psoriasis. When arriving for their consultation, patients see a dedicated psoriasis nurse first. During these consultations, the nurse asks patients a series of questions relating to their medical files and checks whether changes/additions to the existing information about the patient are necessary. After the consultation with the nurse, the patient sees the physician. The physician examines the patient in line with analysing the severity of the disease. During this time, the doctor can decide if changing the patient's medication is necessary. The consultation ends with a brief word with the secretary, who schedules the patient's next consultation.

Figure 5. Overview of the patient pathway



* All activities performed at the dermatology department of the hospital

4.3.3. Costing data

Using the process maps and the methods outlined for obtaining the costs using TD-ABC, we calculated the cost for the different dependent variables. Given the structure (i.e., patients see both a nurse and a physician) of consultations conducted at PsoPlus as described above, we analyse the costs by dividing the patient into two groups: known vs. new. In doing so, we see that costs vary between patients for the different consultation types. If we focus on the results of the nurse consultation, we see a difference of 137% when comparing the minimum values, €4.89 vs. €11.61. However, the difference between the maximum values is limited to only 16% (€26.28 vs. €30.56). When considering the average cost of the nurse consultation, existing patients have a cost of €13.24, whereas new patients have a cost of €21.05, resulting in a cost differential of 59%. From observing the consultation, we saw that new patients to the department spent more time with the nurse due to the completion of medical files; thus, this could be the reason for cost differences.

Similarly, when considering the cost of the physician in isolation, we see cost differences between the two groups of patients. A percentage difference of 120% is obtained when looking at the minimum costs: €13.65 vs. €30.03. There was no difference between the patient groups' costs when analysing the maximum amounts. Existing patients cost, on average, €37.02 versus new patients, with an average doctor consultation of €50.36. Like the nurse, the doctor spends more time with new patients to understand their history of psoriasis and previous treatments. Furthermore, they take more time to determine an appropriate treatment course moving forward; this increased time with the patient could explain the cost differences between the groups.

Finally, we consider the cost results for the total consultation, considering all the consultations together. As expected, we see the same cost difference in total consultation between the patient groups. The minimum costs for existing patients amount to €25.09, whereas new patients have a minimum cost of €44.53, resulting in a 77% difference. In some cases, existing patients can also take up more time with medical staff, evident in the maximum cost of €93.39. However, new patients still have a higher maximum cost of €109.89. Overall, new patients have, on average, 40% higher costs associated with the consultation than patients returning to the department for a follow-up consult (€53.14 vs. €74.29). We present the cost results for the consultations in Table 11.

Table 11. Breakdown of the costs of the different consultations

	Existing patients	New patients	% difference
Secretary	€2.88	€2.88	-
Nurse consultation			
Min	€4.89	€11.61	137%
Max	€26.28	€30.56	16%
Mean (SD)	€13.24 (€3.77)	€21.05 (€5.81)	59%
Physician consultation			
Min	€13.65	€30.03	120%
Max	€76.45	€76.45	0%
Mean (SD)	€37.02 (€12.75)	€50.36 (€16.39)	36%
Total consultation			
Min	€25.09	€44.53	77%
Max	€93.39	€109.89	18%
Mean (SD)	€53.14 (€14.00)	€74.29 (€20.85)	40%

As previously mentioned, we measure the costs of treatment over one year. To analyse the costs, we divide the patients into their primary medication classifications: topical, systemic, and biological. Not only do we see variations in costs for the consultations, but significant cost variations exist depending on the type of medication used to treat psoriasis. Focusing on the average costs, we see that the yearly average cost of all consultations and topical drugs amounts to €324.93. Patients prescribed biological drugs, however, face an average cost of €11,919.93 for a year. Additionally, patients on systemic medications have an average yearly cost of €1,353.07, a significantly smaller number than those treated with biological drugs.

Furthermore, tremendous variations exist within the different medical categories. For example, the minimum cost for patients on biological drugs is €4,059.47 compared to the maximum of €14,784.61. A factor driving this difference could be the use of generic drugs compared to brand names, whereby generic medications typically cost less. Additionally, we know the yearly costs cover the observed consultation, additional consultations, and medication costs. However, the average cost of the additional consults equals €53.14; thus, if patients require two additional consultations, this value is, at most, €159.42. Comparing this number to the average yearly cost, we can see that the lion's share comprises the medication costs prescribed to a patient. We present the cost breakdown in Table 12.

Table 12. Breakdown of the yearly costs using medical categories

	Min	Max	Mean (SD)
Patients on topical medication	€156.31	€642.19	€324.93 (€183.87)
Patients on systemic medication	€209.24	€9,780.45	€1,353.07 (€1,743.59)
Patients on biological medication	€4,059.47	€14,784.61	€11,919.93 (€2,967.08)

4.3.4. Regression results

For the regression model focused on the nurse's consultation, we found that patient status significantly impacts costs ($p < 0.001$). The results show that when comparing existing patients to new ones, the cost of the nurse consultation increases. As mentioned, new patients require more time with the nurse, most notably in completing the medical files. When patients arrive at their consultation, the nurse asks questions about their psoriasis history and other topics. It takes longer than a returning patient who needs to update some information. Thus, these findings suggest that the increased number of fields to be computed during the consultation may cause cost variability between patients.

Furthermore, we found that patients with a personality type classified as having a high disease burden were a significant factor in driving costs ($p < 0.001$). As patients are categorized as having a higher disease burden, the greater the impact on nurse consultation costs. Patients with a high disease burden typically ask more questions about the disease and treatment options, lengthening the consultation time and impacting costs.

Finally, we see the nurse itself impacts the consultation costs ($p < 0.001$). For our analysis, there was a difference in the age of the nurses conducting the consults. Thus, these results imply that the older nurse takes longer to complete the consultation than the younger nurse. Of course, there are many reasons for this difference, not only age; it is vital to acknowledge that one nurse may have treated more complicated patients who inherently require more time. However, we did not make any adjustments to this. The explanatory power of this regression model reached 30% (Table 13).

Table 13. Regression results for the nurse's consultation

	Coefficient	**Std. Error**	**P-value**	**95% Conf. interval**		**R^2**
Patient status	0.354	0.099	**<0.001***	0.159	0.550	**0.295**
Burden of disease	0.024	0.005	**<0.001***	0.015	0.035	
Nurse	0.154	0.051	**0.003***	0.053	0.255	
Constant	2.233	0.051	**<0.001***	2.221	2.420	

#We used a logarithmic transformation for total treatment costs with a skewed distribution:
$\log Y_i = \alpha + \beta_1 X_i + \varepsilon_i$: β_1 x 100 measures the approximate percentage change in ŷ when x increases by one unit.

* **Significant at $p \leq 0.05$**

The therapy switch ($p = 0.002$) is a significant variable for the doctor's consultation regression model. Treatment switches typically occur when the physician is unsatisfied with the overall performance of a drug prescribed to a patient. If this is the case, the physician takes time to explain the reason for changing the medication and other important implications of new drugs. The results show that a change in therapy leads to an increase in consultation costs.

Furthermore, we found that personality type - engagement with the disease - contributes to cost variability ($p = 0.038$). We see from the results that the consultation cost decreases as engagement with

the disease increases. If patients are highly engaged, they are more likely to follow medical guidelines and adhere to the course of treatment than patients classified as having lower levels of engagement. If patients are highly engaged, the physician will likely spend limited time discussing the disease and answering questions, impacting costs. The explanatory power of this regression model only reached 20% (Table 14).

Table 14. Regression results for the doctor's consultation

	Coefficient	**Std. Error**	**P-value**	**95% Conf. interval**		**R^2**
Therapy switch	8.274	2.581	**0.002***	3.165	13.384	**0.196**
Engagement with disease	-0.720	0.343	**0.038***	-1.400	-0.040	
Constant	49.295	7.836	**<0.001***	33.784	64.805	

#No transformation was performed on the dependent variable:
$Y_i = \alpha + \beta_1 X_i + \varepsilon_i$: β1 is the expected change in the outcome Y_i per unit change in X_i. Therefore, increasing the predictor X by 1 unit (or going from 1 level to the next) is associated with increasing Y by β1 units.

* **Significant at p ≤ 0.05**

For the final regression model, we see the therapy switch as impacting costs (p <0.001). As mentioned before, if the physician decides to change the course of treatment during the consultation, they will spend more time explaining the new drug to the patient. Additionally, the patient is likely to have questions regarding the medication. From the results, we see that when a therapy switch occurs, the total cost of the consultation increases.

Furthermore, we see that patient status plays a significant role in explaining the costs for the total consultation (p = 0.004). If patients are new, this leads to higher total consultation costs relative to existing patients. Again, this potential can be explained by the longer time required by the nurse to fill out the medical file. Additionally, the physician will take more time to get to know the patient and their history with the disease, leading to higher overall consultation costs. The explanatory power of this regression model only reached 22% (Table 15).

Table 15. Regression results for the total consultation

	Coefficient	**Std. Error**	**P-value**	**95% Conf. interval**		**R^2**
Therapy switch	10.593	2.618	**<0.001***	5.411	15.775	**0.224**
Patient status	14.688	5.055	**0.004***	4.682	24.693	
Constant	49.012	1.635	**<0.001***	45.777	52.247	

#No transformation was performed on the dependent variable:
$Y_i = \alpha + \beta_1 X_i + \varepsilon_i$: β1 is the expected change in the outcome Y_i per unit change in X_i. Therefore, increasing the predictor X by 1 unit (or going from 1 level to the next) is associated with increasing Y by β1 units.

* **Significant at p ≤ 0.05**

4.4. Discussion

With the growing need to reduce and curb costs, providers are forced to investigate their internal processes to identify ways to optimize the use of resources and reduce their expenditures [271]. With this in mind, measuring costs accurately and understanding the determinants of variability remains a fundamental consideration for hospitals and policymakers. Currently, in the disease domain of psoriasis, we see a lack of understanding of costs from the provider's perspective. Papers typically look at the societal costs of the disease, i.e., the patient's loss of work and impact on family income or the cost-effectiveness of the medications used for treatment [109–111]. Thus, our analysis aims to provide initial insights into understanding costs in this domain and how using costs can improve existing processes.

When considering the results, we see that patients' status plays a role in driving consultation costs when looking at the results of the regressions and the high-level view of costs. At the time of this analysis, the dermatology department did not distinguish between new and existing patients coming for consultations. Thus, their initial scheduling patterns (i.e., a mix of patients) were neither effective nor efficient for the medical staff involved. If the hospital seeks to optimize its consultation schedule, one way to do this is to reorganize the consultation to account for these patient differences. Operations management literature frequently discusses approaches for scheduling rules within hospitals. Cox et al. (1985) investigate several methods of using new and returning patients to an ear, nose, and throat clinic to improve patient waiting times and utilization [272, 273]. By taking this approach, the department could move towards dedicated intake and follow-up consultation days, which may lead to better use of expensive resources and create more efficiency as medical staff have to perform similar steps for different categories of patients. Of course, we recognize that patients are complicated, and this solution may not improve the consultation process drastically, but it could assist with creating more lean consultation processes.

Additionally, the regression results show that personality type is essential in driving cost variations between patients. If the department aims to optimize its care delivery, it could use these findings to its advantage. The personality types in question are obtained via a questionnaire; thus, one could consider having patients complete the survey when booking their appointment. That way, the department knows the different personality types of the patients upfront. One suggestion could be to educate staff on how to deal with the different types of patients and the typical issues they face. For example, educational material that covers all the FAQs relating to the disease and the medication they will take could be developed. Evidence shows that educational material positively impacts patients and can reduce resource utilization [274].

Furthermore, adjustments could be made to optimize the consultation schedule. Patients categorized as having lower levels of engagement and a higher disease burden can be grouped and scheduled together as they typically require more consultation time. They could be assigned to designated staff with the appropriate training. In doing so, we could optimize resources and expand the

discussion around personalized care. Personalized health care represents a medical approach prioritizing patient involvement, prevention, prediction, collaborative decision-making, and care coordination to enhance outcomes while managing costs [275–277]. Evidence suggests that if patients are knowledgeable about their disease and have confidence in managing it, greater outcomes, lower costs, and higher satisfaction with healthcare experiences can be achieved [278, 279]. The regression results of the doctor's consultation show that patients with higher engagement with the disease decrease consultation costs, potentially supporting this viewpoint. Of course, we understand that a potential drawback means all patients must book their appointments via an online system, which requires a significant financial investment. However, an integrated information system is necessary if providers want to implement VBHC effectively [21].

As mentioned, we measure costs linked to one year of treatment, given the limited view of costs for this disease from an academic perspective. From this analysis, we see that the direct costs of medication carry the bulk of the expenses for our patients. These findings are supported by Burgos-Pol et al. (2016), who conducted a systematic review of psoriasis costs for several European countries, taking a societal view. They find the average costs for treating psoriasis to be between $2,077 and $13,132, similar to our results. They concluded medication was the major contributor to annual costs, specifically using biological medication to treat more severe patients [107]. Given the financial burden experienced globally, reimbursement changes are an important topic to touch upon and whether they would be appropriate for this chronic disease domain. When we measure costs with a longitudinal view, several challenges come to light, making reimbursement initiatives like bundled payments very difficult. Firstly, it is hard to predict upfront how well patients are doing on a particular course of treatment; this can only be determined at the time of the consult. This factor makes it extremely difficult to determine which bundle will be appropriate for a patient. Secondly, patients are highly complex, which implies severity is not necessarily stable and can fluctuate regardless of treatment [264]. For example, evidence supports the claims of a relationship between psychosocial stress and the worsening of psoriasis [280]. Thus, multiple bundles would need to be constructed to account for the fluctuation inherently linked to this disease. Thirdly, the patient demographics, i.e., age, BMI, etc., can change over time, further highlighting the complexity of the disease and making implementing an appropriate reimbursement system very challenging. If we seek to use medications to determine changes to the reimbursement system, we could consider doing so specifically for biological drugs. Following medical guidelines, once patients are prescribed biological drugs, they will likely remain on these or move to other biologics for several months and, in certain instances, years [281]. Thus, fluctuations in patient demographics and other characteristics are irrelevant. Therefore, bundled payments may be appropriate for these clusters of patients prescribed biological drugs for an extended period.

If we shift our focus to costs, we see a large body of literature demonstrating the value of implementing TD-ABC within departments for various diseases. For example, in a systematic review conducted by Etges et al. (2020), they looked at the impact of TD-ABC specifically for inpatient

management. Their analysis concluded that a clear view of costs was obtained by implementing TD-ABC, which could further support providers seeking to increase value via greater transparency [41]. Numerous other studies provide similar findings in that TD-ABC allowed hospital management to advance their strategy, identify variations in processes causing inefficiencies, and make informed decisions regarding resource allocation [44, 48, 282].

While costs run rampant, we struggle to find studies using TD-ABC to measure cost within dermatology, specifically psoriasis. We recognize that TD-ABC is not the only suitable method, and other approaches have been used within dermatology; thus, when broadening our scope, we find one interesting example by Papadaki and Popesko (2015). Their investigation showed the benefits of using Activity-Based Costing (ABC) to calculate costs for treating skin disorders like psoriasis, varicose ulcers, and eczema. The authors compared the ABC system to the traditional costing system in the hospital. They concluded that they obtained more accurate costing results using ABC and highlighted the benefits of greater access to information for managers looking to reduce costs [283].

Thus, we aim to contribute academically to the field of dermatology with our findings. Though we take a limited perspective, the consultation view only, our findings offer insights into how providers can use cost information to improve their processes to achieve better care delivery. While the findings of this study are highly relevant, several important limitations should be mentioned.

We take a limited view of the treatment pathway; we only consider the costs of consultations within the dermatology departments, not the costs of treating patients' comorbidities. At the time of data collection, patients could decide where they would seek services for comorbidities; thus, this perspective fell outside the scope of this study. However, taking the VBHC perspective, it becomes crucial to consider these costs if we move towards a value system whereby we treat patients for a given disease and the related comorbidities. Given the proximity of psoriasis and several comorbidities, it would be interesting to consider the associated costs and the corresponding drivers of the referral departments treating the comorbidities for these patients.

Moreover, given the structure of PsoPlus, which is unique to the specific hospital in question, we might be limited in generalizing our findings to other dermatology departments. Most other dermatology departments operate differently; most patients only see a physician during their consultation. Thus, one consideration for future research may be to conduct a similar analysis at a department closely linked to clinical guidelines for treatment. To broaden the scope, benchmarking across different dermatology departments may be interesting to deepen our understanding of costs and cost variability drivers for this disease and ensure equal care delivery.

In addition, the explanatory power of all three regression models is limited. These findings lead us to believe that additional independent variables may contribute to explaining consultation costs even more. However, this in no way limits our conclusions. As mentioned, very little is known about costs from the provider's perspective for psoriasis. Thus, through our research, we aim to contribute to the literature on costs in a dermatology setting.

Finally, we take a narrow perspective on costs, namely consultation costs. Further analysis could be done whereby we measure the outcomes and costs of patients on a longitudinal basis. Within psoriasis, little is known about the outcomes achieved in everyday clinical practice, making it extremely difficult to link costs to outcomes and obtain a corresponding value score. More research is needed to measure outcomes and advance the discussion on obtaining greater value.

4.5. Conclusion

In conclusion, we propose how the department could modify its care pathway to optimize its processes and impact care delivery. By using TD-ABC, we could measure the costs linked to the different types of consultations. Additionally, through empirical analysis, we identified patient status, personality type, the nurse conducting the consultation, and therapy switch as relevant drivers of cost variability. Through our investigation of costs and the associated drivers, we could offer suggestions on how the dermatology department could reorganize itself to optimize the use of expensive resources. These findings highlight the importance of studying costs and how they could be used to improve business operations management.

5. Cost Variability Drivers in the Treatment of Luminal B Early-Stage Breast Cancer

5.1. Introduction

We have seen a steady migration of the healthcare sector towards a value-based care delivery model over the years [18, 284], thanks to the introduction of the Value-Based Healthcare (VBHC) framework by Porter and Teisberg [18]. The framework was presented as the solution to the sector's challenges. The increase in the aging population, the persistent financial pressure, and, notably, the acknowledgment that the current fee-for-service system no longer aligns provider incentives with patient outcomes are some factors contributing to the need for change [24, 30, 72]. While the framework consists of several elements, the overarching argument centres around achieving the highest value for patients [21], with value defined as the health outcomes achieved per unit cost of treatment [20, 285].

As VBHC gained popularity, a growing body of research emerged, with academic studies taking two perspectives, one measuring medical outcomes and the second the accurate measurement of costs [27, 41, 286]. Despite academic progress, the rise in healthcare expenditure continues, enhancing the need for policymakers, scholars, and providers to understand costs. Previous studies point to the fact that increased cost transparency results in a better understanding of costs and identifying relevant drivers of costs [262]. These insights provide essential information for stakeholders to make impactful adaptations to cost-reduction strategies and assess ways to modify the reimbursement system. As part of the VBHC framework, one costing method suggested to assist with this is Time-Driven Activity-Based Costing (TD-ABC) [18].

TD-ABC is an accounting method used across industries to measure the cost of providing a service or producing a product by estimating resource use and understanding workflows [43]. It was developed as an alternative to traditional Activity-Based Costing (ABC) to address limitations faced by practitioners when applying the approach to their organizations. TD-ABC differs from ABC by employing a time-based approach, where the cost of activities is estimated based on the required time [26]. TD-ABC was suggested as the ideal costing method to measure the cost component within the VBHC framework [30, 287]. The ease of implementation and focus on two key parameters - the resource unit cost and the time required for each activity - have contributed to its increasing popularity and widespread use [30, 45, 288].

TD-ABC has proven to be a valuable tool for healthcare managers, offering practical operational improvement solutions [289]. The bottom-up costing approach ensures costs are measured more accurately at the patient level instead of at a broader cost or service level [42]. The patient-level perspective creates flexibility to add additional activities based on the needs of patients, capturing the system's complexity [43]. According to Porter, patients often require varying levels of care, translating into resource use fluctuations and cost variation [30]. The dynamic nature of TD-ABC provides opportunities for in-depth analysis of population variability. It helps identify cost drivers, making it easier to move towards risk stratification, an important consideration for future alternative payment models [44]. Since the introduction of VBHC, we have seen an increase in the number of studies applying TD-ABC to health care [27, 290], mainly focusing on identifying cost-saving opportunities and improving resource management. However, the discussion regarding the significance of TD-ABC in the context of reimbursement changes often remains limited despite its valuable insights into cost perspectives and variability.

To show the value TD-ABC can bring to reimbursement decisions, we selected breast cancer as the disease of focus. Breast cancer remains the most prevalent cancer among women across the globe, and its incidence continues to rise [291]. We specifically study the molecular subtype luminal B, the most biologically distinct subtype, resulting in a wide range of treatment options [292]. Luminal B is commonly detected and represents an aggressive form of breast cancer [293, 294]. It is characterized by low estrogen (ER) and progesterone receptors (PgR) [295] and a high proliferation index (Ki63) [296]. In some cases, the expression of growth factor receptor genes universally referred to as HER2-enriched is found [257]. The longitudinal nature of the disease and the variety of therapies available enhance the reasoning for investigating this disease.

Amidst the intricate nature of the disease, a closer examination of the existing literature on breast cancer costing unveils a predominant reliance on claim data for cost assessment [119–122]. While we value the large quantities available within these datasets and the results obtained within these studies, Porter argues that actual costs should be measured to move the sector toward achieving value [21]. These findings highlight the relevance of our contribution to moving towards a narrative of using actual costs as opposed to claims data to make more informed decisions within the sector, particularly generated towards influencing reimbursement reform.

The present study employs TD-ABC to estimate treatment expenses and pinpoint the elements contributing to the cost variance for early-stage luminal B breast cancer cases. Our investigation delves into the drivers of cost fluctuations on two tiers: the full treatment cycle and the surgical facet of the clinical pathway. By systematically examining costs and identifying relevant cost drivers, our study seeks to enhance the dialogue on using cost data to develop more effective reimbursement strategies, alleviating the system's financial stress. Through exploring costs, we aspire to pave the way for insightful discussions that harness the understanding of costs as a catalyst for effective reimbursement transformations.

5.2. Methods

We employed an empirical retrospective study design to measure costs over the entire care cycle. We conducted our research at the breast clinic of AZ Sint-Blasius Dendermonde, a general hospital in Belgium. A multidisciplinary team (MDT), responsible for all medical decisions, provides care to all patients at the clinic. All patients are surgically treated by the same oncoplastic surgeon, thus controlling for hospital and physician variability. The ethical committee of the hospital approved this study **(B0122021000004).** Informed consent was not required as we used anonymized data from patients.

5.2.1. Data collection

We collected data from patient files of individuals who received treatment for early-stage invasive luminal B breast cancer between January 2018 and December 2020. As mentioned above, luminal B cancers translate into significant variations in treatment when compared to other molecule subtypes, making it highly relevant to investigate. We excluded patients with different molecular cancer subtypes based on this narrowed focus. Additionally, we excluded male patients due to the limited occurrence of breast cancer in this gender group.

Following the steps suggested when applying TD-ABC, we initially developed process maps detailing the necessary activities and resources for treating patients throughout the care cycle [290]. We built on previous research at the same institution, which involved constructing detailed generic treatment pathways for patients. One can find a complete overview of the generic treatment pathway in the supplementary appendix of our previous publication [226].

We developed these pathways by directly observing activities and conducting face-to-face interviews with the medical staff and physicians. During the interviews, the medical staff and physicians provided average time estimates for all common activities identified during the process mapping. To supplement the surgery times, we obtained actual time stamps from the ICT system of the operating room. This approach for time estimates aligns with how existing literature suggests collecting them [27]. The complete care cycle includes triple assessment (clinical exam, standard imaging, and biopsy procedure), neo-adjuvant therapy when required (chemotherapy and target therapy), surgical intervention (breast-conserving surgeries (BCS) or mastectomies (ME) along with either sentinel node biopsies (SNB) or axillary lymph node dissections (ALND), additional breast surgery for some patients, a post-surgery stay, and all activities related to adjuvant treatment (chemotherapy and target therapy, radiation, and hormonal therapy).

5.2.1.1. Cost data

We collaborated with the finance department to obtain all financial data from the hospital's accounting system. The costs used in the study are from the hospital's perspective. Given the sensitive

nature of remuneration data, we consulted a published study that measured salary data in Belgium using a cost-based pricing approach to determine personnel costs. The Belgian Health Care Knowledge Centre conducted the research, which they published in 2012 [251]. We applied an indexation of 12.7% to the salary amounts to account for inflation, ensuring the wages were comparable to the actual salaries of the hospital. The personnel costs include the annual salaries paid by the employer and all social contributions. To determine the practical capacity, we distinguished between in-house medical personnel and senior medical staff operating independently (i.e., not formally employed by the hospital). We used 1,620 hours for the in-house medical team and 2,400 hours per year for senior medical staff; the hospital provided the practical capacity amounts. These capacities consider all possible vacation, clinical, and administrative breaks.

We calculated the machine costs based on the annual depreciation of its actual purchase value using the straight-line method over five years. Additionally, we took into account all maintenance costs for the machines. We based the practical capacity of the machines on the working hours of the in-house medical staff. Facilities costs for each department included all maintenance and depreciation expenses. Indirect costs for the departments, including food, linen, heating, and electrical fees, were included in addition to maintenance and depreciation costs. The pharmaceutical department of the hospital provided the unit cost of the direct medical materials used during surgery and the cost of neo-adjuvant and adjuvant medication. We again applied the in-house medical staff's practical capacity to calculate the facilities' practical capacity. We calculated the resource cost for the general hospital as a flat rate representing the amount reimbursed for a one-day hospital stay, with 24 hours as the practical capacity for this resource.

Using financial data and practical capacity rates, we calculated each resource's capacity cost rate (CCR). These rates were allocated to patients via timestamps to calculate the total treatment costs based on the activities in their medical files. It is important to note that the same operating team, consisting of a breast surgeon, a nurse, an operating room assistant, and an anaesthetist, performed all surgeries. We made no adjustments to the time of activities based on the characteristics of patients. The CCR used can be found in Appendix Chapter 5.

5.2.1.2. Clinical data

We extracted several patient and disease factors from the patient's electronic health records to investigate which characteristics impact cost variability. The continuous variables we recorded were age at diagnosis, the patient's height, and body mass index (BMI). Medical literature shows that women diagnosed with breast cancer before age 40 typically develop more aggressive cancers, requiring equally aggressive treatment interventions. As women age, the risk of developing breast cancer increases [297, 298]. Research shows higher BMI scores are linked to postmenopausal cancer [299].

We extracted the menopausal status of women at the time of treatment. Menopausal status can affect the prognosis of breast cancer [300]. Based on the clinical and chemical confirmation, we coded this variable as pre, peri, or post-menopause [301]. The number of pregnancies (e.g., one, two,, or more) was noted. Information about other risk factors, such as comorbidities and familial occurrence [302, 303], was gathered. For comorbidities, we used the total number registered per patient to code this variable (e.g., zero, one, two, etc.). For familial occurrence, we noted whether there was any family history of breast cancer or other cancers. On average, women who report familial cancer have a higher probability of developing breast cancer in their lifetime [303].

It should be noted that the breast clinic performs multiple gene panel testing for Hereditary Breast Ovarian Cancer (HBOC) on patients who meet the a, b, and c testing criteria. Some of these gene mutations moderately to strongly increase the risk of cancer developing [302]. For patients who tested positive for a, b, and c criteria, we recorded whether they opted for different surgery or breast reconstruction at a later stage and the positive presence of a genetic mutation (coded as 0 or 1). We also documented which patients required the insertion of an intravenous portal catheter for chemotherapy during their breast surgery (coded as 0 or 1). Additionally, we noted whether the tumour was multifocal or unifocal. Multifocal tumours are found in multiple locations within the same quadrant, while unifocal tumours are located in a single spot [304], coded as 0 or 1.

We collected classical diagnostic parameters, including the diameter of the tumour (T), nodal status (N), and tumour grade (G). For the diameter of the tumour, T1 served as our reference group, while T3 and T4 (T3: > 50mm and T4: inflammatory breast cancer) were combined into one group. For nodal status, we combined N2 and N3 (N2: 4 to 9 nodes positive and N3: 10 nodes or more positive) into one group and used N0 as the reference. G1 (G1: low) served as our reference group for tumour grade. Additionally, we considered pathological staging biomarkers such as the Ki-67 proliferation index (Ki-67 < 20% served as the reference group), ER, PR, and HER2 as independent categorical variables coded as either 0 or 1. However, for patients who received neo-adjuvant/systemic treatment (chemotherapy and/or target therapy) before surgery, the outcome of the clinical staging was used instead. The abovementioned disease factors are critical in determining patients' treatment pathways [305].

5.2.2. Data analysis

We calculated the mean costs for each building block in the treatment path using TD-ABC; these include the triple assessment, neo-adjuvant therapy, surgical intervention, post-surgery stays, and adjuvant therapy. We reported each main cost segment's standard deviation, minimum, and maximum amounts. Furthermore, we provided the frequency for each cost segment, noting that not all patients underwent the same treatment interventions. We base the overall cost for each component on the CCR and the time spent on each activity.

Regarding the patient and disease factors, we reported the continuous variables' mean, standard deviation, and range of values. We calculated the frequency and percentage of occurrence for the categorical variables across each independent variable. We conducted the following tests to understand the relationship between the independent and dependent variables. For the continuous independent and dependent variables, we used bivariate regressions. The Mann-Whitney U test was used for the dummy variables. The Kruskal-Wallis test was used when variables had more than two outcomes.

Moreover, correlations were examined among all the dependent and independent variables to gain insight into the underlying relationships. A strong correlation was identified between age and menopausal status ($r = 0.7717$). We introduced an interaction term as an independent variable in the stepwise regression models to address these robust correlations. This interaction term, however, did not exhibit significance in explaining the variance within the final regression models. As a result, it was excluded from the final model. The comprehensive correlation matrix is available in Appendix 4AK.

Upon investigating the two dependent variables, treatment, and surgical costs, we identified skewness and kurtosis, resulting in a heteroscedastic variance of errors. The dependent variables underwent a natural logarithm (ln) transformation to address this and achieve normality. The ln transformation significantly improved the skewness and kurtosis of the distributions for treatment costs (skewness = 0.0155, kurtosis = 0.6435) and surgical costs (skewness = 0.0061, kurtosis = 0.4672).

We ran a stepwise regression with forward elimination, including all the abovementioned patient and disease characteristics. The literature commonly uses stepwise linear regression for variable selection to identify appropriate regression models [306]. To determine the variables retained in the model, we utilized a significance level of 0.05. Furthermore, we assessed the presence of multicollinearity using the tolerance and variance inflation factor (VIF). We did not find multicollinearity in either model. We performed regression diagnostics using the coefficient of determination (R^2) and analysed the residuals. To assess normality, we examined histograms and Q-Q plots of the data and conducted the Jarque-Bera test. We respected the normality of residuals for the total treatment and surgery cost regression ($p > 0.122$ and $p > 0.557$, respectively). For both regressions, we reported exponential coefficients given the ln transformation. We consolidated all sample data in Microsoft Excel and used the Software Tool for Data Analysis and Statistics, STATA 13 (StataCorp LP, College Station, TX).

5.3. Comparison between claims and TD-ABC data

In the content of VBHC, TD-ABC is the suggested technique to use when measuring costs more accurately to find ways to optimize and achieve efficiency gains. However, as mentioned before, many studies analysing costs in breast cancer continue to use claims data instead of real costing data. While discussing which method is superior in achieving efficiency is not the paper's objective, comparing claims data and TD-ABC is relevant to further the debate on costs and cost variability. To add to the discussion, we selected 19 patients from the 106 files under the guidance of the breast doctor to make

a cost comparison. As we used the exact timing obtained from the ICT department for determining operating costs, we deemed this the most relevant component of the pathway to compare. Only costs directly linked to time were included in the analysis; thus, the cost of the direct materials used was not included. The 19 patients represent a mix of the four distinct surgical types, allowing for a fair comparison between the two costing methods. The financial department provided all cost charge numbers, concise explanations of these charges, and the amounts of their respective claims. These claims amounts were compared for the costs calculated using TD-ABC for the operating room intervention.

5.4. Results

5.4.1. Patient and disease factors

After applying the exclusions and removing patients with missing data points, we obtained a dataset of 106 patients. The analysis included women aged 40 and 65, comprising 49.1% of the total patients. The minimum and maximum ages were 36 and 89, averaging 63 years. For BMI measurement, we found 38.7% categorized as overweight, followed by 34.9% classified as in the normal BMI range. We registered the fewest number of women in the premenopausal group, only 7.5%. This was followed by 17.0% in perimenopausal women and the majority, 75.5%, in postmenopausal women. 24.5% of the women had either hypertension or obesity as comorbidities.

Breast cancer was only found in 37.7% of patients for familial occurrence, followed by 16.0% who reported both breast and other types of cancer (e.g., ovarian cancer). No previous history of cancer was recorded for 46.2% of women. For the number of pregnancies, 32.0% of women had one, followed by 30.2% who had two. 4.7% of patients required the placement of an intravenous port for chemotherapy during surgery. Finally, 2.8% required reconstruction surgery and tested positive for the HBOC gene panel testing.

All patients included in the study tested positive for ER. Based on pathological outcomes, 76.0% of patients tested positive for PR, 32.1% for HER2, and 60.4% had a proliferation index (ki63) within the 20-50% range. For the diameter of the tumour, a large concentration of patients, 48.1%, had a tumour size between 20 and 50 mm (T2); this was closely followed by 43.4% with a tumour size less than 20 mm (T1). 59.4% of patients had N0 for nodal status, indicating a maximum lymph node involvement of 0.2 mm. And finally, for the grade of the tumour, a high-grade tumor, G3, was found in 59.4% of the patients, and only 15.0% had multifocal tumours.

Regarding surgical interventions, we noted the different surgeries performed: 76.4% of patients underwent breast-conservative surgery, followed by 23.6% requiring mastectomies. In 11.3% of the patients, further breast-conservative surgery was necessary. Table 16 provides an overview of the study's included patient and disease-specific characteristics.

Table 16. Overview of Patient and Disease Characteristics

Patient & disease factors	All patients n=106 (%)	Mean (SD)	Min	Max	P-value total costs	P-value surgery costs
Age at diagnosis		**63.1 (± 13.0)**	**36**	**89**	**<0.002**	0.146
≤ 40	8 (7.5%)	38.4 (± 1.4)	36	40		
40 – 65	52 (49.1%)	55.5 (± 7.0)	40	65		
> 65	49 (46.2%)	74.4 (± 6.9)	65	89		
BMI		**27.2 (± 5.5)**	**18.1**	**44.7**	0.487	**<0.020**
< 18.5 (underweight)	2 (1.9%)	18.1 (± 0.9)	18.1	18.2		
18.5 – 24.9 (normal)	37 (34.9%)	22.2 (± 1.9)	18.6	24.8		
25 – 29.9 (overweight)	41 (38.7%)	27.3 (± 1.4)	25.3	29.4		
> 30 (obese)	26 (24.5%)	34.8 (± 4.1)	30.1	44.7		
Height (m)		**1.6 (± 0.1)**	**1.5**	**1.8**	0.902	0.928
< 1.6	25 (23.5%)	1.5 (± 0.4)	1.5	1.6		
1.6 – 1.7	62 (58.5%)	1.6 (± 0.3)	1.6	1.7		
> 1.7	19 (17.9%)	1.7 (± 0.4)	1.7	1.8		
Menopausal status					**<0.021**	0.463
Pre-menopause	8 (7.5%)					
Perimenopause	18 (17.0%)					
Post-menopause	80 (75.5%)					
Comorbidities*					0.282	0.765
Diabetes	8 (7.5%)					
Heart disease	12 (11.3%)					
Kidney	8 (7.5%)					
Hypertension	26 (24.5%)					
Hypotension	2 (1.9%)					
Obesity	26 (24.5%)					
Auto-immune disease	5 (4.7%)					
Familial occurrence*					0.768	0.363
Breast cancer only	40 (37.7%)					

Breast and other cancers	17 (16.0%)					
No previous history	49 (46.2%)					
Number of pregnancies					0.450	0.944
0	13 (12.3%)					
1	34 (32.0%)					
2	32 (30.2%)					
3 or more	27 (25.5%)					
Genetic Mutation confirmed	3 (2.8%)				0.299	**0.075**
Reconstruction post-surgery	3 (2.8%)				0.249	**<0.011**
Intravenous port chemotherapy required	5 (4.7%)				0.213	0.213
Molecular receptors						
ER+	106 (100.0%)					
PR+	71 (76.0%)				0.446	0.411
HER2+	34 (32.1%)				**<0.000**	0.319
Ki-67 index					0.271	0.354
< 20%	18 (17.0%)					
≥ 20 and < 50%	64 (60.4%)					
≥ 50%	24 (22.6%)					
Classical staging parameters						
Diameter of tumour					0.233	**<0.009**
T1: ≤ 20mm	46 (43.4%)					
T2: 20mm – 50mm	51 (48.1%)					
T3: > 50mm	5 (4.7%)					
T4: Inflammatory breast cancer	4 (3.7%)					
Nodal status					0.099	**<0.000**
N0: less than 0.2mm impacted	63 (59.4%)					
N1: 1 to 3 nodes positive	31 (29.2%)					
N2: 4 to 9 nodes positive	8 (7.5%)					
N3: 10 nodes or more positive	1 (0.9%)					

Grade of tumour					0.037	0.227
G1: low	5 (4.7%)					
G2: intermediate	38 (35.9%)					
G3: high	63 (59.4%)					
Multifocal tumour					0.930	0.593
Yes	16 (15.0%)					
No	90 (85.0%)					
Additional factors noted						
Surgery type						
Breast conservative surgery	81 (76.4%)					
Mastectomy	25 (23.6%)					
Additional surgery	12 (11.3%)					
* Not mutually exclusive ranges						

5.4.2. Treatment costs

Using TD-ABC, we found that the mean and median total cost per patient were €30,033 and €15,330, respectively (IQR: €32,277 - €13,715). Total treatment costs ranged between €5,219 and €123,683, with a standard deviation of €27,530. All 106 patients underwent the triple assessment to diagnose luminal B breast cancer. The costs of diagnosing breast cancer ranged between €2,149 and €2,892, with a mean and median cost of €2,701 and €2,827, respectively. The triple assessment step represented 14.9% of the total costs.

Seven patients required neo-adjuvant therapy, an intervention necessary before surgery to reduce the tumour size. Three treatment options exist for neo-adjuvant therapy: chemotherapy only, a combination of chemotherapy with trastuzumab, and finally, chemotherapy with trastuzumab and pertuzumab; these drug combinations resulted in a mean cost of €15,460, €22,616, and €37,797, respectively. It is evident from the average prices that the drug mix utilized significantly drives up total treatment costs.

The entire surgical intervention step accounted for 13.8% of the overall costs, with an average cost of €2,389 and €2,289, respectively. Costs increased by approximately €875 for additional surgery, such as a mastectomy or breast conservation surgery. Post-surgery stay costs were standardized for all patients and included a flat hospitalization rate. The cost per patient amounted to €1,185.

Adjuvant therapy comprised approximately 61.9% of the total cost for patients. The administration of adjuvant treatment resulted in the highest increase in cost. The drug mix of

chemotherapy with trastuzumab and pertuzumab resulted in an average cost increase of €87,148. Radiation therapy, which was necessary for 88.6% of patients, resulted in an average cost of €6,364. The cost variation between the minimum and maximum amounts, €5,576 and €6,829, respectively, was relatively limited. Finally, hormonal therapy was necessary for 93.4% of patients. These costs ranged between €476 and €1,729, with an average cost of €1,285 per patient. Table 17 provides a complete breakdown of costs.

Table 17. Breakdown of cost components

Cost components (€)	# of Patients	Mean	Std. Dev	Min	Max
Diagnosing – triple assessment	106	2,701	271.62	2,149	2,892
Neo-adjuvant therapy					
Chemotherapy*	2	15,460	-	15,460	15,460
Chemotherapy +Trastuzumab*	2	22,616	-	22,616	22,616
Chemotherapy + Trastuzumab + Pertuzumab	3	37,797	1,005	37,217	38,958
Surgical intervention					
Breast conservative surgery	81	2,289	499	1,464	3,733
Mastectomy	25	2,389	518	1,793	3,712
Additional surgery	12	875	434	277	1,795
Post-surgery hospitalization†	106	1,185		1,185	1,185
Adjuvant therapy					
Chemotherapy	27	16,000	3,335	2,921	17,780
Chemotherapy + Trastuzumab	14	44,424	7,614	26,986	49,603
Chemotherapy + Trastuzumab + Pertuzumab	6	87,148	21,869	66,125	110,866
Radiation therapy	94	6,364	530	5,576	6,829
Hormonal therapy	99	1,285	283	476	1,729
Total treatment costs		**30,033**	**27,530**	**5,219**	**123,683**

* The patients for neo-adjuvant therapy had the same treatment regime. Hence, there was no difference in the costs.

† All patients had the same standardized post-surgery costs with a fixed rate for hospitalization.

5.4.3. Cost variability drivers

Our analysis identified age at diagnosis as a statistically significant variable ($p < 0.000$) in explaining treatment costs, with treatment costs decreasing as age increases. Additionally, we found HER2-enriched tumours to be a statistically significant disease-specific characteristic in explaining treatment costs ($p < 0.000$), with treatment costs rising in the presence of these tumours.

Regarding classical staging parameters, we identified grade 3 tumours as a significant factor ($p < 0.002$), with larger tumour grades leading to increased treatment costs. We merged N2 and N3 nodal status into one variable and found that patients with four or more nodes impacted were statistically significant ($p < 0.008$), with treatment costs increasing as nodal status increased. Our regression model explained 49% of the variability in treatment costs (Table 18).

Table 18. Regression model for total treatment costs

Total Treatment Costs #	**Coefficient (β)**	**P-value**	**95% Conf. Interval**		**R^2**
Age	-0.022	**0.000***	-0.031	-0.014	**0.492**
HER2-enriched	0.681	**0.000***	0.452	0.910	
G3	0.336	**0.002***	0.123	0.550	
N2_N3	0.289	**0.008***	0.077	0.502	
Constant	10.897	**0.000***	10.349	11.445	

#We used a logarithmic transformation for total treatment costs with a skewed distribution:
$\log Y_i = \alpha + \beta_1 X_i + \varepsilon_i$: $\beta_1 \times 100$ measures the approximate percentage change in $\hat{y}$ when x increases by one unit.

*** Significant at $p \leq 0.05$**

We identified future breast reconstruction ($p < 0.000$) as a statistically significant factor in determining surgery costs. The need for future reconstruction increased surgery costs. Additionally, we found that positive nodes between 1 and 3, 4 and 9, and 10 or more were statistically significant when considering classical staging parameters ($p < 0.005$ and $p < 0.000$). Surgery costs decreased when moving from less than 0.2 mm of impacted nodes to 1 to 3 positive nodes. However, surgery costs increased when we moved to the range of 4 or more positive nodes. Overall, the second model had an explanatory power of 48% (Table 19).

Table 19. Regression model for surgery costs

Surgery Costs #	Coefficient (β)	P-value	95% Conf. Interval		R^2
Reconstruction	0.358	**0.000***	0.183	0.533	**0.477**
N1	-0.154	**0.005***	-0.262	-0.047	
N2_N3	0.355	**0.000***	0.254	0.456	
Constant	7.618	**0.000***	7.581	7.656	

#We used a logarithmic transformation for total treatment costs with a skewed distribution:
$\log Y_i = \alpha + \beta_1 X_i + \varepsilon_i$: β_1 x 100 measures the approximate percentage change in ŷ when x increases by one unit.

*** Significant at $p \leq 0.05$**

5.4.4. Claims data versus TD-ABC

As mentioned, our analysis involves comparing claims data to costs determined through TD-ABC for the operating room segment of the treatment pathway in a selected group of patients. Our findings reveal variations between the two costing methods across all selected patients. First, we display the descriptive statistics of the cost comparison of the four surgical procedures (Table 20) and compare the costing systems per patient (Table 21).

When considering claims data, BCS + SN boasts the highest mean cost at €1,680.43. In contrast, ME + SNB demonstrates the lowest mean cost of €683.93. The standard deviations reveal that BCS + ALND exhibits the least variation at €41.60, and ME + ALND displays the highest at €535.40. The minimum and maximum costs further elucidate the cost range for each surgery type, with ME + SNB having a range of €629.03 to €826.97 and BCS + SN having a substantial range of €772.32 to €3,542.49. Furthermore, the TD-ABC cost estimates, which provide an alternative perspective, demonstrate that BCS + SN remains the most expensive procedure, with a mean cost of €917.92. In contrast, ME + SNB still represents the least costly surgery option with a mean cost of €903.30. The standard deviations show that ME + SNB has the lowest variability, totalling €137.65. Conversely, similar to the claims data, ME + ALND exhibits the highest variability at €856.39. Additionally, when considering the minimum and maximum costs, ME + SNB demonstrates a cost range of €749.7 to €1,124.55, while ME + ALND displays a notably wider range, spanning from €795.41 to €2,578.24.

Table 20. Descriptive statistics of claims vs. TD-ABC

Type of costs	Surgery type	Mean	Std.	Min	Max
Claims	BCS + SN	€1,680.43	€1,142.03	€772.32	€3,542.49
TD-ABC Costs	BCS + SN	€917.92	€408.96	€438.85	€1,343.98
Claims	BCS + ALND	€812.36	€41.60	€781.98	€857.94
TD-ABC Costs	BCS + ALND	€1,031.30	€284.92	€667.42	€1,289.12
Claims	ME + SNB	€683.93	€84.99	€629.03	€826.97
TD-ABC Costs	ME + SNB	€903.30	€137.65	€749.71	€1,124.55
Claims	ME + ALND	€1,156.27	€535.40	€689.08	€1,657.20
TD-ABC Costs	ME + ALND	€1,298.26	€856.39	€795.41	€2,578.24

When examining the actual costs, it becomes evident that the expenses derived from claims data significantly surpass those calculated through TD-ABC for patients undergoing breast-conserving surgery with sentinel node intervention. For patients 3 and 5, these differences are particularly stark—€3,542.49 compared to €1,270.83 and €1,880.34 compared to €978.26. Unfortunately, the rationale behind the substantial cost disparities among all patients with the same surgical intervention is not discernible from the details provided in the claims output, representing a limitation of using claims data.

According to the claim's sheets, patients undergoing breast-conserving surgery with auxiliary dissection exhibit a more consistent cost pattern. The standard operating costs associated with this procedure fall between €781.98 and €857.94. Interestingly, upon examining costs calculated via TD-ABC, we observe higher expenses than the claims data. Further investigation highlights considerable fluctuations, primarily focusing on patients' time in the operating room. This variability explains the absence of a standardized cost range for these patients when TD-ABC is employed. Costs for this procedure range from €667.42 to €1,289.12, aligning with operating room times spanning 73 to 141 minutes.

Comparable outcomes emerge when examining the two distinct mastectomy interventions. In most instances, expenses computed through TD-ABC surpass those acquired from the claim's sheets. Once more, we note a tendency towards more consistent cost values within the patient cohort when looking at the claims data. For instance, in cases where patients require a mastectomy with a sentinel node procedure, the claims data spans a range of €629.03 to €826.97. However, when scrutinizing the costs attributed to TD-ABC, a wider spectrum emerges, stretching from €749.71 to €1,124.55.

Furthermore, when considering patients needing mastectomy and auxiliary dissection, with specific reference to patient 18, an extensive disparity becomes apparent between the costs derived from claims data and those calculated through TD-ABC. Interestingly, this difference is especially noticeable because patient 18 spent 282 minutes in the operating theatre. However, this extended time isn't accurately represented in the claims data. It's important to emphasize that the timestamps from the operating room data reveal significant fluctuations in the duration of time. Table 21 provides a comprehensive summary of the comparison between claims data and TD-ABC analysis of the 19 patients.

Table 21. Claims vs. TD-ABC comparison

Patient number	Surgery type	Claims costs	TD-ABC costs
Patient 1	BCS + SN	€1,434.69	€1,343.98
Patient 2	BCS + SN	€772.32	€557.70
Patient 3	BCS + SN	€3,542.49	€1,270.83
Patient 4	BCS + SN	€772.32	€438.85
Patient 5	BCS + SN	€1,880.34	€978.26
Patient 6	BCS + ALND	€857.94	€1,252.55
Patient 7	BCS + ALND	€857.94	€1,161.12
Patient 8	BCS + ALND	€781.98	€667.42
Patient 9	BCS + ALND	€781.98	€786.27
Patient 10	BCS + ALND	€781.98	€1,289.12
Patient 11	ME + SNB	€826.97	€859.41
Patient 12	ME + SNB	€697.70	€1,124.55
Patient 13	ME + SNB	€629.03	€914.26
Patient 14	ME + SNB	€636.90	€868.56
Patient 15	ME + SNB	€629.03	€749.71
Patient 16	ME + ALND	€697.70	€969.13
Patient 17	ME + ALND	€1,657.20	€795.41
Patient 18	ME + ALND	€1,581.10	€2,578.24
Patient 19	ME + ALND	€689.08	€850.27

5.5. Discussion

We aim to demonstrate the importance of measuring early-stage luminal B breast cancer costs in the context of VBHC. Due to the global rise in healthcare expenditures, the need for estimating costs and understanding cost variability has become critical for policymakers, scholars, and providers [262]. Providers can adjust current processes due to transparency by eliminating wasteful activities, removing redundant processes, and modifying resource use [30]. Additionally, without proper measurement of patient outcomes and costs, it can be increasingly challenging to accurately assess the impact of

significant changes related to reimbursement improvements [24, 55]. Through a comprehensive analysis of costs at both the treatment cycle and surgical intervention levels, we uncover critical insights that can enhance the quality of care delivery. These findings are also significant in guiding reimbursement reforms, especially as we transition toward integrated bundled payment systems.

Considering total treatment costs, age was a significant patient characteristic driving costs. The analysis revealed that patients younger than 40 had 66.9% higher total treatment costs than patients above 65; thus, the average treatment costs decreased as a patient's age increased. One could attribute these higher costs to younger patients presenting more aggressive forms of cancer, necessitating equally aggressive medical interventions [126, 307, 308]. Knowing that age is a significant cost driver could allow managers to develop more tailored treatment plans for younger women, representing fundamental reform for the sector.

In addition, age could serve as a valuable factor for facilitating discussions related to reimbursement. Using risk adjustments, for example, at the age level makes it possible to account for the significant cost variation between patients. Literature focusing explicitly on reimbursement changes, such as bundled payments, emphasizes implementing risk adjustments [24, 116]. They argue that by determining the risk profile of individuals and adjusting the bundle accordingly, one can avoid cherry-picking by the provider [53]. A well-known phenomenon is when providers prevent treating complex patients or only younger, healthier patients [213]. By ensuring we accurately risk adjust, we can provide all patients access to treatments. The discourse concerning risk adjustments holds significant importance as it constitutes one of the pivotal prerequisites for attaining value within the bundled payments framework, as Porter and Kaplan emphasized [24]. Thus, studying cost variability drivers is imperative to effectively accommodate patient and disease characteristics when designing reimbursement reform initiatives.

Furthermore, grade 3 tumours were also significant in explaining the costs of the classical staging parameters. Tumours classified as higher grade tend to grow and spread faster and are considered more aggressive than other tumour grades [309]. Additionally, as the number of impacted nodes increased from four to ten or more, the cost of treatment increased. The outcome of the triple assessment confirms the grade of the tumour and the nodal status; thus, if we stick within the context of reimbursements, bundles developed for this disease could be further adjusted based on the outcomes of these results.

When considering surgical interventions, it is essential to note that although surgical costs represent only a limited segment of the total costs, they are not determined by standardized medical schemes, as is the case with the administration of neo/adjuvant therapy [305]. Although one can only choose between conservative breast surgery and mastectomy, variability in procedures is likely to exist, given the difference in patient characteristics. Additionally, surgical interventions require using an expensive hospital resource, the operating room. Studies show operating rooms represent, on average,

40% of hospital revenue and equate to equally high running costs [310, 311]; thus, understanding their drivers can have a resounding impact on how operating rooms are managed.

The analysis of surgical costs revealed that future reconstruction was a significant cost driver. By using prior knowledge of patients coupled with the need to place an expander during surgery (a requirement for future reconstruction) [312], medical practitioners can use this information to improve the current surgery planning further. Hospital surgery schedules could be improved by incorporating patient characteristics into the intervention-based scheduling system.

Drawing from operational management literature, one way to achieve this is by adopting priority rules, a popular way to schedule patients. This approach develops schedules based on different factors, such as outpatient surgeries first, elective surgeries last, and surgeries for children first [313]. While this approach focuses on duration variability [314], patient and disease characteristics could impact duration, translating into cost impacts.

We find evidence from existing literature that using priority rules combined with interventions can reduce costs [315]. In addition to lowering costs, efficient and effective scheduling can improve patient care quality by reducing waiting times across the care trajectory [316]. Furthermore, studies show the increased volume of similar procedures results in favourable medical outcomes [62], higher efficiency levels by physicians, and reduced costs through standardization [317, 318].

Next to changes regarding the operating room, an alternative process improvement initiative to be considered by hospitals is having multidisciplinary surgery days, an approach used by the hospital under study. All breast cancer surgeries are performed one day a week, with all necessary physicians available for potential interventions. For example, plastic and general surgeons can take measurements for future reconstruction and insert central line catheters, thus streamlining processes and activities. Dedicated multidisciplinary outpatient surgery days provide an interesting adaptation to existing scheduling that other institutions could consider in combination with cost variability drivers and priority rules. Furthermore, bundled payments could be constructed to encourage better use of resources through multidisciplinary surgery days.

While surgery represents only a tiny fragment of the total cost of treating breast cancer, it is an essential step in the treatment pathway [252]. Therefore, in considering future reimbursement design, one might consider using the surgical intervention as an episode-based bundle. We noted one study that evaluated episode-based bundles for breast reconstruction. Their findings suggest developing separate bundles for medical and surgical care with necessary adjustments based on procedure type, comorbidities, and existing cancer therapies [319]. Another study focused on developing a framework for bundled payments in breast cancer screening, thus providing considerations for episodic specialty bundles [320]. The findings in prior literature present evidence for considering episode-based bundles for the surgery component of treatment and emphasize that this step may be better suited [75]. When expanding our focus to academic studies looking into cost measurement for diseases, we see that most studies investigating bundled payments rely solely on claims data, overlooking the importance of using

actual costs. Despite claims data being widely available, accurate cost measurement is crucial for identifying cost drivers and determining the most appropriate bundling approach [321]. This statement is further supported by our analysis.

When we compare claims and TD-ABC costing, several intriguing insights are observed even when examining data from a limited number of patients. Our analysis reveals that specific surgical interventions are booked using standardized claims amounts. Yet, these costs significantly increase when we calculate expenses using TD-ABC. Upon closer examination, we observed that this was primarily attributed to the prolonged time patients spent in the operating room, surpassing the previously established "average times" used to determine the claims amounts. In this instance, TD-ABC asserts its relevance as a robust costing methodology when assessing elements of the treatment process predominantly influenced by time, such as the usage of operating rooms. However, in scenarios like the neo-adjuvant and adjuvant therapy, where treatment follows established protocols and is not significantly influenced by time, TD-ABC loses some relevance in determining or measuring costs since these interventions are driven by the direct medications used and not the time spent in the hospital. Additionally, examining claims sheets alone does not provide a definitive explanation for the variations in billing for patients requiring the same medical interventions, which becomes problematic when determining which services should be included within bundled payments.

While our analysis offers a limited perspective on surgical intervention, the disparities observed between the various costing systems underscore the urgency of thoroughly examining expenses, especially in achieving more precise cost estimations. These differences also prompt crucial inquiries about whether claims data remains optimal for establishing bundle prices and assessing their effectiveness in cost reduction. While the debate of which costing system is better is beyond this paper's scope, value exists in using TD-ABC for changes to the reimbursement system. If we analyse our empirical results, the outcomes of pathological staging could be one avenue to consider. The treatment costs for patients with N2 and N3 nodal status have an average of 58.77% higher surgery costs than those with a nodal status of N0. This illustrates patient cost differences and the importance of significant disease factors in determining episode-based bundles.

Additionally, if we use the VBHC agenda as a guideline, an interesting discussion arises when considering integrating care delivery across care facilities. We see evidence of exploration in a KCE report based in Belgium, where the research centre is encouraging the development of a network of certified multidisciplinary breast units to improve the survival rate of patients [322]. Several valuable observations became apparent while developing the process maps and studying early-stage breast cancer, particularly when considering establishing centralized facilities. Firstly, the diagnostic work-up for assessing breast cancer is standardized (i.e., the triple assessment). Secondly, surgical intervention follows one of two options (breast conservative surgery or mastectomy), again a standard pathway. Thirdly, neo-adjuvant and adjuvant therapy are more complicated and highly dependent on the patient and the severity of the disease. Thus, as a starting point, we could construct centralized facilities

covering diagnostic and surgical interventions, including post-multidisciplinary meetings. Surgical facilities can be established, for example, at the severity level, allowing for greater specialization on the level of treatment.

Moreover, the cost drivers identified in the surgical regression are typically obtained during the diagnostic work-up of patients; thus, they could be used to determine which surgical facilities a patient should attend. Further adjustments can be made at the provider level regarding staffing allocation and care pathway optimization. By taking this perspective, we show the value of cost studies, particularly TD-ABC, to identify opportunities for further improvement within the sector and how they can start the discussion to move towards bundled payments.

While our insights are relevant, we note several limitations of our study; firstly, given that average timestamps were used across many of the cost components except for surgery, we run the risk that our time estimates minimized the variation in total costs. Using average times, however, is consistent with the methodological description of TD-ABC [30]. Secondly, our analysis only focused on patients classified as luminal B; a similar assessment for the remaining molecular subtypes could serve as interesting future research. The decision to use luminal B is only based on the fact that this molecular subtype varies considerably in pathology, translating into different treatment pathways with varied costs. Finally, while we only considered variability within one hospital, scholars could consider a similar investigation across providers to understand cost differences between hospitals. These insights will help implement bundled payments, as the same lump sum is granted to all providers.

5.6. Conclusion

Given the increase in healthcare costs, studying cost variability has become an essential topic for policymakers, providers, insurers, and scholars alike. Through our analysis, we investigated the impact of several patient and disease factors driving cost variability for early-stage luminal B breast cancer patients.

Significant variables explained total treatment costs, such as age at diagnosis, HER2-enriched, grade 3 tumours, and four or more positive nodes (N2_N3). Furthermore, reconstruction and positive nodes categorized as N1 (1-3 nodes), and four or more positive nodes (N2_N3) were identified as significant cost drivers for the surgery component. These insights allowed us to suggest how bundled payments could be designed via risk adjustments using the significant preoperative variables identified in the regression model. Additionally, through our focus on surgery costs, we provided considerations for episodic-based bundles and potential ways existing processes could be improved, reducing expenses.

Our study offers valuable information to stakeholders that can assist in making informed decisions and enhancing patient value. Furthermore, given that providers and insurers share in the savings and losses obtained by the bundle, identifying cost drivers and using them to make appropriate risk adjustments for patients is beneficial for both parties.

6. Comparing Theoretical Perspectives and Practical Applications of Bundled Payments: An Overview and Identification of Gaps

6.1. Introduction

Healthcare expenditures are constantly rising across the globe. This collective rise in healthcare expenditures can be attributed to various factors, including demographic changes (e.g., an aging population and differences in disease prevalence), the increasing cost of care, rising incomes, characteristics of healthcare systems (e.g., reimbursement models), and technological advances [323]. Several strategies have been deployed across the globe in an attempt to tackle the expenditure issue. The most notable is Value-Based Healthcare (VBHC) [18], which serves as a framework for changing the sector across several interconnected mechanisms [21]. A component within this framework of great interest relates to how reimbursements are granted to providers for care delivery.

Various reimbursement models are used worldwide, with the fee-for-service (FFS) system dominating most healthcare systems. In the FFS model, providers receive a predetermined fee for each service they render. Nevertheless, the FFS system is associated with several significant drawbacks. Currently, the FFS model reinforces a segmented approach to patient care, compensating providers separately for their services [21]. Many are highly critical of this fragmentation, citing its adverse effects on the healthcare system, including diminished service quality, hindered coordination, and impeded efficiency initiatives, ultimately resulting in suboptimal patient care, overutilization, and wastefulness [324]. The challenges posed by the FFS system have spurred calls for reform in how providers are reimbursed.

Several reimbursement systems have been suggested, such as Value-Based Payments and Global Payments (Capitation). A Value-Based Payments system links payments to the provider's improved patient treatment performance. This system holds healthcare providers accountable for costs and the quality they achieve [69]. Global Payments, on the other hand, are considered a form of bundled payments; however, bundles are constructed at a higher level rather than at the level of treatment or condition [325].

Though not a new concept, bundled payments have recently gained popularity as a promising method that could restrict rising financial expenditure and link reimbursement to value rather than the number of services provided [70]. Essentially, bundled payments represent a lump sum paid to hospitals to reimburse a patient's entire episode of care [72]. Payers often look at overall variation and mean pricing in historical payments for all facets to establish a case rate when determining the bundle amount. They then negotiate with hospitals and healthcare professionals (HCPs) to adjust a bundle price based on initial patient and disease characteristics [75]. Payers then pay providers either retrospectively, in which providers retain a fee-for-service arrangement but with a retrospective reconciliation period, or prospectively, in which payers make a lump sum upfront; for both systems, the bundle is divided at the discretion of the facilities and departments [68, 75]. Bundled payments require providers to assume clinical and financial responsibility for treated patients [326]. A strength of bundled payments is that they incentivize quality improvements and cost reduction through increased accountability and better care coordination in a highly fragmented sector [41, 71]. Furthermore, it aims to better align providers' interests via the fixed payment for all services provided.

However, this system is not without its challenges. These include defining and tracking care, limiting the financial risks for providers, avoiding the potential risk of cherry-picking and gaming the system, and limiting the choice of providers [75, 327–329]. Regarding its effectiveness, the literature is ambiguous, with some studies reporting lower medical spending and improved quality of care while others say adverse effects [76]. While the objectives of bundled payments may appear straightforward, the implementation, specifically the design, remains challenging [75]. Interestingly, a scoping review of bundled payments' design and implementation process reported that these elements were often also sources of complexity when developing bundled payments [330]. However, in 2016, Porter and Kaplan outlined five necessary conditions when constructing bundles to ensure the greatest value is obtained for patients [24]. We aim to conduct a scoping literature review of bundled payments and compare the findings to the five conditions necessary for achieving value as defined by Porter and Kaplan. This paper aims to provide an overview of the comparison and identify gaps between the theoretical perspective and the practical application of bundled payments in the literature. We discuss several necessary considerations needed to bridge the gap between theory and practice and offer alternative reflections regarding the future of the reimbursement landscape.

6.2. Methodology

This scoping literature review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [117]. We aimed to investigate how the five conditions of Porter and Kaplan's bundled payment design are addressed in the literature (Table 22) [24].

Table 22. Overview of the five conditions for designing bundled payments

Condition	Description
1. Payment covers the overall care required to treat a condition	The bundled payment should cover the cost of treatment over the complete cycle of care. The care cycle should be taken from the patient's perspective, encompassing all services linked to treatment and managing comorbidities and complications.
2. Payment is contingent on delivering good outcomes	The bundled payment should be linked to obtaining relevant patient outcomes for a specific disease. For example, a reduction in pain, mobility function, and complications.
3. Payment is adjusted for risk	The bundled payment should be risk-adjusted to account for the inherent complexity between patients.
4. Payment provides a fair profit for effective and efficient care.	A bundled payment should cover all costs of necessary care, plus a margin, for providing effective and efficient care through their clinical and administrative processes. All unnecessary services and inefficient care should not be rewarded.
5. Providers are not responsible for unrelated care or catastrophic cases	Providers should only be accountable for care related to the condition; thus, responsibilities should be defined at the bundle's start. "Stop-loss" provisions should be in place to avoid financial risk for unusually high-costing patients (i.e., catastrophic or outlier cases).

Source: Porter ME, Kaplan RS. How to pay for health care. Harvard Business Review. 2016 Jul 1;94(7-8):88-98.

6.2.1. Scoping review

6.2.1.1. Search strategy

The comprehensive literature search was conducted from November 2022 to January 2023 using the following eight databases: Web of Sciences, Scopus, Embase, Cinahl, PubMed/Medline, OvidSP, Science Direct, and Cochrane Library. The research strategy employed covered the following six keywords: "bundled payment," "bundle," "health care," "payment system," "reimbursement," and "risk adjustment." Multiple combinations were used, and no restrictions were placed initially to maximize the search results. The search strategies used across the various databases are listed in Appendix Chapter 6.

6.2.1.2. Search strategy

Mendeley was used to merge all the results and remove duplicates. The review and selection of eligible articles were conducted in two steps. In the first step, two reviewers (R.L. and F.V.R.) independently screened all titles and abstracts of the articles in parallel using the Rayyan QCRI application [138]. Articles were included if they (1) discussed the construction or performance of bundled payments, (2) discussed risk adjustments within bundles, and (3) discussed other essential factors relating to the composition of bundles. A disagreement between the two parties regarding the appropriateness of an article was resolved by a third reviewer (E.R.). Based on the inclusion criteria, potentially eligible articles were subjected to full-text screening by ER, RL, and FVR. All articles in the second stage were subjected to several exclusions: (1) articles published as abstracts for conferences;

(2) papers not written in English; (3) systematic reviews; and (5) grey literature namely, descriptive articles, opinion-based papers, or blogs.

6.2.1.3. Data extraction

Microsoft Excel was used to extract and consolidate all the information retrieved from articles. General characteristics of the articles were collected, covering publication year, the paper's aim (e.g., the performance and/or construction of the bundle, etc.), countries where the analysis was conducted, and whether a retrospective or prospective view was taken. Furthermore, we noted the type of journal in which the article was published.

Porter and Kaplan's five conditions guided our data extraction process to obtain an overview of how these elements have been addressed in current literature. For the first question about overall care provided, we extracted information regarding the episode of care as mentioned in the articles. We looked at the services described in the episodes, as this indicated the start and end points of care. Furthermore, we noted the exact duration of the bundled payment. By screening all the articles, we provided an overview of the different episodes of care in the literature.

The second question pertains to the payment being contingent on delivering good outcomes. Given the description by Porter and Kaplan, who recommend outcomes be deemed relevant for patients, we specifically focused on how papers measured outcomes (e.g., specific ways to measure quality targets) and the perspective of these outcomes (e.g., procedural or patient).

The third condition relates to bundled payments needing to be risk-adjusted; thus, we looked at which methods are typically used for risk adjustments (e.g., statistical analysis) and which factors are generally used for risk adjustments (e.g., patient, disease, or other characteristics).

For the fourth condition, payment provides a fair profit for effective and efficient care; we screened papers across several categories. Firstly, we extracted information regarding the type of cost data used in the studies (e.g., claims data; real costs = variable, fixed, etc.). We then extracted information about the costing methods (e.g., TD-ABC or other methods) and noted whether bundles were paid via a retrospective or prospective system. To obtain a profit, we looked at how articles calculated the bundle target price (e.g., historical claims data). Given the ambiguity surrounding the use of 'profit' by Porter and Kaplan, we looked at how papers measured savings under bundled payment schemes. Additionally, we extracted information on how articles shared profits among providers. Finally, we looked at approaches to achieving efficient and effective care across diseases.

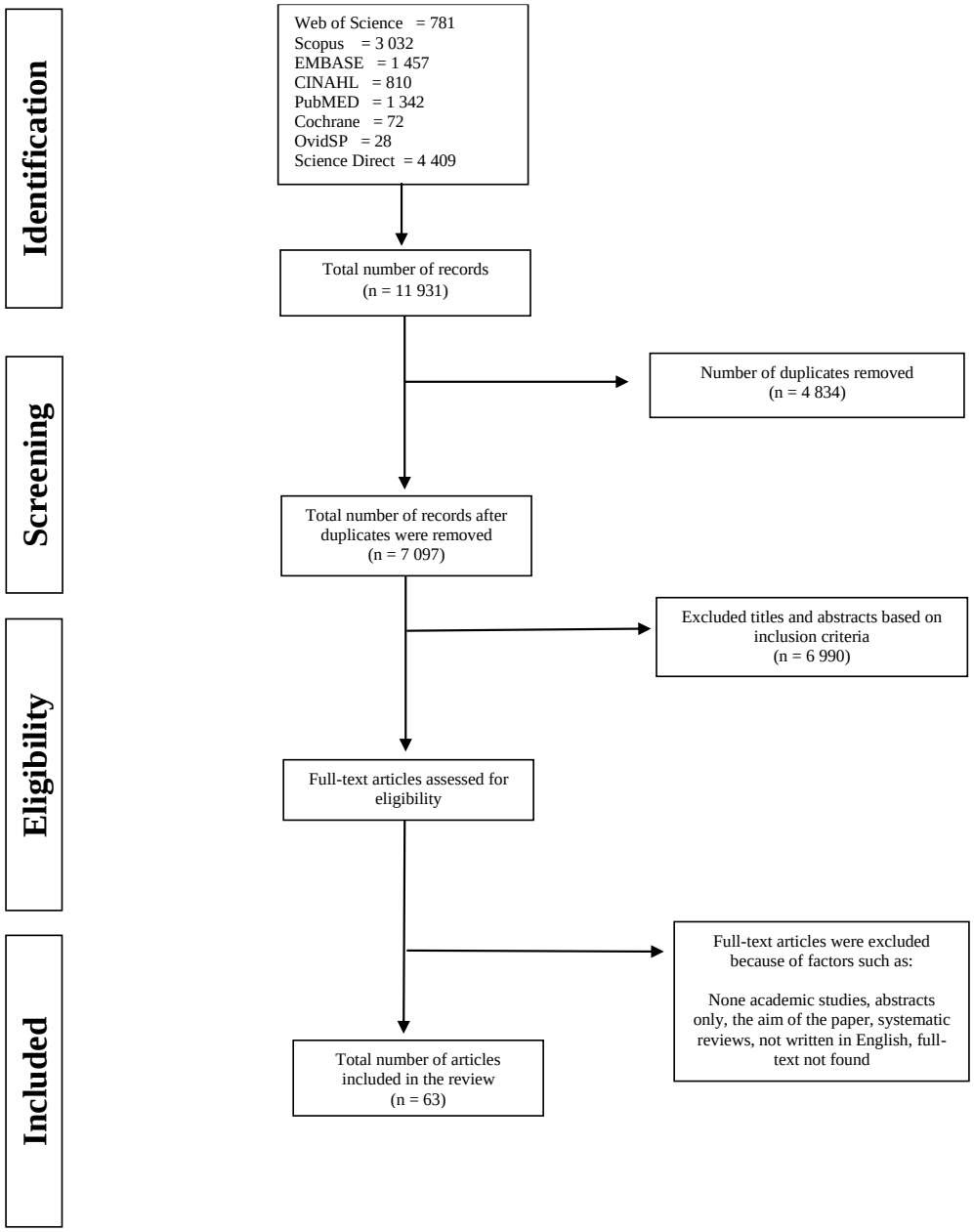
For the final condition of unrelated care and catastrophic cases, we looked explicitly at whether or not papers defined unrelated care and mentioned provisions to limit financial exposure or loss in the event of significant complications with patients (e.g., stop-loss mechanisms).

6.3. Results

6.3.1. Study selection

The initial search identified 11,931 citations. After removing duplicates, 7,097 studies remained to be screened based on title and abstract. After the initial review, 115 potentially relevant articles remained for full-text screening. 63 articles remained after screening and applying the exclusion criteria. The number of articles in each selection phase can be found in the flow diagram in Figure 6.

Figure 6. PRISMA and meta-analyses flow diagram of relevant articles



6.3.2. General study characteristics

All papers included in the review were published between 2011 and 2022. For the study's aim, we found that they focused on either (1) constructing bundles (n = 20), (2) assessing their performance along several measures (n = 39), or (3) a combination of both the construction and performance (n = 4). Many studies used data collected from the United States (n = 58), followed by the Netherlands (n = 2) and Taiwan (n = 2). Regarding the data perspective, most studies used a retrospective approach (n = 29) for their collection efforts, with only a handful using prospectively collected data (n = 2) and retrospective use of prospectively collected data (n = 2). For many articles, it was not clear how the data was collected (n = 30). We identified three main categories for journal type for which the studies were published: disease or disorder-specific (n = 40), health policy or services-related journals (n = 22), and finally, others (n = 1) relating to the management science category. We present a full overview of the study characteristics in Table 23.

Table 23. Overview of the general characteristics of papers

Characteristic	% (n)	References
Year of publication		
2011	3.2% (2)	[326, 331]
2013	1.6% (1)	[332]
2014	1.6% (1)	[333]
2015	4.8% (3)	[70, 334, 335]
2016	7.9% (5)	[77, 213, 336–338]
2017	15.9% (10)	[64, 320, 321, 339–345]
2018	20.6% (13)	[346–357]
2019	17.4% (11)	[358–368]
2020	15.9% (10)	[319, 369–377]
2021	6.3% (4)	[128, 378–380]
2022	6.3% (4)	[381–384]
The rationale of the paper		
Construction of bundle	31.7% (20)	[70, 213, 319–321, 331–333, 350, 352, 355, 356, 360, 361, 363, 364, 375, 377, 380, 384]
Performance of bundle	61.9% (39)	[64, 128, 326, 335–349, 351, 353, 354, 357–359, 362, 365, 367–374, 376, 378, 379, 381, 383]
Construction and performance of the bundle	4.8% (4)	[77, 334, 366, 382]
Location of data collection		
The Netherlands	3.2% (2)	[128, 326]
Taiwan	3.2% (2)	[345, 351]
Canada	1.6% (1)	[360]
United States	92.1% (58)	[64, 70, 77, 213, 319–321, 331–344, 346–350, 352–359, 361–384]
Data collection perspective		
Retrospective	46.0% (29)	[70, 77, 213, 320, 333, 334, 340, 344, 345, 348–350, 353, 354, 359, 362, 364, 365, 367, 368, 373, 375–378, 380–382, 384]

Prospective	3.2% (2)	[355, 371]
Retrospective use of prospectively collected data	3.2% (2)	[360, 361]
Not clearly stated	47.6% (30)	[64, 128, 319, 321, 326, 331, 332, 335–339, 341–343, 346, 347, 351, 352, 356–358, 363, 366, 369, 370, 372, 374, 379, 383]
Type of journal		
Health disease or disorder specific journals	63.5% (40)	[70, 77, 213, 320, 321, 333, 336, 337, 339–343, 345, 346, 348–350, 353–356, 359–371, 375–377, 380, 381]
Other healthcare journals	34.9% (22)	[128, 319, 326, 331, 332, 334, 335, 338, 344, 347, 351, 352, 357, 358, 372–374, 378, 379, 382–384]
Others	1.6% (1)	[64]

6.3.3. The payment covers the overall care required to treat a condition

Based on the literature, many studies describe treatment services as an episode of care. We see various "episodes" with varying services and durations across disease domains. We identified one study focusing on the diagnostic phase of treatment. The bundle was constructed using the services utilized for mammography imaging for breast cancer screening, and the duration was 364 days or until the next screening moment [320]. Some studies utilized disease-diagnostic groups (DRGs) to define the episode of care and used 90 days as the time frame [357, 360, 374]. We identified the use of treatment-based bundles in oncology; these bundles only covered the costs relating to primary cancer treatment (e.g., adjuvant therapy for head and neck cancer) and drug costs [355, 356].

Acute care-only episodes covered services relating to surgical interventions (elective or emergency surgeries) and in-hospital stays. No specific duration was provided, but the bundle was initiated at the start of the inpatient stay until discharge or only lasted the period of the surgical intervention. The most common episode of care is related to acute care plus post-acute care (PAC) services. This episode represents the index hospitalization (72 hours before the procedure) and all additional post-acute care services (e.g., readmissions, complications, and rehabilitation). We identified a range of episode durations starting from the index hospitalization, with a duration ranging from 30 days to two years PAC. In some articles, only PAC was considered an episode of care.

We found several articles covering the full care cycle across different diseases. One episode for diabetes included a range of services (consultations with GPs, nurse practitioners, medical specialists, self-management, and lifestyle interventions), but the exact duration was unclear [128]. Another study defined a full care cycle for breast cancer from diagnosis to 18 months after initial treatment started [345]. Another study on actinic keratosis did not clearly define the episode but mentioned it included services for office visits, procedures, and prescriptions; however, the duration was unclear [77]. Finally, one paper constructed a detox episode divided into three main service categories: detox only, detox and outpatient, and outpatient only with 90-day durations [321]. When Porter and Kaplan suggested bundles, they strongly recommended that the payment cover the full care cycle plus all services related

to complications and comorbidities. The literature shows that bundles do not always encompass the entire care cycle but encompass predetermined services for a specific time. These findings highlight a significant difference between bundled payments' theoretical and practical applications. A complete overview of the episodes of care and their corresponding descriptions and durations can be found in Table 24.

Table 24. Definition of care episodes

Episodes of care	Description	Duration	References
Diagnostic screening episodes	The bundle includes mammography screening, including all imaging for breast cancer diagnosis.	364 days or date before the next screening	[320]
Treatment based	Adjuvant therapy & medications only	1 year Not clearly defined	[355] [356]
DRG-based	Some studies defined the episode of care based on DRG codes	DRG classification 90-day episode	[360] [357, 374]
Acute care only episode	The episode covers the length of in-patient stay until discharge. Emergency cases were also classified in this episode of care. Surgical interventions only – all services related to elective surgery.	It starts with an in-patient stay and ends with a discharge Only surgical intervention	[352] [70, 368, 371]
Acute and post-acute care	Index hospitalization + post-acute care/services for a pre-defined disease	An in-patient stay + 30 days post-discharge An in-patient stay + 60 days post-discharge An inpatient stay + 90 days post-discharge An in-patient stay + 1 or 2 years	[213, 333–335, 338, 339, 351, 353, 377, 385] [333, 377] [319, 333, 338, 340–342, 344, 346–350, 354, 359, 361, 362, 365, 367, 369, 370, 376–382, 386–389] [319]
Post-acute care only	All services related to post-acute services (e.g., skilled nursing, rehabilitation service etc.)	90-days	[341, 390]
Full cycle of care	Including consultations, diagnostic tests, surgical interventions, medication management, physical and rehabilitation, readmissions, or complications – for **breast cancer** For treatment of chronic diseases covering services such as consultations with GPs, nurse practitioners, and medical specialists, self-management and lifestyle interventions, diabetic foot care, and care coordination – for **diabetes**	From diagnosis to 18 months Not clearly defined	[345] [128]

	Outpatient setting which includes all office visits, procedures, and medications – **actinic keratosis**	Not clear	[77]
	Detox episodes with different services like detox only, detox and outpatient, and outpatient only – **substance abuse**	90-days	[321]

6.3.4. The payment is contingent on delivering good outcomes

As mentioned, when scoping the articles, we primarily examined how studies measured "good outcomes." Most of these papers use data from the United States and apply the CMS perspective. This government institution determines a set of outcomes that must be adhered to. As a result, many papers do not provide full detail on how good outcomes are measured but reference CMS targets. However, Finkelstein et al., who investigated the CRJ model, did describe the method in more detail. Using Hospital Compare data, a Composite Quality Score (CQS), measured across four categories with a total of five points, resulting in a maximum of 20 points, was used. The authors measured the THA/TKA complication measure and the HCAHPS patient experience measure. A minimum of five points is necessary to reach the quality target [346].

In a European context, specifically the Netherlands, one article mentioned that the quality of care delivered is monitored by an external branch organization (INEEN) for primary care. This organization reports disease-specific performance indicators annually [128]; however, the exact measurement method was not discussed.

Finally, Whitcomb et al. measured quality using established national metrics. They mention surgical quality targets were measured using Surgical Care Improvement Project measures, Agency for Healthcare Research and Quality (AHRQ) Patient Safety Indicators, and CMS Hospital-Acquired Conditions. They do not detail how these are measured in the study [334].

It should be noted, however, that based on Porter and Kaplan's description, it is still unclear how outcomes and quality measures are directly linked to the bundle. They state that the payment of the bundle should be tied to achieving good outcomes relevant to the patient; specific outcomes such as function, pain reduction, and limiting complications are examples mentioned. However, based on the description and the application in the studies, no clear direction is provided on how we go about linking outcomes directly to the bundle. An overview of the outcome measures is shown in Table 25.

Table 25. Overview of outcome target measures

Outcomes target measures	Description	The type of outcomes measured	Reference
Composite Quality Score (CQS)	The score is calculated using data from Hospital Compare. CQS is capped at a maximum of 20 points. Quality measures are divided into four categories, and a minimum of 5 points needs to be achieved to reach a quality target.	Complication Measure & Hospital Consumer Assessment for Health Plan Survey = patient experience measure	[346]
Quality assessed by external organizations	Quality is monitored by a branch organization of primary care providers (INEEN) in the Netherlands that annually reports disease-specific performance indicators.	Disease-specific	[128]
National metrics on quality	All surgical quality metrics came from Surgical Care Improvement Project measures, Agency for Healthcare Research and Quality (AHRQ) Patient Safety Indicators, and CMS Hospital-Acquired Conditions.	Procedure-level outcomes	[334]

6.3.5. The payment is risk-adjusted

Several studies in the review adjusted for risk. If we categorize those accordingly, we see most papers adjusted for patient characteristics (n = 14). These cover categories such as age, the existence of comorbidities, BMI, gender, etc. For disease characteristics, adjustments were made for the severity of the disease (e.g., Medicare severity diagnosis-related groups). Adjustments for treatment characteristics typically occur at the level of procedural factors (e.g., number of implants). Moreover, adjustments were made for medications (e.g., adjuvant therapy drugs and other drugs), and several studies adjusted for institutional factors like hospital characteristics (e.g., size and number of beds) and geographical location/region. Additionally, studies included market-related factors (e.g., availability of PAC services).

We identified several methods for measuring risk adjustment, although multivariate regression analysis was the most common approach. This can further be divided into linear models (n = 10), generalized linear models (n = 2), and logistic regression models (n =1). We identified one paper that utilized a mix of regression models with difference-in-difference analysis and another that used linear mixed effects regressions. While many articles discuss risk adjustments - their methods to identify risk factors, the vast categories used, and sometimes the dollar amount added to the bundle - they mainly focus on the financial risk aspect. Nonetheless, the definition described by Porter and Kaplan emphasizes that risk factors should be linked to bundled payments and outcome expectations. Given the inherent complexity of patients, they argue that providers should be rewarded for taking on more challenging cases. Surprisingly, we miss the link to outcome expectations in the literature. A complete overview of the factors used for risk adjustment and the corresponding methods is presented in Table 26.

Table 26. Risk adjustment methods and characteristics

Characteristics for risk-adjustment	**Description**	**References**
Patient characteristics	Characteristics outside of the hospital's control – explicitly relating to demographic information like age, gender, marital status, etc.	[70, 77, 213, 321, 338, 350, 355, 360, 361, 371, 377, 380, 381, 388, 390]
Disease characteristics	This relates to all characteristics associated with the severity of the disease.	[338]
Treatment characteristics	These represent all factors relating to procedure-related elements, like the number of additional implantation procedures. Medication-related, like the use of adjuvant therapy and other drugs.	[350, 361, 388, 390] [70, 361, 377]
Institutional characteristics	Variables associated with the hospital (size, number of beds), geographical region, and market-related factors	[321, 338, 350, 381, 388, 390]
Methods for risk-adjustments	**Description**	**References**
Multivariate regressions analysis	Linear models Generalized linear models Logistic models	[70, 77, 213, 350, 355, 360, 361, 377, 380, 390] [321, 388] [381]
Mixed approach	Papers used a combination of techniques to adjust for risk, for example, difference-in-difference & regression models.	[338]
Other statistical analysis	Linear mixed-effects regression	[371]

6.3.6. The payment provides a fair profit for effective and efficient care

As a starting point, we extracted data on the types of costs used within the studies. A theme emerged in that most papers used claims data followed by actual costs in the determinants of bundles. To investigate costs further, we looked at the two types of costing data separately to understand how they impact decisions linked to the bundle (Tables 27 and 28). For many studies utilizing claims data, no description was provided for costing methods. Regarding the payment system employed for reimbursement within the bundles, most studies opted for the retrospective payment system. The prospective payment system was used in three studies.

For the papers using claims data, several strategies were employed to set the target price of the bundle. The majority of the methods used historical data as their foundation. We noted three studies that used historical data combined with risk adjustments [344, 369, 380]. Two studies used historical data with some discount amounts granted to providers for participation in the bundle [338, 354]. Two studies used historical performance data to set the target price of the bundle [340, 348]. Several studies mentioned using the CMS method to set target prices, either through a mix of statistical analysis to account for patient mix [391] or through the use of historical prices with a discount depending on the length of the episode [341, 342, 346, 347, 359, 370, 386]. One paper used DRGs to set 90-day episode target prices [388]. Another paper set up a financial group that worked closely with clinicians to determine the overall services in a bundle and derive a target price [334]. The sum of the index hospitalization payments with the post-operative hospital admission and outpatient payments was used

in another article [377]. One study constructed three bundles; thus, three target prices were based on the number of imaging services included [320]. Finally, one study used simulation techniques, namely Monte Carlo simulation, to set the target price [356]. Most papers used the reconciliation method to determine if the expenditure costs were lower than the target price when using claims data.

Gainsharing models were described for the division of profits. CMS uses a system for the CJR model, whereby profit can only be obtained if quality measures are met and the cost of providing care is lower than the target price of the bundle [346]. We only identified one article that evaluated the use of effective and efficient clinical and administrative processes in their study. They discussed using standardized quality indicators to improve patient's medical adherence. Again, the definition does not provide sufficient detail, so we limited our discussion to obtaining efficacy in processes. It should be noted that no direct discussion of a fair profit was identified within any of the studies. Table 27 provides an overview of the elements relating to profit and efficient care for papers using claims data.

Table 27. Fair profit and effective and efficient care – for claims data

Costing data used in papers	**Description**	**References**
Claims	Papers typically used Medicare claims data or other insurance-related data	[77, 128, 319–321, 333–335, 338, 342, 345–351, 353, 354, 356, 359, 361, 362, 365, 369, 370, 374, 377, 378, 380–382, 385, 388–391]
Payment system types	**Description**	**References**
Retrospective	Payers retain an FFS arrangement and continue to compensate providers directly. But total costs are reconciled against the predetermined target price	[321, 331, 334–336, 338, 340–344, 346–349, 353, 354, 357, 359, 361, 365, 366, 368–370, 372–374, 381–383]
Prospective	Payers make a single lump-sum payment to a convener who then distributes payment to the various providers involved in the episode of care.	[351, 356, 375]
Target price estimation methods	**Description**	**References**
Historical data and risk adjustments	Target prices are determined based on historical data and risk adjustment models of patients and other hospitals.	[344, 369, 380]
Historical payments and a discount	The exact method was not clearly stated. Prenegotiated target rate discounted at 2% to 3% for participation within the bundle.	[338] [354]
Using historical performance data	Simply using historical performance measures to determine the target price	[340, 348]
CMS methodology	Made up of two parts: (1) creating a compound lognormal regression model that includes patient case-mix and hospital characteristics. (2) using a linear model to analyse the spending trend for peer groups of hospitals with similar characteristics. The Centres for Medicare & Medicaid Services (CMS) set the target price based on the provider's historic average episode cost, discounted by 3% for 30 and 60-day episodes and 2% for 90-day episodes.	[391] [341, 342, 346, 347, 359, 370, 386]
DRGs to define target prices	Historical pricing methodology via DRGs to define 90-day target prices	[388]
Financial group model	Examination of all payments made to providers for a certain disease, then with a clinical group narrowed down which	[334]

	services to include in the bundle, then derived an overall price based on included services.	
Based on provider costs	The sum of the index hospitalization payments and the post-operative hospital admission and outpatient payments.	[377]
Multiple bundle prices for one disease	3 bundle prices were developed based on which imaging services were included	[320]
Simulation techniques	Simulation techniques like Monte Carlo were used to determine bundle price	[356]
Ways to calculate the profit	**Description**	**References**
Reconciliation of FFS vs. bundle target	Total episode payments (reimbursed under FFS) were reconciled against a target bundled price after a certain period.	[334, 338, 341, 342, 348, 359, 360, 365, 387, 391]
Methods for dividing profit/loss	**Description**	**References**
Gainsharing	A predetermined quality measure must be met. Then a comparison between actual cost and the bundled price are made. If a saving is found these went into a "saving pool". Funds were then allotted to stakeholders on an agreed-upon rate. Providers' gainsharing payment was 40% above the standard Medicare reimbursement. The gains were subject to meeting specific quality metrics. Stop-gains and stop-losses were placed to cap profits and losses. Scorecards were used to track the performance of stakeholders. Providers with better outcomes received a higher percentage of the gain shared sum, while those with worse performance received less. The gainsharing was capped at 20% of the reconciled sum. Quality-dependent gainsharing programs to boost quality among stakeholders	[334] [385] [346] [387]
Way to achieve effective and efficient care	**Description**	**References**
Adherence to quality indicators	Pre-defined standardized quality indicators could lead to greater medication adherence.	[345]

Papers considering real costs used a combination of fixed, direct, and indirect costs [384], and another used variable costs only [213]. It was noted that three studies used TD-ABC to measure costs within the bundles. Other studies mentioned the use of expenses obtained from the accounting systems within their organizations. Similar to the findings of claims data, most papers used the retrospective payment system, with only one article using the prospective payment design.

Only two articles discussed the target price of the bundle for the papers using real costing data. Again, one article used Monte Carlo simulation to set an appropriate bundle price [355]. The remaining paper employed the mean reimbursement rate under the FFS system [376].

Regarding the reconciliation of profits, one paper calculated the contribution margin, the difference between variable costs and the target price, to estimate profit [213]. Using the contribution margin is directly linked to using real costing data and is a common method used in finance and accounting. The remaining papers discussing profits within the bundle context reconciled the bundle target price to the FFS price.

No discussion was found regarding how profits should be divided, what metrics should be used to obtain fair profit, and ways to measure effective and efficient care when considering papers using real costing data. Table 28 provides an overview of the elements relating to profit and efficient care for papers using real costing data.

Table 28. Fair profit and effective and efficient care – for real costing data

Costing data used in papers	**Description**	**References**
Real costs	Costs are calculated using the accounting systems of hospitals	[70, 213, 367, 376, 384]
Mix of costs	Costs obtained from literature and national averages	[379]
	Group costs (resource utilization) + claims data + FFS	[339, 352, 355]
Costing methods used in papers	**Description**	**References**
TD-ABC	Using TD-ABC to measure costs	[339, 376, 384]
Other approaches	Micro-costing algorithms	[70]
	Costing accounting system of hospital	[213, 367]
	Admin claims data + fully loaded procedure-level costs	[355]
Payment system types	**Description**	**References**
Retrospective	Payers retain an FFS arrangement and continue to compensate providers directly. But total costs are reconciled against the predetermined target price	[339, 367, 376, 379]
Prospective	Payers make a single lump-sum payment to a convener who then distributes payment to the various providers involved in the episode of care.	[355]
Target price estimation methods	**Description**	**References**
Mean reimbursement rate of FFS	Calculated target price as mean reimbursement in the current fee-for-service reimbursement system	[376]
Simulation techniques	Simulation techniques like Monte Carlo were used to determine bundle price	[355]
Ways to calculate the profit	**Description**	**References**
Reconciliation of FFS vs. bundle target	Total episode payments (reimbursed under FFS) were reconciled against a target bundled price after a certain period.	[339, 376]
Measuring contribution margin	Calculated as the difference between reimbursement and variable costs.	[213]
Methods for dividing profit/loss	**Description**	**References**
Nothing stated		
Way to achieve effective and efficient care	**Description**	**References**
Nothing stated		

6.3.7. Providers are not responsible for unrelated care or catastrophic cases

For the final element, we looked at how papers determined unrelated care. Based on the episode of care under investigation, most papers clearly stated the inclusion and/or exclusion criteria for patients or services within the bundle; this limits the potential for unrelated services to be included. The definition brought forward is well understood within the given literature.

Not all papers discuss catastrophic cases; however, the identified ones use stop-loss provisions to limit providers' financial risk within the bundle. A cap, i.e., 20% or 40%, was mentioned for these provisions. This follows the suggestion by Porter and Kaplan, whereby stop-loss conditions should be in place to limit the provider's exposure to high costs in more challenging cases. An overview of the papers that discuss unrelated care and catastrophic cases is presented in Table 29.

Table 29. Providers are not responsible for unrelated care or catastrophic cases

Unrelated care	**Description**	**References**
A clear design of the bundle	Explicit inclusion and exclusion criteria are necessary to avoid unrelated care, for example, exclusion based on Medicare eligibility for end-stage renal disease.	Most papers have clear inclusion and exclusion criteria.
Catastrophic cases	**Description**	**References**
Stop-loss provisions	The stop-loss provision is activated when the FFS amount exceeds the target price. For example, gains and losses are set at 20% above or below the target price. Monte Carlo simulations could be used to determine appropriate thresholds.	[346, 355]
	Authors propose stop-loss provisions through a particular mechanism whereby the provider is only responsible for a beneficiary's second-stage costs below a certain threshold. The insurer burdens any realized second-stage costs over the prespecified threshold.	[64]

6.4. Discussion

In this study, our objective is to assess the alignment between the key conditions proposed by Porter and Kaplan, deemed essential for developing bundled payment systems, and their practical application in the existing literature. The comparison enables us to discern the disparities between the idealized formulation of bundled payments presented by Porter and Kaplan and the current strategies and practices documented in the literature. By doing so, we aim to highlight the fundamental gaps contributing to the complexity of implementing and designing effective bundles across disease domains. In studying these differences, considerations, and suggestions are provided to further the dialogue on reimbursement reform.

Upon comparing the five conditions to the prevailing literature, it becomes evident that some fundamental aspects are absent from the discourse surrounding bundled payment systems. For example, the discussion about care coordination is notably absent in the five conditions, and there is a limited dialogue on the optimal approaches for managing this aspect within the literature. However, a study

addressing the issue shows that care coordination is critical within a bundle. It highlights that if care pathways are not well managed, it can have resounding negative consequences for the patient [331]. Furthermore, very little is said about antitrust concerns, administrative complexity, and how best to deal with them when implementing bundled payments. These points highlight a few fundamental gaps in implementing reimbursement reform, particularly bundled payments, within the sector.

When analysing the conditions sequentially, as a starting point, Porter and Kaplan suggest bundles should cover the full cycle of care; therefore, they should include all services related to a particular medical condition, ranging from prevention through early detection, diagnosis, treatment, recovery/rehabilitation, and long-term sustainability of health [18, 24]. However, various studies have focused on specific parts of the care cycle, such as diagnosis or treatment, rather than the complete care cycle [320, 355, 356]. Some studies that claim to cover the full cycle do not include all the necessary services. For example, Kirby et al. defined bundles for actinic keratosis but excluded pathology services, which are occasionally required for diagnosis [77]. Additionally, other studies emphasize the difficulty of designing full care cycle bundles when considering multimorbidity patients since treatment start and end points may overlap [328]. Therefore, it can be argued that implementing bundled payment systems on the entire care cycle might be more complex than initially envisioned by Porter and Kaplan.

In the context of outcome assessment, it is essential to prioritize patient-centric perspectives, as advocated by Porter [20]. It is crucial to differentiate between outcomes that genuinely matter to patients and those centred on patient satisfaction measures or procedural indicators. Nevertheless, specific bundles still utilize quality indicators lacking direct patient relevance. CMS quality measures frequently used in literature in the United States are an excellent example of this [334]. If the goal is to advance toward a value-based system, the focus should be on outcomes significant to patients. It is essential to mention that discussions are changing; for example, in psoriasis, an overview of patient-relevant outcomes has recently been published, signifying a vital shift in bringing patients into a more central role in managing and treating the disease [392].

Furthermore, we see the development of institutions like the International Consortium for Health Outcomes Measurement (ICHOM) focused on developing patient-relevant outcome sets to help us determine which outcomes should be measured. While the example above shows that we are moving positively, more work is necessary to measure and apply these patient-relevant outcomes to academic studies. Additionally, our investigation indicates that precise definitions are needed to determine appropriate quality targets for these measures, a fundamental discussion currently missing.

In developing bundled payment models, it is widely acknowledged that including risk adjustments is essential to accommodate the inherent cost variability. The prevailing approach in most studies involves implementing risk adjustments at the patient level. Nevertheless, findings from Yount et al. indicate that such adjustments, based solely on patient factors, may not adequately address the financial risk borne by providers within the framework of bundled payment arrangements [70].

Furthermore, the research conducted by Malik et al. underscores the significance of extending risk adjustments beyond patient-specific factors. They advocate for considering additional factors, such as regional cost variations, to enhance the effectiveness of bundled payment initiatives [388]. This recognition of regional cost differences is particularly notable in the design of more recent programs, such as BPCI Advanced and CJR, which incorporate diverse metrics, including regional pricing, as part of their risk adjustment strategies [380].

While many studies focus on risk adjustments, outcome expectations are missing. When considering this in terms of risk factors, the expected outcomes for healthcare providers should be adjusted to account for the complexity and inherent challenges of treating complex patients. If these risk factors are considered when determining outcome expectations, HCPs can be appropriately rewarded for managing challenging cases and achieving appropriate outcomes relative to their complexity. However, the discussion tends to focus on whether the existing risk factors comprehensively address the financial risks associated with caring for complex patients rather than centring on outcome expectations [70]. This discrepancy draws attention to the disparity between the initial conditions outlined in bundled payment arrangements and the current practices prevalent in the literature.

When considering VBHC, a critical aspect relates to using actual cost data. Porter and Kaplan suggest using actual costs obtained via TD-ABC [30]; nonetheless, most studies used historical claims data within their analysis and did not describe their cost calculation method. Only a handful of studies used real costs and described their methods, with only three using TD-ABC. These findings represent a massive inconsistency between the original conceptualization of bundles and what is currently being done in academic studies. Based on the existing literature, it is established that TD-ABC allows a better understanding of the main cost drivers and can be used to determine the future bundle target price [452]. However, almost all included studies discuss using historical expenses to set bundle prices. Suppose historical values are consistently utilized to ascertain the cost of treatment within a bundle. In that case, this approach retains a connection to the amounts patients pay rather than accurately reflecting the genuine costs the healthcare provider bears. This practice contributes to the continuation of the existing issue at hand. Therefore, policymakers are encouraged to push for the development of standardized costing systems if we seek to implement a reimbursement structure like bundled payments. One study conducted in Belgium in radiotherapy provided evidence of implementing a national-level TD-ABC perspective of costs to advise policy implications focused on reimbursement changes [289]. These standardized costing approaches are fundamental, as we need to understand and measure the costs of all care providers.

Additionally, Porter and Kaplan discuss the need for a fair profit, whereby costs should cover all the necessary care plus a margin, but do not provide further detail on how this profit should be calculated or measured. This ambiguity is further translated into academic studies, as no study explicitly discusses how to measure it. The only discussion that links to profit centres around comparing the costs

incurred for treatment and the target price of the bundle. If costs incurred are lower than the target price, providers receive the excess amount as a reward (up to a specified limit) for providing services at reduced costs. The opposite occurs when the expenses exceed the set bundle price, resulting in losses.

Furthermore, one would expect that the calculation of setting appropriate bundle prices would differ depending on the cost perspective you take, i.e., actual costs vs. historical claims. However, two papers using TD-ABC to measure costs still used historical FFS amounts to set the prices of bundles [339, 376]. The study of Sibia et al. compares actual provider expenses to a set target price based on historical patients' claims, which is not intuitive. The idea put forward by Porter and Kaplan regarding fair profit represents a major gap in the formulation of bundled payments. Standardization is further emphasized from this perspective, as the target price should ideally cover all providers' expenses, not only one hospital. It is vital to mention that when discussing such matters, we cannot ignore the ethical issues that arise around obtaining profits, particularly in the healthcare sector. This could be one of the reasons why this particular topic is not fully addressed in existing papers.

Finally, an essential aspect discussed by Porter and Kaplan relates to excluding unrelated services and care not linked to the condition in question. From the literature, we see a great deal of emphasis placed on describing the inclusion and exclusion of patients to outline the necessary care services; thus, the discussion around what constitutes unrelated care within the theoretical definition and application is clear.

Likewise, Porter and Kaplan mention stop-loss provisions to limit the exposure providers may face with complex patients. The definition does not specify an exact approach to calculating the stop loss provision; however, one study mentions winsorization, a statistical technique to handle outliers, but does not apply it to their analysis [365]. Moreover, the stop-loss mechanism is not sufficiently elaborated or fully understood in the handful of studies that use it. However, they remain a crucial part of bundle design; thus, further investigation is necessary to incorporate them into the bundle.

With this analysis, we focus on bridging the gap between the theoretical framework brought forward by Porter and Kaplan and the existing literature. Based on the insights obtained, we propose a set of recommendations and thought-provoking considerations derived directly from our analysis to enrich the discourse surrounding reimbursement reform. Given the complexity of patients and diseases, we oppose the suggestion that bundles should cover the entire care cycle of disease. While we acknowledge the efforts of Porter and Kaplan in their quest to reform the reimbursement landscape, it’s apparent from the applications found in the literature that the implementation of bundles for the entire cycle of care may not be appropriate. For example, evidence shows that bundles are potentially better suited to surgical interventions as they follow a standardized procedure [75]. This view is further supported by the number of studies exploring bundled payments for total joint arthroplasty surgical intervention in the review. Furthermore, as we increase the type and number of services included in the bundle, we must acknowledge the associated administrative burden, hampering institutions' ability to initiate reform measures.

When deliberating the potential inclusions for the bundle of services, a crucial factor to contemplate is whether the scope of the bundle should encompass the costs associated with direct medications. Several points should be mentioned based on insights from this investigation and our challenges in developing bundles for chronic psoriasis. Firstly, differences exist in how direct medications are reimbursed depending on which country you base yourself on, so a universal approach is irrelevant. Secondly, substantial cost disparities exist between generic and brand-name pharmaceuticals, influencing the cost of treatment and, subsequently, the costs incurred within the bundle. This point was particularly apparent when considering the cost differences of biological drugs used to treat psoriasis patients. Suppose bundle prices are based on brand-name drugs. In that case, physicians are incentivized to prescribe generic medicines as these are less expensive, resulting in significant savings when reconciling expenses within the bundle to the target price. Thus, if medication costs are included within the bundle, strategic guidelines are necessary to ensure good prescribing habits among physicians to ensure standardization of practices.

Interestingly, separate bundles specifically linked to medication costs could also be formulated. Spinks et al. and Ward et al. investigate the feasibility of bundled payments within the oncology setting using only direct medications and expenses linked to adjuvant therapy [355, 356]. Using direct medications represents an interesting alternative to constructing bundles not initially outlined by Porter and Kaplan. Still, it shows the importance of evaluating many perspectives to find the most appropriate reimbursement solution.

Furthermore, it is imperative to reconsider all disease domains and accept that a one-size-fits-all solution may not be the answer for introducing bundles. Chronic diseases, for example, are incredibly complicated given the involvement of comorbidities and severity fluctuations impacting treatment selection; thus, determining the appropriate services is challenging. Moreover, given the patient mix, one can argue that the probability of finding standardized care among patients is slim. Hence, we face the prospect of creating numerous distinct care bundles to address the requirements of the diverse patient population dealing with chronic ailments. If we hone in on one of the goals of the VBHC initiative, namely personalized care, then developing a bundle based on a patient's needs moves us one step closer to realizing this dream. However, this may not be the answer the healthcare system needs now. If we closely consider the application of bundles in literature, perhaps the right starting point is to apply them to defined episodes of care (i.e., components of the care pathway) and not the entire care cycle. If we seek to simplify matters more, ideally, bundles are introduced in episodes following standardized clinical interventions, as we see with total joint arthroplasty. If we stick to standardized interventions, the oncology field might serve as an additional disease domain for implementing bundles. By adopting bundled payments for episodes of care while maintaining fee-for-service systems or even other explored systems like capitation or value-based payments for the more intricate stages of the clinical pathway, we embrace a mixed-methods approach to reimbursement. By conducting this analysis on bundled payments and developing a deeper understanding of the challenges associated with designing a single

reimbursement system, moving towards a setting whereby we embrace different methods to account for the inherent complexity may be the solution the system needs to achieve effective change.

Next to the services included in the bundle, it is important to discuss the duration of the bundle. In studying the applications of bundles, we saw that the primary model of services within the bundles tested was the acute care and PAC care services with varying durations. Ideally, when discussing reimbursement reform, we want to ensure that institutions in the same geographical region, for example, adhere to the same services and a specific duration for the bundle. One of the ways to achieve this could be by linking duration to appropriate clinical protocols and guidelines. Clinical guidelines provide clear directives for particular aspects of healthcare practice, grounded in the most current and robust available evidence [393]. Currently, papers use either 30, 60, or 90 days of PAC services as the duration of the bundle. However, if we seek to make bundles equal, clinical guidelines could help us to determine the most optimal bundle duration.

Alongside patient-centric outcomes, an obvious missing dialogue links to clinical targets, making connecting outcomes and the bundle challenging. Suppose the goal is to change the reimbursement system universally. In that case, consideration should be given to first agreeing to what constitutes appropriate clinical targets within bundles. Of course, it is important to recognize that universal reimbursement reform is well beyond our reach, given the inherent differences between countries (i.e., political and geographical differences). However, the discussion remains essential even on a country-specific basis. A starting point to advancing this narrative must be clearly defining disease-specific outcomes. The further development of patient-relevant outcomes sets through academic research and institutions like ICHOM will further facilitate these efforts. Once more, clinical guidelines serve as a crucial knowledge repository for diseases, aiding in identifying suitable disease-specific outcomes. Importantly, stakeholder engagement may offer an additional mechanism whereby physicians, researchers, patient advocacy groups, and payers can enter into meaningful dialogue around quality targets and ensure all interests are aligned. Finally, many articles in the review discussed bundled payment pilot projects, which are essential contributors to the topic. Feedback loops, especially around insights gained and experiences learned, are critical for determining the effectiveness of bundles and the appropriateness of quality targets that have been set. Additionally, we need to decide which approaches are relevant to linking bundled payments and achieving better outcomes, as this is not evident from the current literature or the definition of Porter and Kaplan.

As mentioned, we support investing time and effort into developing standardized costing approaches that hospitals should implement. Again, the suggestion is not to look at developing universally relevant costing approaches. However, hospitals within similar regions should be able to do critical benchmarking analyses that enhance the use of resources and help improve the way care is delivered.

A large focus of prior research has focused on cost variability and identifying relevant cost drivers. The strength of investigating cost drivers means these insights can be used to make appropriate

risk adjustments, which is well documented in the existing literature included in the review and our academic studies across disease domains. However, some additional mechanisms may be relevant if the idea is to limit the provider's potential risk. For example, scholars often discuss risk pooling approaches in supply chain management whereby individual demand and/or lead time variabilities are consolidated through aggregation to reduce variability and limit uncertainty and risk [394]. While the discussion around risk pooling within healthcare expands, the perspective usually covers inventory pooling, trans-shipments, etc. [395]. However, some opportunities still exist for fully utilizing this approach to reduce financial exposure; for example, instead of shifting all clinical and financial responsibilities onto the provider within the bundle, we could pool the costs of a predetermined episode of care and distribute them among providers, payers, and even patients. This may mitigate the concerns linked to bundles, whereby providers may incur hefty losses when treatment costs exceed reimbursement targets [329]. If we consider creating more patient-centred care, including patients in the potential risks may result in greater preventative behaviour and adherence to medical treatments.

To summarize, it is important to emphasize several points; firstly, if we have any hope of addressing the reimbursement concerns, the involvement of patients in managing and treating disease needs to become a priority. Including patients in critical decision-making underpins one of the fundamental concepts of VBHC. The patient's involvement may be pivotal when determining disease-specific outcomes and the associated target measures, ensuring value is obtained.

Secondly, the development differences between countries make it very difficult to agree to some of the conditions. For example, discussions of gainsharing and fair profit are grossly misplaced for countries with highly complex political climates and failing healthcare systems. The concern of these countries is not centred around reimbursement changes, i.e., the level of profits gained, but rather on obtaining equal access to healthcare services, addressing failing healthcare infrastructure, increasing the number of skilled workers, and more. Thus, the discussion around reimbursement, particularly bundled payments, seems to be concentrated in an American and Western European context, again highlighting the narrative that a global solution for reimbursement changes is optimistic.

Finally, while it is important to acknowledge the efforts made in suggesting an alternative payment system, this analysis has made it clear that formulating a singular payment system to tackle the present deficiencies effectively might be hopeful. This scoping review reveals a substantial discussion regarding bundles, allowing us to reevaluate this reimbursement system and gain deeper insights into the potential hurdles of crafting bundles for various diseases. Considering this perspective, it could prove valuable to reassess alternative reimbursement systems, examining their strengths, weaknesses, design complexities, and implementation obstacles. By conducting comprehensive comparisons across these schemes, a potential solution could emerge that draws upon the strengths of each system, allowing for a mixed methods solution.

While the study results show that significant gaps remain between the proposed conditions of bundled payments and the applications across disease domains, the results should be interpreted within

the context of their design and limitations. Firstly, as we employed a scoping review approach, valuable academic contributions on bundled payments may have been overlooked. However, we employed a broad search strategy covering eight databases and systematically obtained the necessary data. Secondly, we did not perform a quality assessment of the articles; as a result, lesser-quality articles may be included in our analysis. Thirdly, only one reviewer extracted information about the five conditions of Porter and Kaplan; thus, bias could arise based on interpreting the different elements included in the results. Despite these limitations, this study provides scholars and providers with valuable insights regarding developing bundled payments; conversely, designing bundled payments is incredibly complex, and one solution may not fit all medical domains.

6.5. Conclusion

While the conditions presented by Porter and Kaplan can be considered a standardized approach for designing and implementing bundles, we can conclude that one size does not fit all. The inherent differences between disease areas and patients highlight the challenge of developing effective bundles. For example, studies argue that planned elective operations may be more suitable for bundles than emergency procedures and chronic disease domains; this contradicts the initial proposal that bundles can be designed for all disease areas. Furthermore, a significant struggle resides in the lack of a clear and concise definition of the various elements, which is apparent when comparing the theoretical idea to academic applications. From this analysis, it is important to conclude that too much ambiguity exists, hampering our efforts to make reimbursement system advancements. This is evident in the gaps between the literature and the theoretical vision of Porter and Kaplan. To advance discussions around reimbursement changes, we offer some food for thought necessary to consider when implementing reform changes.

7. General conclusion

This thesis contributes to the value agenda by focusing on two components: the measurement of costs (i.e., excluding the direct measurement of outcomes) and the move towards bundled payment implementation in the sector. My thesis highlights the importance of costs, particularly how accurate cost measurements and the insights they generate can positively impact the industry. From this perspective, my thesis focuses on answering questions relating to costs. By exhaustively reviewing the current state of the literature on costs and variability, can we identify critical gaps for future research? We answer this question in Chapter 2 by systematically reviewing the literature and providing a comprehensive overview of studies focused on measuring cost variability across disease domains. In doing so, we identify potential gaps in the literature and offer suggestions for future research. Secondly, by measuring costs accurately, can we generate relevant insights for managerial staff to make more informed strategic decisions within a hospital context? Moreover, can we identify the significant drivers contributing to cost variations in the treatment pathway by investigating cost variability for various medical diseases? We answer these questions in Chapters 3, 4, and 5 by initially taking a limited number of patient files within a disease domain and later expanding on this research by considering a greater dataset and different views of disease areas. Through this analysis, we focus on drivers of costs relating to both patient and disease-specific characteristics.

Further, by measuring and understanding cost drivers, can these insights into cost and the relevant drivers provide sufficient insights to make more informed decisions, mainly on the level of reimbursement reform, and shift the sector towards bundled payment schemes? Given the inherent challenges associated with transforming the reimbursement system, Chapter 6 identifies the challenges we face in how bundled payments are theoretically envisioned and currently being applied in the existing literature, limiting implementation and design efforts. These questions serve as the foundation and objective of each chapter in my thesis. By answering these questions and through the insights generated, we aim to contribute academically to healthcare management and to practitioners and policymakers looking to obtain greater value for patients. The overarching contribution of my thesis is to add to the broader discussion of fundamental reform in the sector, with a particular focus on costs and the critical role they play in moving the industry toward a more sustainable future. In the following sections, I summarize each chapter's main findings, discuss the implications of my research, and focus on outlining several limitations of this dissertation. To end, I make some suggestions for future research on the topic.

7.1. Summary of findings

Chapter 2 starts with a systematic literature review of costing papers from the hospital's perspective. Through this study, we show the value cost variability studies have for providers and policymakers, especially as they move towards obtaining greater efficiency and, thus, value when delivering care. This systematic review provides an overview of the main types of cost variability drivers found in the literature. From these findings, we systematically present the main types of drivers and show which variables were significant in explaining cost variation for a range of medical domains. We systematically categorized the drivers of costs into broad categories, such as patient, disease, treatment, and hospital factors. We provided an exhaustive list of potential factors for future research, considering cost variability drivers. Through this study, we found significant ground to cover, particularly the level and quality of reporting methods utilized to measure costs in future investigations. Based on these findings, this chapter makes concrete suggestions for methodological improvements in hospital cost variability studies.

Using an exploratory approach, Chapter 3 illustrates how to measure costs over the complete care cycle for early-stage breast cancer using TD-ABC. Based on a limited number of patients, this chapter generates initial insights into the drivers of cost variability for breast cancer across the four main molecular subgroups. For example, we found evidence that disease characteristics such as severity, HER2-enriched, and triple-negative cancer forms significantly impact treatment costs across the different subtypes. Similarly, variation within molecular subtypes - for example, patient factors such as age and the presence of gene mutation - contribute to differences in treatment cost variability. These initial findings of measuring costs by applying TD-ABC over a care cycle highlight the fundamental benefit of investigating costs and understanding cost variations within a disease.

In Chapter 4, we measure the consultation costs and drivers linked to this component of the disease using TD-ABC. We identified patient status, personality type, the nurse conducting the consultation, and therapy switch as relevant drivers of cost variability in a dermatology setting through empirical analysis. These cost drivers were identified for the nurse, doctors, and full consultation. These insights allowed us to propose how the department could implement changes based on significant cost drivers to impact care delivery. Through this limited view of the care pathway, we show the value of using this costing approach to measure and understand costs in a disease domain with little prior knowledge of actual costs.

In Chapter 5, we build on our initial findings in the application of breast cancer and focus on one molecular subtype that offers variation in patient mix and treatment options. Using statistical analysis, we empirically analyse a more extensive patient dataset to identify relevant cost drivers for the complete treatment cycle and the surgical intervention within the treatment pathway. For the complete care cycle, we identified a mix of characteristics such as age at diagnosis, HER2-enriched, grade 3 tumours, and positive nodes as cost drivers. Regarding the surgery component, nodal status and

the need for future reconstruction played a vital role in cost determination. Using this analysis, we make process improvement recommendations for providers regarding optimizing the surgical intervention. By investigating cost drivers, we also suggest how bundled payments could be designed via risk adjustments using the significant preoperative variables identified in the regression model.

Chapter 6 discusses the second element of the value agenda, bundled payments. Through this scoping literature review, we compare the existing literature on bundled payments to the five conditions defined by Porter and Kaplan regarding which aspects should be included to achieve value. This analysis shows that designing and implementing adequate bundled payments is more challenging than anticipated. For one, bundled payments may not be the most appropriate reimbursement system for all disease domains; fundamental differences exist between disease domains and patients, leading to complications in determining appropriate care services. Additionally, the definitions outlined by Porter and Kaplan remain ambiguous in some aspects; for example, many articles do not even discuss fair profit, a critical aspect of obtaining the buy-in from providers to move towards this reimbursement system. Our analysis highlights the significant gaps between the theoretical idea and the bundle's application, which we believe impacts our ability to change and advance the reimbursement system towards a value-driven perspective. To contribute academically, we offer suggestions that could be used as food for thought on some crucial questions. With these findings, my research has several important implications.

7.2. Implications of research

As a starting point, the systematic literature review study provides a more nuanced understanding of cost variability in healthcare. In taking the cost perspective of the hospital, we further emphasize the importance of understanding costs from the provider's perspective and not necessarily from a societal standpoint. If we consider the rising expenditures in the sector, the costs incurred in the hospital become very important if we try to find optimal ways to address this problem. Moreover, deep diving into the literature gave a concise overview of the types of costs used, the costing methods applied, the description of costs, and the characteristics used to determine variability. In doing so, we contribute by identifying potential gaps in the existing literature and uncovering areas for further analysis and consideration. The insights generated, like the need for better details regarding the costing methods used within papers and recommendations on the level of methodology, are highly relevant for academic scholars looking to contribute to healthcare management, disease-specific domains, and health policy research on costs.

Additionally, our single case study on a limited dataset of patients, taking a medical classification perspective (i.e., molecular subtypes) and using an accounting technique, shows the value of using a multidisciplinary approach to conducting research. Through this research, we contributed to the academic literature by demonstrating the importance of TD-ABC in measuring the costs of the full care cycle for breast cancer, which had not previously been done. Furthermore, this study suggested

potential reasons for cost variations across and between the different molecular subtypes that were not previously known in the literature. These findings are highly relevant as they contribute to discussing variability within a single disease domain. Our results show that complexity and variation can arise even within standardized medical areas due to several factors relating to the patient and the disease. An additional academic contribution is using a limited number of patients to determine the initial reasons for variation within a condition. Scholars can apply the same approach to investigate variability to understand the determinants of costs as a starting point.

Furthermore, we applied TD-ABC to two different medical diseases, one in oncology and the other in dermatology, on a larger dataset of patients. For both disease areas, we contribute to the academic literature by accurately measuring costs for various treatment pathway components to better understand the dollar cost of treating patients. Costs taken from the provider perspective in psoriasis are still underexplored. Additionally, by empirically investigating which patient and disease characteristics explain cost variation, we contribute to discussing early-stage luminal B breast cancer and psoriasis. In combining TD-ABC with empirical investigations, we show the value of studying costs and their appropriate drivers for these healthcare sectors. By investigating the drivers, we provide useful information to make fundamental decisions that could lead to improved cost management and better allocation of resources.

Moreover, while reform is necessary, implementing bundled payments may not be obvious when discussing reimbursement changes. We make several highly relevant academic contributions by assessing the existing literature on bundled payments and comparing it to the five conditions laid out by Porter and Kaplan. Several discrepancies exist between the elements considered to offer value to patients via bundles. While Porter and Kaplan suggest that bundles should cover the full range of services for treating a patient, studies argue that they may be better suited to components of the treatment pathway rather than the full cycle of care. Additionally, the link between outcomes and bundles remains ambiguous, making it difficult to understand how value can be obtained via this reimbursement system. Likewise, there is no explicit discussion regarding what constitutes a fair profit, both in the literature and in the definition by Porter and Kaplan. Additionally, we find virtually no discussion of efficient and effective care. These findings highlight the difficulties and gaps in current theoretical perspectives on this approach to payment reform, suggesting that the implementation and design of bundled payments may be less straightforward than initially thought. These findings are important for academic scholars and future research efforts seeking to contribute to policy decisions on moving toward the effective implementation of bundles in practice.

From a management perspective, several important implications arise from my research. Firstly, my research shows the fundamental importance that costs play in healthcare. While costs are fully explored in other industries, the importance of accurately measuring costs was really emphasized when the VBHC framework was introduced. Nonetheless, calculating costs and understanding what drives costs represent the foundation for everything, even healthcare. Thus, TD-ABC has proven its worth as

an approach. Managers can quickly implement TD-ABC to get an initial view of their processes and related costs and start making effective decisions regarding curbing the rising healthcare expenditure.

Secondly, by measuring costs for a disease domain over the treatment cycle, managers and providers can better understand the costs associated with resources used in treatment. Important decisions can be made on how to use resources more optimally to reduce costs and eliminate potential unnecessary services while still ensuring the value provided to patients. Additionally, if we move to understand costs across multiple providers, we can fully develop standardization regarding costs across the sector. We have already discussed the value of deploying standardized costing methods, emphasizing how this can enable greater benchmarking activities. Standardization of methods is necessary if we want to optimize care pathways and cluster services in specific geographical locations to lead to even more effective and efficient care. My research further emphasizes the importance of moving toward standardization on a cost level within the sector.

Thirdly, through the empirical examination of cost variability drivers, we propose suggestions on how managers can use these insights for cost savings opportunities. Immense consideration can be given to targeting areas of high-cost variability and standardizing procedures, allowing hospitals and departments to reorganize themselves to ensure better care delivery.

Finally, costs will be fundamental in determining or changing the current reimbursement system. Through knowledge of costs, providers and policymakers are encouraged to use costs incurred by hospitals to determine appropriate metrics for reimbursement reform. Managers and policymakers can use the insights generated across the different studies to impact healthcare delivery positively. By improving their understanding of costs and variability, they can identify cost savings opportunities and improve the quality and efficiency of healthcare service delivery.

7.3. Limitations

While the contributions of the thesis are clear, it is crucial to emphasize several limitations of our research. First, while we recognize the importance of all six elements that comprise the value agenda, we take a narrow perspective and only concentrate on two. I acknowledge the need for all six components to be explored together to move toward a value-driven system; however, the results obtained across the different chapters show that even studying them in isolation can lead to considerable contributions to the discussion of VBHC.

Second, we take an even limited perspective, whereby we only measure the costs linked to treatment and not the patient-reported outcomes. By excluding outcomes, this dissertation does not directly address how adjusting costs can impact patient outcomes or the corresponding value metric obtained. Patient metrics such as physical function, patient satisfaction, and symptom improvement represent essential factors of the VBHC as they provide insights into the impact of healthcare interventions on the well-being of patients. One reason for excluding patient outcomes is that this data is still relatively limited and not measured by hospitals. If we are to reach a point where outcomes

become available, significant buy-in from multiple stakeholders (providers and patients) is necessary. Thus, with a limited perspective, the sole focus of my thesis was on measuring costs more accurately, identifying the main drivers, and explaining how these insights can help hospital providers and impact policymaking regarding necessary reform measures. The absence of patient-reported outcomes limits our ability to discuss the full impact of costs on value.

Third, TD-ABC is applied to a disease domain of a single centre for both disease areas under investigation. The existing structure of the dermatology department treating psoriasis patients differs from that of other hospitals treating similar patient populations. These differences can impact the cost variability drivers identified within the analysis, making it extremely difficult to generalize our findings to a comparative hospital or healthcare setting. Thus, the distinct setup of hospitals and departments can lead to differences in the underlying cost structures and their corresponding drivers. In contrast, however, for breast cancer, the treatment pathway is often highly standardized due to well-established guidelines and protocols. This standardization reduces the variation in treatment practices across different healthcare centres, making generalizing the findings related to cost drivers easier. While generalizations are critical for implementing changes in healthcare, it is always important to consider the specific context and local factors that may influence cost drivers and resource allocation.

Fourth, following the definition of the full cycle of a medical disease, we only consider one component of the condition, i.e., consultation costs, for psoriasis. Given the chronic nature of the disease and the importance comorbidities play in treating psoriasis, this limited view implies the insights generated are limited and do not allow us to make generalizations for the complete care cycle. However, this in no way reduces the value of our findings, given the limited prior knowledge of costs in this specific disease area.

Fifth, while the systematic and scoping reviews provide a comprehensive literature overview, some important academic papers may have been inadvertently excluded due to limitations in the search strategy or the inclusion criteria. Additionally, the interpretation of the papers could potentially be biased by the reviewers. Thus, potential opportunities for future research exist whereby a broader range of studies are considered to obtain an even greater comprehension of the topic.

Finally, the final chapter primarily focuses on the theoretical perspective of bundled payments and the application found in the existing literature. While this approach offers valuable insights and comparisons, it is essential to recognize that translating theory into practice may face various challenges and complexities. For one, ambiguity still exists on how bundles should be designed and implemented. For example, the discussion surrounding fair profit and how it should be measured remains unclear. This uncertainty and the complexity of the disease have made it extremely difficult to empirically design bundles within psoriasis, limiting our ability to bridge the gap between theory and practice.

7.4. Future research avenues

To conclude this thesis, I outline several important suggestions for future research in the field. For the effective and meaningful implementation of VBHC, it is crucial to consider all six agenda elements, for instance, integrating care delivery into several specialized sites, using IPUs, and developing an enabling information systems infrastructure. These components need to be considered in tandem to understand the feasibility of the VBHC framework.

Furthermore, while we took a single-site perspective, benchmarking across sites and locations can play a fundamental role in future research. By comparing providers across a particular medical disease, we can quickly identify differences in the treatment pathway and potential areas for process improvement. Additionally, if we compare the outcomes and costs, we can determine which provider obtains the best results at lower or maintained cost levels. Once we understand the inherent differences between providers, we can implement VBHC healthcare initiatives that could have resounding knock-on effects on the level of quality we obtain. While this may seem obvious, we still lack literature exploring benchmarking analysis and highlighting future research opportunities. From our own experience, we acknowledge the difficulty of benchmarking, for instance, the lack of standardization regarding hospital accounting systems, making cost comparisons nearly impossible. Additionally, not all healthcare providers are interested in collaborating on research in the field. This difficulty means there is a tremendous gap in the research. Future perspectives could contribute to the discussion of costs within healthcare by exploring the impact of standardization of costing methods and further assisting in understanding the differences in treatment costs for disease domains.

Additionally, when discussing VBHC, the equation of outcomes over costs remains at its core; however, no exact methods exist regarding how one should combine outcomes and costs to obtain a single value score. Many studies focus on measuring outcomes or costs in isolation for different disease domains. One of the reasons for this could relate to the limited access to data, particularly on the level of outcomes. While Porter and Kaplan highlight the importance of measuring outcomes meaningful to patients, many studies still focus on measuring outcomes related to existing processes. For example, studies confuse process improvement measures such as mortality and safety indicators [21] as relevant measures for patients. This confusion further exasperates the difficulty of calculating the value for patients. Of course, we acknowledge that data relating to patient-relevant outcomes remains limited, and this should not deter researchers; however, this lack of data hampers our efforts to move toward a truly value-driven system. Therefore, scholars looking to contribute to research on VBHC could consider measuring both patient outcome targets and their associated costs of the medical disease to obtain the most critical factors necessary to calculate the value for patients. Additionally, researchers could explore different methodologies to compute a score for value, i.e., directly linking outcomes and costs. In doing so, we may be able to relate process improvement initiatives to the value obtained,

allowing providers and policymakers to understand how changes to the care delivery pathway will impact costs and outcomes.

Furthermore, we only considered costs incurred from the hospital's perspective when conducting our systematic review. However, societal costs play a significant role in the sector. Scholars could consider a similar study, using an alternative lens to assess which factors drive cost variability. An overview of the different characteristics leading to cost variability at the level of societal costs provides significant insights for policymakers seeking to implement reforms within disadvantaged communities, for example.

Another important aspect is the cultural appetite of providers to accept fundamental reform measures like VBHC. The degree to which VBHC can be investigated within an institution depends heavily on the buy-in of hospital staff. Furthermore, introducing the VBHC framework implies that healthcare institutions will undergo tremendous change. Departments must move from their current siloed structures to IPUs, thus impacting healthcare delivery by bringing all relevant medical practitioners together. With these fundamental changes, leadership style and organizational culture will play a massive role in migrating toward reform. Scholars seeking to contribute to the field could assess how leadership style could impact individual employees' willingness to accept the VBHC framework. Additionally, researchers could consider how the existing organizational culture within hospitals plays a role in the acceptance of the VBHC framework.

8. Appendix

8.1. Appendix Chapter 2

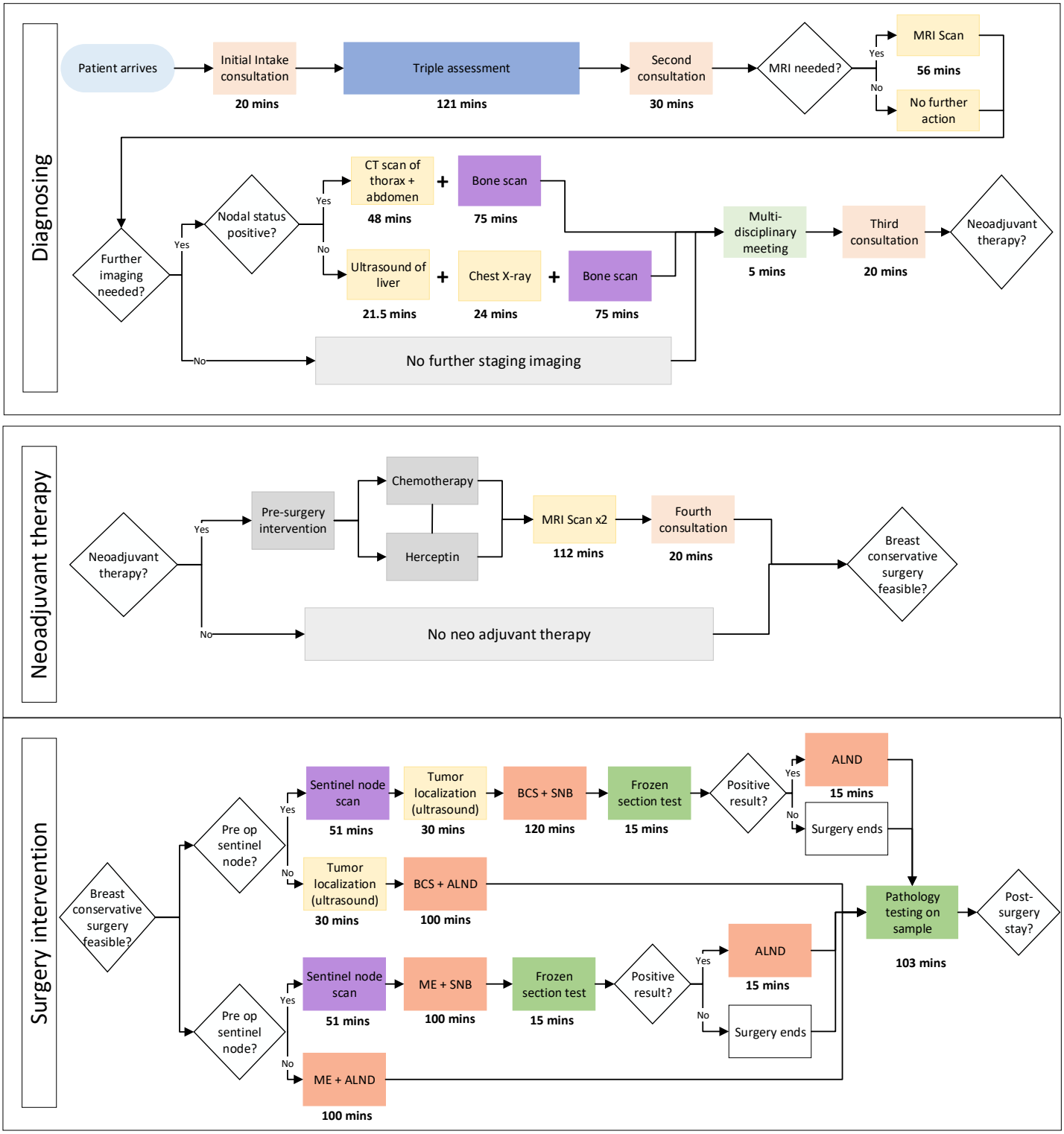
Appendix 2A. Search strategies for each journal

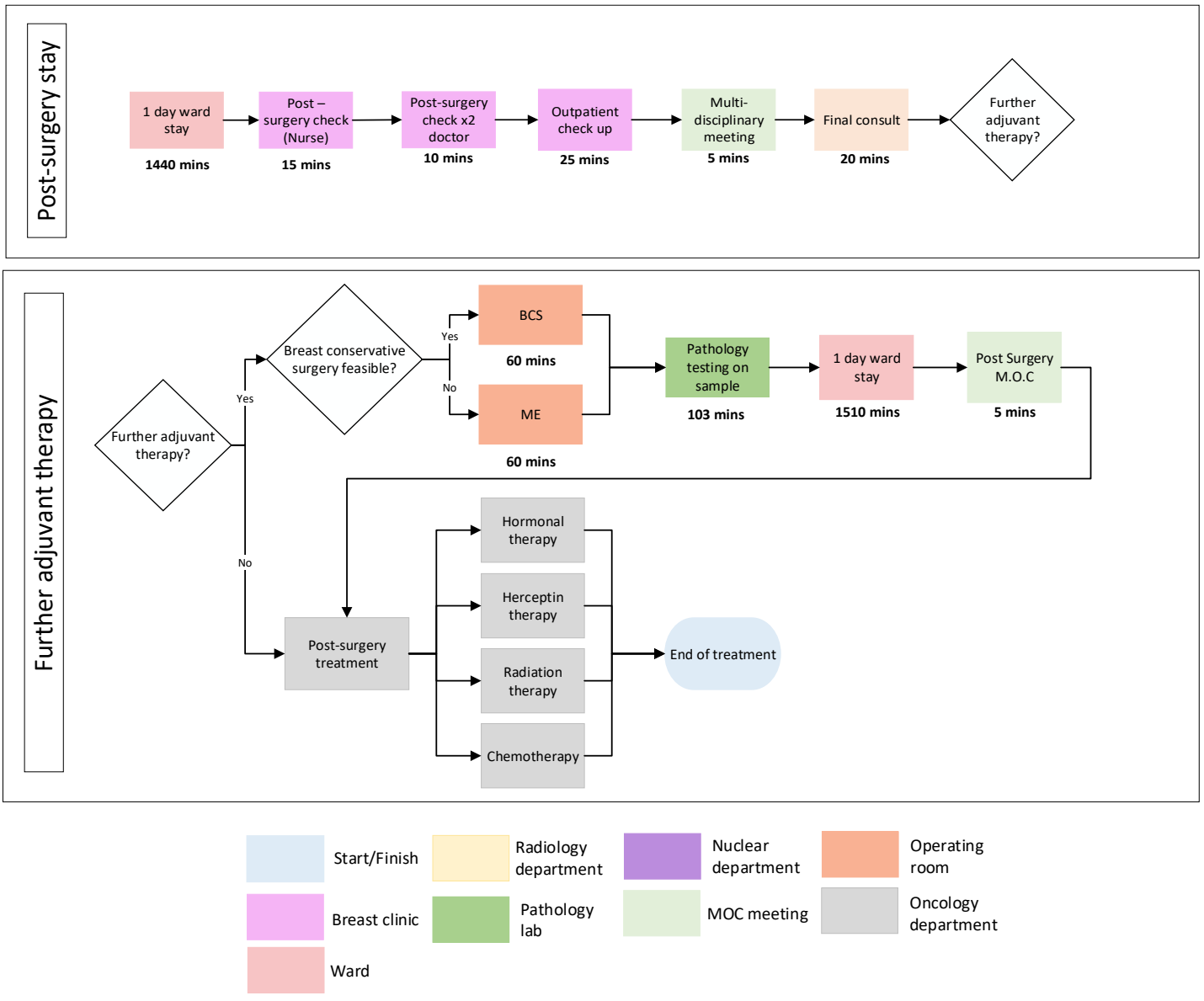
Database	Search strategy
PubMed/MEDLINE	(((hospital cost[MeSH Terms]) AND hospital costs[MeSH Terms])) AND ((((((((((cost variability) OR costs variability) OR variation in cost*) OR cost variation) OR costs variation) OR cost variance*) OR cost difference*) OR costs difference*) OR cost driver*) OR costs driver*)
EMBASE	hospital cost*' AND ('cost* variability' OR 'variation in cost*' OR 'cost* variation' OR 'cost variance*' OR 'cost difference*' OR 'cost driver*' OR 'costs driver*')
WebOfScience	TS=(‘hospital NEAR cost*’) AND TS=(‘cost NEAR variability’ OR ‘costs NEAR variability’ OR ‘variation NEAR in NEAR cost*’ OR ‘cost NEAR variation’ OR ‘costs NEAR variation’ OR ‘cost NEAR variance*’ OR ‘cost NEAR difference*’ OR ‘costs NEAR difference*’ OR ‘cost NEAR driver’ OR ‘costs NEAR driver*’)
OvidSP	hospital cost*' AND ('cost* variability' OR 'variation in cost*' OR 'cost* variation' OR 'cost variance*' OR 'cost difference*' OR 'cost driver*' OR 'costs driver*')
Scopus	('hospital AND costs' OR 'hospital AND cost') AND ('cost AND variability' OR 'costs AND variability' OR 'variation AND in AND cost' OR 'variation AND in AND costs' OR 'cost AND variation' OR 'costs AND variation' OR 'cost AND variance' OR 'cost AND variances' OR 'cost AND difference' OR 'cost AND differences' OR 'costs AND difference' OR 'costs AND

	differences' OR 'cost AND driver' OR 'cost AND drivers' OR 'costs AND driver' OR 'costs AND drivers')
CINAHL	TX ((“hospital cost” OR “hospital costs”)) AND TX ((“cost variability” OR “costs variability” OR “variation in cost” OR “variation in costs” OR “cost variation” OR “costs variation” OR “cost variance” OR “cost variances” OR “cost difference” OR “cost differences” OR “costs difference” OR “costs differences” OR “cost driver” OR “cost drivers” OR “costs driver” OR “costs drivers”))
Science Direct	(“hospital cost” OR “hospital costs”)) AND (“cost variability” OR “costs variability” OR “variation in cost” OR “variation in costs” OR “cost variation” OR “costs variation” OR “cost variance” OR “cost variances” OR “cost difference” OR “cost differences” OR “costs difference” OR “costs differences” OR “cost driver” OR “cost drivers” OR “costs driver” OR “costs drivers”)
Cochrane	(((hospital cost[MeSH Terms]) AND hospital costs[MeSH Terms])) AND ((((((((((cost variability) OR costs variability) OR variation in cost*) OR cost variation) OR costs variation) OR cost variance*) OR cost difference*) OR costs difference*) OR cost driver*) OR costs driver*)

8.2. Appendix Chapter 3

Appendix 3A. A full overview of the treatment path




Post-surgery stay
1 day ward stay
1440 mins
Post – surgery check (Nurse)
15 mins
Post-surgery check x2 doctor
10 mins
Outpatient check up
25 mins
Multi-disciplinary meeting
5 mins
Final consult
20 mins
Further adjuvant therapy?
Further adjuvant therapy
Further adjuvant therapy?
Yes
No
Breast conservative surgery feasible?
Yes
No
BCS
60 mins
ME
60 mins
Pathology testing on sample
103 mins
1 day ward stay
1510 mins
Post Surgery M.O.C
5 mins
Post-surgery treatment
Hormonal therapy
Herceptin therapy
Radiation therapy
Chemotherapy
End of treatment
Start/Finish
Radiology department
Nuclear department
Operating room
Breast clinic
Pathology lab
MOC meeting
Oncology department
Ward

Appendix 3B. Resource cost per minute – medical personnel, machines & departments

Resource – medical personnel[1]	Cost per minute ($/min)
Breast doctor[2]	$2.36
Breast nurse[3]	$0.75
Radiologist	$5.75
Radiologist nurse	$0.68
Secretary	$0.79
Pathology technician	$0.86
Pathologist	$3.77
Anaesthetist	$3.83
Operating room assistant	$0.59
Operating room nurse	$0.76
Oncologist	$2.51
Pharmacist	$1.14
Assistant pharmacist	$0.66
Administrator	$0.71
Nuclear doctor	$2.72
Psychologist	$0.79
Radiation therapist[4]	$0.35
Resource – machines[5]	
Mammogram machine	$1.25
Ultrasound machine	$0.12
MRI machine	$3.32
Tissue processing machine	$0.12
Cover staining machine	$0.11
CT machine	$1.10
X-ray machine	$1.22
Bone scanning machine	$0.03
Biopsy machine	$0.08
Resource – medical departments	
Oncology	$3.30
Radiology	$8.27
Pathology	$1.39
Operating room	$14.44
MDT meeting facilities	$0.36
Nuclear medicine	$0.84
Breast clinic	$0.29
1 day hospitalization[6]	$0.36

[1]Given the sensitivity surrounding remuneration the cost for medical personnel were calculated using figures from a Belgian study published by the Belgian Health Care Knowledge Centre in 2012, which is a federal research institution focusing on health care research. In order to provide a more accurate salary amount an index of 7.2% was added to account for inflation

[2]Breast doctor's practical capacity on an annual basis = 2,400 hours per year

[3] All in-house medical staff have an annual practical capacity = 1,620 hours per year

[4]Radiation therapist works as a consultant for multidisciplinary meetings. The hourly rate is displayed for this medical personnel. The hospital where this study was conducted does not provide any radiation therapy for the patients. Therefore, the average cost of radiation therapy comes from a study published in the KCE in 2012 on average radiation costs and adjusted this amount for inflation.

[5]Practical capacity of machines is based on the same rate as the in-house medical staff of 1620 hours per year

[6]1 day hospitalization cost represents the 1 day rate for a patient staying in the hospital

8.3. Appendix Chapter 4

Appendix 4A. Correlation Matrix – Psoriasis variables

	Nurse consult cost	Doctors consult cost	Total consult cost	Age	Gender	BMI	Engagement with disease	Burden of disease	DLQI Score	PASI score	PSA	HADS_A	HADS_D	Therapy switch	Patient status	Nurse
Nurse consult cost	1.0000															
Doctors consult cost	0.3400	1.0000														
Total consult cost	0.5796	0.9634	1.0000													
Age	-0.0295	0.0641	0.0471	1.0000												
Gender	-0.1647	-0.0476	-0.0882	0.2108	1.0000											
BMI	0.0622	-0.0214	-0.0008	0.3364	0.2777	1.0000										
Engagement with disease	-0.2832	-0.3589	-0.3925	0.2307	0.1698	0.0641	1.0000									
Burden of disease	0.4289	0.2072	0.3018	-0.1372	-0.2368	0.0801	-0.4297	1.0000								
DLQI Score	0.4338	0.2379	0.3297	-0.1317	-0.2009	0.0538	-0.4599	**0.7975****	1.0000							
PASI score	0.2489	0.2781	0.3119	-0.0643	0.0128	0.0898	-0.4833	0.4157	0.4755	1.0000						
PSA	0.0433	0.0483	0.0542	0.0691	0.2702	0.0785	0.1098	-0.0197	0.0076	-0.1204	1.0000					
HADS_A	0.1244	0.1577	0.1721	-0.1307	-0.3324	-0.0732	-0.1306	0.5235	0.4453	-0.0291	-0.0044	1.0000				
HADS_D	0.1606	0.1176	0.1477	-0.0804	-0.3089	0.0881	-0.1881	0.5782	0.4901	0.0122	-0.0624	**0.7164****	1.0000			
Therapy switch	0.2077	0.4093	0.4139	-0.0388	-0.0026	-0.0171	-0.5289	0.2797	0.3230	0.4008	-0.1438	0.1278	0.1261	1.0000		
Patient status	0.4522	0.2538	0.3488	-0.0232	0.0166	-0.0219	-0.5880	0.2780	0.3729	0.3560	-0.0298	-0.0945	-0.0612	0.3160	1.0000	
Nurse	0.0739	-0.0094	0.0129	0.0151	-0.0611	-0.0365	0.1885	-0.2356	-0.2520	-0.1907	0.0799	0.0267	-0.1329	-0.0802	-0.0821	1.0000

8.4. Appendix Chapter 5

Appendix 5A. The resource cost of medical personnel

Medical personnel	Cost (annual salary)	Practical capacity (in minutes)	Cost per min (€/min)
Breast doctor	€ 316.927,00	144 000	€ 2,20
Breast nurse	€ 68.181,00	97 200	€ 0,70
Radiologist	€ 519.855,00	97 200	€ 5,35
Radiologist nurse	€ 59.992,00	97 200	€ 0,62
Radiation therapist*	€ 18,41	60	€ 0,31
Secretary	€ 60.600,00	97 200	€ 0,62
Pathologist	€ 70.393,00	97 200	€ 0,72
Pathology technician	€ 340.725,00	97 200	€ 3,51
Anaesthetist	€ 346.701,00	97 200	€ 3,57
Operating room assistant	€ 50.737,00	97 200	€ 0,52
Operating room nurse	€ 71.734,00	97 200	€ 0,74
Oncologist	€ 227.194,00	97 200	€ 2,34
Pharmacist	€ 96.986,00	97 200	€ 1,00
Assistant pharmacist	€ 52.765,00	97 200	€ 0,54
Administrator	€ 65.934,00	97 200	€ 0,68
Nuclear doctor	€ 364.406,00	144 000	€ 2,53
Psychologist	€ 70.525,00	97 200	€ 0,73
*Hourly rate			

Appendix 5B. Resource cost medical machines

Machine	Maintenance cost	Depreciation cost	Total cost	Practical capacity (in minutes)	Cost per min (€/min)
Mammogram machine	€ 23.787,00	-	€ 23.787,00	97 200	€ 0,24
Ultrasound machine	€ 3.675,00	€ 9.000,00	€ 12.657,00	97 200	€ 0,13
MRI machine	-	€ 285.349,00	€ 285.349,00	97 200	€ 2,94
Tissue processing machine	-	€ 11.113,00	€ 11.113,00	97 200	€ 0,11
Cover staining machine	€ 1.611,00	€ 9.680,00	€ 11.291,00	97 200	€ 0,12
CT scan machine	€ 55.017,00	€ 41.000,00	€ 96.017,00	97 200	€ 0,99
X-ray machine	€ 24.736,00	€ 80.526,00	€ 105.262,00	97 200	€ 1,08
Bone scanning machine	€ 3.067,00	€ 10.890,00	€ 13.957,00	97 200	€ 0,14
Biopsy machine	€ 1.148,00	€ 6.677,00	€ 7.825,00	97 200	€ 0,08

Appendix 5C. Resource cost medical departments

Department	Maintenance cost	Depreciation cost	Indirect department costs	Total cost	Practical capacity (in minutes)	Cost per min (€/min)
Oncology	€ 20,00	€ 5.527,00	€ 298.814,00	€ 304.361,00	97 200	€ 3,13
Radiology	€ 215.241,00	€ 58.081,00	€ 575.013,00	€ 848.335,00	97 200	€ 8,73
Pathology	€ 11.644,00	€ 9.520,00	€ 127.444,00	€ 148.608,00	97 200	€ 1,53
Operating room	€507,00	€ 57.866,00	€ 1.605.462,00	€ 1.663.835,00	97 200	€ 2,85
General hospital*	-	-	-	€ 468,50	1 440	€ 0,33
Nuclear medicine	€ 4.016,00	€ 258.246	€ 96.754	€ 359.016,00	97 200	€ 3,69
Breast clinic	€ 5.919,00	€ 11.207,00	€ 40.800,00	€ 57.926,00	97 200	€ 0,60
MDT facility	-	-	€ 38.176,00	€ 38.176,00	97 200	€ 0,39
*1-day rate for the patient staying at the hospital						

Appendix 5D. Cost initial consultation - activity

Initial consultation						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Breast clinic	€ 0,60	€ 6,10
Discussion of history	5	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 17,49
		Breast nurse	€ 0,70			
Clinical exam	10	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 34,98
		Breast nurse	€ 0,70			
						€ 58,57

Appendix 5E. Cost mammogram - activity

Triple assessment - mammogram						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Radiology	€ 8,73	€ 46,76
Undress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Imaging	12,5	Radiologist nurse	€ 0,62	Radiology	€ 8,73	€ 119,87
		Mammogram machine	€ 0,24			
Dress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18

Analysis & report	5	Radiologist	€ 5,35	Radiology	€ 8,73	€ 70,35
						€ 289,37

Appendix 5F. Cost ultrasound breast - activity

Triple assessment – ultrasound of breast						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Radiology	€ 8,73	€ 46,76
Undress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Imaging	10	Radiologist	€ 5,35	Radiology	€ 8,73	€ 142,06
		Ultrasound machine	€ 0,13			
Dress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Analysis & report	5	Radiologist	€ 5,35	Radiology	€ 8,73	€ 70,38
						€ 311,57

Appendix 5G. Cost core biopsy – activity

Triple assessment - core biopsy						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Radiology	€ 8,73	€ 46,76
File check	2	Radiologist	€ 5,35	Radiology	€ 8,73	€ 28,15
Prepare	5	Radiologist nurse	€ 0,62	Radiology	€ 8,73	€ 57,22
Punch	15	Radiologist nurse	€ 0,62	Radiology	€ 8,73	€ 155,61
Close wound	10	Radiologist nurse	€ 0,62	Radiology	€ 8,73	€ 93,45
Process sample	5	Technician	€ 0,72	Pathology	€ 1,53	€ 11,76
		Lymph node sectioning machine	€ 0,08			
Analysis & report	10	Pathologist	€ 3,51	Pathology	€ 1,53	€ 50,34
						€ 443,21

Appendix 5H. Cost core biopsy – material

Direct material used	
Localization needle	€ 10,50
Core biopsy needle	€ 15,44

Appendix 5I. Cost second consultation - activity

Second consultation						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Breast clinic	€ 0,60	€ 6,10
Discuss results	25	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 87,46
		Breast nurse	€ 0,70			
						€ 93,55

Appendix 5J. Cost MRI – activity

MRI Scan						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Radiology	€ 8,73	€ 46,76
Undress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Imaging	30	Radiologist nurse	€ 0,62	Radiology	€ 8,73	€ 386,42
		MRI machine	€ 2,94			
Dress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Analysis & report	15	Radiologist	€ 5,35	Radiology	€ 8,73	€ 211,14
						€ 678,68

Appendix 5K. Cost CT scan – activity

CT scan of thorax and abdomen						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Radiology	€ 8,73	€ 46,76
Undress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Prepare patient	15	Radiologist nurse				€ 140,17
Scan	7	Radiologist nurse	€ 0,62	Radiology	€ 8,73	€ 72,33
		CT Scan machine	€ 0,99			
Dress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18

Analysis & report	15	Radiologist	€ 5,35	Radiology	€ 8,73	€ 211,14
						€ 522,77

Appendix 5L. Cost ultrasound - activity

Ultrasound of liver						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Radiology	€ 8,73	€ 46,76
Undress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Scan	7,5	Radiologist nurse	€ 0,62	Radiology	€ 8,73	€ 71,06
		Ultrasound machine	€ 0,13			
Dress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Analysis & report	3	Radiologist	€ 5,35	Radiology	€ 8,73	€ 42,23
						€ 212,42

Appendix 5M. Cost X-ray - activity

Chest X-ray						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Radiology	€ 8,73	€ 46,76
Undress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Scan	10	Radiologist nurse	€ 0,62	Radiology	€ 8,73	€ 104,28
		X-ray machine	€ 1,08			
Dress	3	-	€ 0,00	Radiology	€ 8,73	€ 26,18
Analysis & report	3	Radiologist	€ 5,35	Radiology	€ 8,73	€ 42,23
						€ 245,63

Appendix 5N. Cost bone scan - activity

Bone scan						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Nuclear medicine	€ 3,69	€ 21,59
Prepare patient	15	Radiologist nurse	€ 0,62	Nuclear medicine	€ 3,69	€ 64,66

Scan	20	Radiologist nurse	€ 0,62	Nuclear medicine	€ 3,69	€ 89,09
		Bone scanning machine	€ 0,14			
Imaging reconstruction	5	Radiologist nurse	€ 0,62	Nuclear medicine	€ 3,69	€ 21,55
Analysis & report	15	Nuclear doctor	€ 2,53	Nuclear medicine	€ 3,69	€ 93,36
						€ 290,25

Appendix 5O. Cost multidisciplinary meeting – activity

Bone scan						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Discuss patient file	5	Secretary	€ 0,62	MDT facility	€ 0,39	€ 3,12
		Breast nurse	€ 0,70			€ 3,51
		Breast doctor	€ 2,20			€ 12,97
		Radiologist	€ 5,35			€ 26,74
		Pathologist	€ 3,51			€ 17,53
		Oncologist	€ 2,34			€ 11,69
		Nuclear doctor	€ 2,53			€ 12,65
		Psychologist	€ 0,73			€ 3,63
		Radiation therapist	€ 0,31			€ 1,53
						€ 93,36

Appendix 5P. Cost third consultation - activity

Third consultation						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Breast clinic	€ 0,60	€ 6,10
Discuss results	30	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 104,95
		Breast nurse	€ 0,70			
						€ 111,05

Appendix 5Q. Chemotherapy (EC only)

Chemotherapy – EPIRUBICIN						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Oncology	€ 3,13	€ 18,77
Preparing	25	Assistant pharmacist	€ 0,54	Oncology	€ 3,13	€ 91,85
Confirm treatment	10	Oncologist	€ 2,34	Oncology	€ 3,13	€ 27,34
Medication is given to the patient	180			Oncology	€ 3,13	€ 563,4
Check on patient	7	Oncologist	€ 2,34	Oncology	€ 3,13	€ 38.28
						€ 767,23
Direct medication			Eirenicon accord FL INJ (150ml)			**€ 206,64**
Cost for a single session						**€ 973,86**
Cost of four sessions						**€ 3.895,44**

Appendix 5R. Chemotherapy (Taxol only)

Chemotherapy – Taxol						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Preparing time	20	Assistant pharmacist	€ 0,54	Oncology	€ 3,13	€ 73,46
Confirm treatment	10	Oncologist	€ 2,34	Oncology	€ 3,13	€ 54,69
Preparing medicine	15	Assistant pharmacist	€ 0,54	Oncology	€ 3,13	€ 55,11
Medication is given to the patient	180			Oncology	€ 3,13	€ 563,4
Check on patient	10	Oncologist	€ 2,34	Oncology	€ 3,13	€ 54,69
Cost of resource only						**€ 801,60**
Direct medication			Paclitaxel FL INJ (150ml)			**€ 162,15**
Cost for a single session + medication						**€ 963,75**
Cost of twelve sessions						**€ 11.565,00**

Appendix 5S. Cost target therapy – Herceptin only

Herceptin only						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Preparing time	25	Assistant pharmacist	€ 0,54	Oncology	€ 3,13	€ 91,85
Confirm treatment	5	Oncologist	€ 2,34	Oncology	€ 3,13	€ 27,34
Medication is given to the patient	60			Oncology	€ 3,13	€ 187,80
Check on patient	7	Oncologist	€ 2,34	Oncology	€ 3,13	€ 38,28
Cost of resource only						**€ 372,70**
Direct medication			Herceptin FL PULV SOL PERF (150mg)			**€ 1554,93**
Cost for a single session + medication						**€ 1.927.63**
Cost of 18 sessions						**€ 34.697.34**

Appendix 5T. Cost target therapy – Chemotherapy + Herceptin

Chemotherapy + target therapy						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Preparing time	10	Assistant pharmacist	€ 0,54	Oncology	€ 3,13	€ 36,74
Confirm treatment	5	Oncologist	€ 2,34	Oncology	€ 3,13	€ 27,34
Prepare medicine	7,5	Assistant pharmacist	€ 0,54	Oncology	€ 3,13	€ 27,55
Medication is given to the patient	120			Oncology	€ 3,13	€ 375,75
Check on patient	5	Oncologist	€ 2,34	Oncology	€ 3,13	€ 27,35
Cost of a resource only						**€ 494,70**

Appendix 5U. Cost fourth consultation – activity

Fourth consultation						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Breast clinic	€ 0,60	€ 6,10
Discuss results	15	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 34,98
		Breast nurse	€ 0,70			
						€ 41,08

Appendix 5V. Cost sentinel node scan – activity

Chest X-ray						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Nuclear department	€ 3,69	€ 21,59
Prepare patient	10	Radiologist nurse	€ 0,62	Nuclear department	€ 3,69	€ 43,11
Injection & scan	20	Radiologist nurse	€ 0,62	Nuclear department	€ 3,69	€ 89,09
		Bone scanning machine	€ 0,14			
Imaging reconstruction	5	Radiologist nurse	€ 0,62	Nuclear department	€ 3,69	€ 21,55
Analysis & report	15	Nuclear doctor	€ 2,53	Nuclear department	€ 3,69	€ 93,36
						€ 268,70

Appendix 5W. Cost tumour localization - activity

Tumour localization						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Ultrasound technique	30	Radiologist	€ 5,35	Radiology	€ 8,73	€ 436,69
		Ultrasound machine	€ 0,13			
						€ 436,69

Appendix 5X. Cost tumour localization - materials

Direct material used	
Localization needle	€ 10,50

Appendix 5Y. Cost frozen section - activity

Frozen section biopsy						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Process sample	5	Technician	€ 0,62	Pathology	€ 1,53	€ 11,67
		Biopsy – lymph node sectioning machine	€ 0,08			
Analyse the sample	10	Pathologist	€ 3,51	Pathology	€ 1,53	€ 50,34
						€ 62,01

Appendix 5Z. Cost BCS + SNB – activity

BCS + SNB						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Surgery	72,5	Breast doctor	€ 2,20	Operating room	€2,85	€ 662,65
		Anaesthetist	€ 3,57			
		Operating room assistant	€ 0,52			
Cost without direct materials						**€ 662,65**
Cost of direct materials						**€ 94,07**
Cost of BCS + SNB + direct materials						**€ 756,72**

Appendix 5AA. Direct materials used (BCS+ SNB)

Direct materials	
C-Vax tornado Smoke Evacuation Pencil w/blade electrode	€ 17,29
Protexis Latex Micro-Surgical gloves with Nitrile Coating 5 1/2	€ 0,38
Protexis Latex Micro-Surgical gloves with Nitrile Coating 6 1/2	€ 0,38
Protexis Latex Micro-Surgical gloves with Nitrile Coating 7 1/2	€ 0,38
Hacdil-S 5mg:ml oplossing voor cutaan gebruik	€ 1,33
Mediset - sponsstaafje	€ 0,00
Ethicon Monocryl plus Antibacterial	€ 5,13
Vicryl Plus - Violet gevlochten chirurgisch hechtmateriaal resorbeerbaar	€ 4,30
Skin marker, standard tip	€ 1,01
Titanium Hemostatic clips 9 - small medium	€ 3,81
Borstset Rev04	€ 24,76

Universal handle cover	€ 4,65
Furacine - Zalf	€ 5,72
Jelonet 10x10cm	€ 0,34
Iso-betadine dermicum 10% 125ml	€ 3,39
Spiral drain - Round fluted drain 110 cm	€ 18,75
HP Reinforced Disposable Surgical Gown	€ 2,45
	€ 94,07

Appendix 5AB. Cost BCS + ALND – activity

BCS + ALND						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Surgery	106	Breast doctor	€ 2,20	Operating room	€2,85	€ 968,84
		Anaesthetist	€ 3,57			
		Operating room assistant	€ 0,52			
Cost without direct materials						**€ 968,84**
Cost of direct materials						**€ 663,94**
Cost of BCS + SNB + direct materials						**€ 1.632,78**

Appendix 5AC. Direct materials used (BCS+ ALND)

Direct materials	
C-Vax tornado Smoke Evacuation Pencil w/blade electrode	€ 17,29
Protexis Latex Micro-Surgical gloves with Nitrile Coating 5 1/2	€ 0,38
Protexis Latex Micro-Surgical gloves with Nitrile Coating 6 1/2	€ 0,38
Protexis Latex Micro-Surgical gloves with Nitrile Coating 7 1/2	€ 0,38
Hacdil-S 5mg:ml oplossing voor cutaan gebruik	€ 1,33
Mediset - sponsstaafje	€ 0,00
Ethicon Monocryl plus Antibacterial	€ 5,13
Vicryl Plus - Violet gevlochten chirurgisch hechtmateriaal resorbeerbaar	€ 4,30
Skin marker, standard tip	€ 1,01
Titanium Hemostatic clips 9 - small medium	€ 3,81
Borstset Rev04	€ 24,76
Universal handle cover	€ 4,65
Furacine - Zalf	€ 5,72

Jelonet 10x10cm	€ 0,34
Iso-betadine dermicum 10% 125ml	€ 3,39
Spiral drain - Round fluted drain 110 cm	€ 18,75
HP Reinforced Disposable Surgical Gown	€ 2,45
Medipore + Pad 10x15	€ 0,12
Medipore + Pad 10x25	€ 0,19
Vacuümfles voor wonddrainaige volgens redon; 400 ml	€ 4,16
Metalline - Drainage Pad	€ 0,12
Stella 5X XR/10 DE/DV Gaaskrompresse 10x10cm	€ 0,46
Dermabond topical skin adhesive - lokaal huidhechtmiddel	€ 244,17
Carbon steel surgical blade	€ 0,00
LigaSure curved, small jaw, open sealer/divider 16,5 mm - 19cm	€ 320,65
	€ 663,94

Appendix 5AD. Cost ME + SNB – activity

ME + SNB						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Surgery	100	Breast doctor	€ 2,20	Operating room	€2,85	€ 914,00
		Anaesthetist	€ 3,57			
		Operating room assistant	€ 0,52			
Cost without direct materials						**€ 914,00**
Cost of direct materials						**€ 329,97**
Cost of BCS + SNB + direct materials						**€ 1.243,97**

Appendix 5AE. Direct materials used (ME+ SNB)

Direct materials	
C-Vax tornado Smoke Evacuation Pencil w/blade electrode	€ 17,29
Protexis Latex Micro-Surgical gloves with Nitrile Coating 5 1/2	€ 0,38
Protexis Latex Micro-Surgical gloves with Nitrile Coating 6 1/2	€ 0,38
Protexis Latex Micro-Surgical gloves with Nitrile Coating 7 1/2	€ 0,38
Ethicon Monocryl plus Antibacterial	€ 5,13

Vicryl Plus - Violet gevlochten chirurgisch hechtmateriaal resorbeerbaar	€ 4,30
Skin marker, standard tip	€ 1,01
Titanium Hemostatic clips 9 - small medium	€ 3,81
Borstset Rev04	€ 24,76
Spiral drain – Round fluted drain 110cm	€ 18,75
Setpack Toptex lite RK buikgaas X-ray	€ 2,14
Medipore + Pad 10x10	€ 0,09
Medipore + Pad 10x25	€ 0,19
Versterkte operatiejas voor eenmalig gebruik	€ 2,45
Vacuümfles voor wonddrainaige volgens redon; 400 ml	€ 4,16
Metalline - Drainage Pad	€ 0,12
Dermabond topical skin adhesive - lokaal huidhechtmiddel	€ 244,17
Carbon steel surgical blade	€ 0,00
Stella 5X XR/10 DE/DV Gaaskrompresse 10x10cm	€ 0,46
PCM Comfort abdominal belt – width 24 cm	€ 0,00
	€ 329,97

Appendix 5AF. Cost ME + ALND – activity

ME + ALND						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Surgery	103	Breast doctor	€ 2,20	Operating room	€2,85	€ 941,42
		Anaesthetist	€ 3,57			
		Operating room assistant	€ 0,52			
Cost without direct materials						**€ 941,42**
Cost of direct materials						**€ 650,62**
Cost of BCS + SNB + direct materials						**€ 1.592,04**

Appendix 5AG. Direct materials used (ME+ ALND)

Direct materials	
C-Vax tornado Smoke Evacuation Pencil w/blade electrode	€ 17,29
Protexis Latex Micro-Surgical gloves with Nitrile Coating 5 1/2	€ 0,38
Protexis Latex Micro-Surgical gloves with Nitrile Coating 6 1/2	€ 0,38
Protexis Latex Micro-Surgical gloves with Nitrile Coating 7 1/2	€ 0,38
Ethicon Monocryl plus Antibacterial	€ 5,13
Vicryl Plus - Violet gevlochten chirurgisch hechtmateriaal resorbeerbaar	€ 4,30
Skin marker, standard tip	€ 1,01
Titanium Hemostatic clips 9 - small medium	€ 3,81
Borstset Rev04	€ 24,76
Spiral drain – Round fluted drain 110cm	€ 18,75
Setpack Toptex lite RK buikgaas X-ray	€ 2,14
Medipore + Pad 10x10	€ 0,09
Medipore + Pad 10x25	€ 0,19
Versterkte operatiejas voor eenmalig gebruik	€ 2,45
Vacuümfles voor wonddrainaige volgens redon; 400 ml	€ 4,16
Metalline - Drainage Pad	€ 0,12
Dermabond topical skin adhesive - lokaal huidhechtmiddel	€ 244,17
Carbon steel surgical blade	€ 0,00
Stella 5X XR/10 DE/DV Gaaskrompresse 10x10cm	€ 0,46
LigaSure curved, small jaw, open sealer/divider 16,5 mm - 19cm	€ 320,65
	€ 650,62

Appendix 5AH. Cost pathology test - activity

Pathology test on sample						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Prepare + register sample	3	Technician	€ 0,72	Pathology	€ 1,53	€ 6,76
Process tissue	4	Technician	€ 0,72	Pathology	€ 1,53	€ 9,47
		Tissue processing machine	€ 0,11			

Create slices	4	Technician	€ 0,72	Pathology	€ 1,53	€ 9,01
Stain slices	2	Technician	€ 0,72	Pathology	€ 1,53	€ 4,47
		Cover straining machine	€ 0,12			
Evaluate & report	90	Nuclear doctor	€ 3,51	Pathology	€ 1,53	€ 453,09
						€ 483,07

Appendix 5AI. Cost post-surgery stay – activity

Hospitalization						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
1-day hospitalization	1 440	General hospital	€ 0,33	General hospital	€ 0,33	€ 937,00
Post-surgery check	15	Breast nurse	€ 0,70	Breast clinic	€ 0,60	€ 19,46
Check patient after surgery	5	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 13,89
Evening check	5	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 13,89
Outpatient clinic registration	5	Secretary	€ 0,62	Breast clinic	€ 0,60	€ 6,10
Outpatient clinic discussion	20	Breast nurse	€ 0,70	Breast clinic	€ 0,60	€ 25,95
	5	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 14,00
Psychotherapy	20	Psychologist	€ 0,73	General hospital	€ 0,33	€ 21,02
						€ 1051,48

Appendix 5AJ. Final consultation - activity

Fifth consultation						
Tasks	**Time estimates (mins)**	**Type of resource**	**Cost per minute of resource**	**Department**	**Cost of department**	**Total cost**
Registration	5	Secretary	€ 0,62	Breast clinic	€ 0,60	€ 6,10
Discuss results	10	Breast doctor	€ 2,20	Breast clinic	€ 0,60	€ 34,98
		Breast nurse	€ 0,70			
						€ 41,08

Appendix 5AK. Cost radiation therapy

Types of radiation therapy	
Hypofractionated forw. Plan IMRT - external boost	€ 6.828,99
Standard fractionated forw. Plan. IMRT - no boost	€ 5.576,32
Standard fractionated forw. Plan. IMRT - external boost	€ 6.019,27

Appendix 5AL. Cost hormonal medication

Types of radiation therapy	
Letrozol (inhibitor)	€ 1.379,34
Anastrozol	€ 1.371,12
Exemestan (inhibitor)	€ 2.563,21
Tamoxifen	€ 476,60

Appendix 5AK. Correlation Matrix – Breast cancer variables

	Total treatment costs	Surgery costs	Age	Height	BMI	PR	HER2	Multifocal tumour	Intravenous chemo	Reconstruction	Genetic Mutation	T cat	N cat	G cat	Ki63 cat	Menopausal status	Number of comorbidities	Familial occurrence	Number of pregnancies
Total treatment costs	1.0000																		
Surgery costs	0.0815	1.0000																	
Age	-0.3002	-0.1420	1.0000																
Height	-0.0121	-0.0088	-0.4189	1.0000															
BMI	0.0682	0.2264	0.1576	-0.2109	1.0000														
PR	0.0671	0.0266	-0.1799	-0.0393	0.0536	1.0000													
HER2	0.5277	0.1364	-0.1953	0.0539	0.0063	-0.0045	1.0000												
Multifocal tumour	0.1146	0.0243	0.0546	-0.0356	0.0474	0.1279	-0.0558	1.0000											
Intravenous chemo	0.0807	0.3269	-0.3110	0.0498	-0.0572	0.0616	0.1387	0.0305	1.0000										
Reconstruction	0.1034	0.3540	-0.3174	0.1401	0.0166	0.1198	0.1310	0.0869	0.4987	1.0000									
Genetic Mutation	0.0375	0.1627	-0.2297	0.0232	0.0387	0.1198	0.2538	-0.0720	0.2304	0.3139	1.0000								
T cat	0.1927	0.1444	0.0620	-0.1013	0.2204	0.0577	-0.0481	0.0353	0.0947	-0.0829	0.0726	1.0000							
N cat	0.1112	0.6296	0.0336	-0.0824	0.2707	0.0823	0.0646	0.1470	0.0937	0.08389	0.1213	0.3515	1.0000						
G cat	0.1912	0.1358	0.0887	-0.0731	0.1119	-0.1663	0.0329	-0.0791	0.0962	0.0349	-0.1597	0.3099	0.1274	1.0000					
Ki63 cat	-0.0222	0.0621	0.0014	-0.0717	0.3582	0.0314	-0.0932	-0.1221	0.1219	-0.0154	-0.0154	0.3058	0.0424	0.3786	1.0000				
Menopausal status	-0.1458	-0.1246	**0.7717****	-0.2815	0.1544	-0.2387	-0.1146	0.0057	-0.3954	-0.3782	-0.2846	-0.0124	0.0747	0.0426	-0.0762	1.0000			
Number of comorbidities	-0.0518	0.1369	0.3903	-0.0914	0.4546	-0.1407	0.0495	-0.0121	-0.0565	-0.0313	-0.0916	0.1054	0.2415	0.0565	0.0313	0.2726	1.0000		
Familial occurrence	-0.0480	-0.1224	0.0883	0.0661	-0.1171	-0.1537	0.0305	-0.1267	-0.1170	-0.1582	-0.1582	-0.0193	-0.1360	0.0061	-0.0233	0.0223	-0.1032	1.0000	
Number of pregnancies	-0.1096	0.0804	0.0603	-0.1262	0.0501	0.1007	0.0689	-0.0507	0.0387	-0.0298	-0.1041	-0.0689	0.0943	-0.0439	0.0825	0.0990	0.1691	0.1018	1.0000

8.5. Appendix Chapter 6

Appendix 6A. Search strategies for each journal for scoping review

Database	BOOLEAN Search strategy
Web of Science	(n= 781)
• Bundled payment / bundles / health care / payment system / reimbursement / risk adjustment	TS=('bundled NEAR payment' OR 'bundled NEAR payments*') AND TS=('bundle' OR 'bundling' OR 'bundled' OR 'bundles') AND TS= ('health NEAR care' OR 'healthcare' OR 'value NEAR based NEAR healthcare') AND TS= ('payment NEAR system' OR 'payment NEAR systems' OR 'payment NEAR design' OR 'payment NEAR designs' OR 'payment NEAR model' OR 'payment NEAR models' OR 'Payment NEAR study' OR 'Payment NEAR studies*') AND TS=('reimbursement' OR 'reimbursement NEAR design' OR 'reimbursement NEAR study*') AND TS=('risk NEAR adjustment' OR ' Risk NEAR adjusted OR 'risk NEAR adjust*')
• Bundled payment / bundles / health care / payment system	TS=('bundled NEAR payment' OR 'bundled NEAR payments*') AND TS=('bundle' OR 'bundling' OR 'bundled' OR 'bundles') AND TS= ('health NEAR care' OR 'healthcare' OR 'value NEAR based NEAR healthcare') AND TS= ('payment NEAR system' OR 'payment NEAR systems' OR 'payment NEAR design' OR 'payment NEAR designs' OR 'payment NEAR model' OR 'payment NEAR models' OR 'Payment NEAR study' OR 'Payment NEAR studies*')
• Bundled payment / bundles / payment system / reimbursement	TS=('bundled NEAR payment' OR 'bundled NEAR payments*') AND TS=('bundle' OR 'bundling' OR 'bundled' OR 'bundles') AND TS= ('payment NEAR system' OR 'payment NEAR systems' OR 'payment NEAR design' OR 'payment NEAR designs' OR 'payment NEAR model' OR 'payment NEAR models' OR 'Payment NEAR study' OR 'Payment NEAR studies*') AND TS=('reimbursement' OR 'reimbursement NEAR design' OR 'reimbursement NEAR study*')
• Bundled payment / bundles / health care	TS=('bundled NEAR payment' OR 'bundled NEAR payments*') AND TS=('bundle' OR 'bundling' OR 'bundled' OR 'bundles') AND TS= ('health NEAR care' OR 'healthcare' OR 'value NEAR based NEAR healthcare*')
• Bundled payment / bundles / payment system / risk adjustment	TS=('bundled NEAR payment' OR 'bundled NEAR payments*') AND TS=('bundle' OR 'bundling' OR 'bundled' OR 'bundles') AND TS= ('payment NEAR system' OR 'payment NEAR systems' OR 'payment NEAR design' OR 'payment NEAR designs' OR 'payment NEAR model' OR 'payment NEAR models' OR 'Payment NEAR study' OR 'Payment NEAR studies*') AND TS=('risk NEAR adjustment' OR ' Risk NEAR adjusted OR 'risk NEAR adjust*')
Scopus	(n=3032)
• Bundled payment / bundles / health care / payment system / reimbursement / risk adjustment	('bundled AND payment' OR 'bundled AND payments') AND ('bundle' OR 'bundling' OR 'bundled' OR 'bundles') AND ('health AND care' OR 'healthcare' OR 'value AND based AND healthcare') AND ('payment AND system' OR 'payment AND systems' OR 'payment AND design' OR 'payment AND designs'

	OR ‘payment AND model’ OR ‘payment AND models’ OR ‘payment AND studies’ OR ‘payment AND study’) AND (‘reimbursement’ OR ‘reimbursement AND design' OR 'reimbursement AND study’) AND (‘Risk AND adjustment’ OR ‘risk AND adjusted’ OR ‘risk AND adjust’)
• Bundled payment / bundles / health care / payment system	('bundled AND payment' OR 'bundled AND payments') AND ('bundle’ OR ‘bundling’ OR 'bundled' OR 'bundles') AND ('health AND care' OR 'healthcare’ OR ‘value AND based AND healthcare’) AND (‘payment AND system’ OR ‘payment AND systems’ OR ‘payment AND design’ OR ‘payment AND designs’ OR ‘payment AND model’ OR ‘payment AND models’ OR ‘payment AND studies’ OR ‘payment AND study’)
• Bundled payment / bundles / payment system / reimbursement	('bundled AND payment' OR 'bundled AND payments') AND ('bundle’ OR ‘bundling’ OR 'bundled' OR 'bundles') AND (‘payment AND system’ OR ‘payment AND systems’ OR ‘payment AND design’ OR ‘payment AND designs’ OR ‘payment AND model’ OR ‘payment AND models’ OR ‘payment AND studies’ OR ‘payment AND study’) AND (‘reimbursement’ OR ‘reimbursement AND design' OR 'reimbursement AND study’)
• Bundled payment / bundles / health care	('bundled AND payment' OR 'bundled AND payments') AND ('bundle’ OR ‘bundling’ OR 'bundled' OR 'bundles') AND ('health AND care' OR 'healthcare’ OR ‘value AND based AND healthcare’)
• Bundled payment / bundles / payment system / risk adjustment	('bundled AND payment' OR 'bundled AND payments') AND ('bundle’ OR ‘bundling’ OR 'bundled' OR 'bundles') AND (‘payment AND system’ OR ‘payment AND systems’ OR ‘payment AND design’ OR ‘payment AND designs’ OR ‘payment AND model’ OR ‘payment AND models’ OR ‘payment AND studies’ OR ‘payment AND study’) AND (‘Risk AND adjustment’ OR ‘risk AND adjusted’ OR ‘risk AND adjust’)
EMBASE	(n=1457)
• Bundled payment / bundles / health care / payment system / reimbursement / risk adjustment	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘health care’ OR ‘healthcare‘ OR ‘value based healthcare’) AND (‘Payment system*’ OR ‘payment design*’ OR ‘payment model*’ OR ‘payment study’ OR ‘payment studies’) AND (‘reimbursement’ OR ‘reimbursement design’ OR ‘reimbursement study’) AND (‘risk adjustment’ OR ‘risk adjusted’ OR ‘risk adjust’)
• Bundled payment / bundles / health care / payment system	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘health care’ OR ‘healthcare‘ OR ‘value based healthcare’) AND (‘Payment system*’ OR ‘payment design*’ OR ‘payment model*’ OR ‘payment study’ OR ‘payment studies’)
• Bundled payment / bundles / payment system / reimbursement	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘Payment system*’ OR ‘payment design*’ OR ‘payment model*’ OR ‘payment study’ OR ‘payment studies’) AND (‘reimbursement’ OR ‘reimbursement design’ OR ‘reimbursement study’)
• Bundled payment / bundles / health care	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘health care’ OR ‘healthcare‘ OR ‘value based healthcare’)

• Bundled payment / bundles / payment system / risk adjustment	'bundled payment*' AND ('bundle*' OR 'bundling') AND ('Payment system*' OR 'payment design*' OR 'payment model*' OR 'payment study' OR 'payment studies') AND ('risk adjustment' OR 'risk adjusted' OR 'risk adjust')
CHINAL	(n= 810)
• Bundled payment / bundles / health care / payment system / reimbursement / risk adjustment	TX (("bundled payment" OR "bundled payments")) AND TX (("bundle" OR "bundles" OR "bundled" OR "bundling")) AND TX (("health care" OR "healthcare" OR "value-based healthcare")) AND TX (("payment system" OR "payment systems" OR "payment design" OR "payment designs" OR "payment model" OR "payment models" OR "payment studies" OR "payment study")) AND TX (("reimbursement" OR "reimbursement design" OR "reimbursement study")) AND TX (("risk adjustment" OR "risk- adjusted" OR "risk-adjust"))
• Bundled payment / bundles / health care / payment system	TX (("bundled payment" OR "bundled payments")) AND TX (("bundle" OR "bundles" OR "bundled" OR "bundling")) AND TX (("health care" OR "healthcare" OR "value-based healthcare")) AND TX (("payment system" OR "payment systems" OR "payment design" OR "payment designs" OR "payment model" OR "payment models" OR "payment studies" OR "payment study"))
• Bundled payment / bundles / payment system / reimbursement	TX (("bundled payment" OR "bundled payments")) AND TX (("bundle" OR "bundles" OR "bundled" OR "bundling")) AND TX (("payment system" OR "payment systems" OR "payment design" OR "payment designs" OR "payment model" OR "payment models" OR "payment studies" OR "payment study")) AND TX (("reimbursement" OR "reimbursement design" OR "reimbursement study"))
• Bundled payment / bundles / health care	TX (("bundled payment" OR "bundled payments")) AND TX (("bundle" OR "bundles" OR "bundled" OR "bundling")) AND TX (("health care" OR "healthcare" OR "value-based healthcare"))
• Bundled payment / bundles / payment system / risk adjustment	TX (("bundled payment" OR "bundled payments")) AND TX (("bundle" OR "bundles" OR "bundled" OR "bundling")) AND TX (("payment system" OR "payment systems" OR "payment design" OR "payment designs" OR "payment model" OR "payment models" OR "payment studies" OR "payment study")) AND TX (("risk adjustment" OR "risk- adjusted" OR "risk-adjust"))
PubMed	(n= 1342)
• Bundled payment / bundles / health care / payment system / reimbursement / risk adjustment	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND (((health care) OR healthcare) OR value-based healthcare) AND (((((((payment system) OR payment systems) OR payment design) OR payment designs) OR payment model) OR payment models) OR payment studies) OR payment study) AND (((reimbursement) OR reimbursement design) OR reimbursement study) AND ((((risk adjustment) OR risk-adjusted) OR risk-adjust)
• Bundled payment / bundles / health care / payment system	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND ((((health care) OR healthcare) OR value-based healthcare) AND (((((((payment system) OR payment systems) OR payment design) OR payment designs) OR payment model) OR payment models) OR payment studies) OR payment study)

• Bundled payment / bundles / payment system / reimbursement	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND (((((((payment system) OR payment systems) OR payment design) OR payment designs) OR payment model) OR payment models) OR payment studies) OR payment study) AND (((reimbursement) OR reimbursement design) OR reimbursement study)
• Bundled payment / bundles / health care	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND (((health care) OR healthcare) OR value-based healthcare)
• Bundled payment / bundles / payment system / risk adjustment	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND (((((((payment system) OR payment systems) OR payment design) OR payment designs) OR payment model) OR payment models) OR payment studies) OR payment study) AND (((risk adjustment) OR risk-adjusted) OR risk-adjust)
Cochrane	(n = 72)
• Bundled payment / bundles / health care / payment system / reimbursement / risk adjustment	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND (((health care) OR healthcare) OR value-based healthcare) AND (((((((payment system) OR payment systems) OR payment design) OR payment designs) OR payment model) OR payment models) OR payment studies) OR payment study) AND (((reimbursement) OR reimbursement design) OR reimbursement study) AND (((risk adjustment) OR risk-adjusted) OR risk-adjust)
• Bundled payment / bundles / health care / payment system	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND ((((health care) OR healthcare) OR value-based healthcare) AND (((((((payment system) OR payment systems) OR payment design) OR payment designs) OR payment model) OR payment models) OR payment studies) OR payment study)
• Bundled payment / bundles / payment system / reimbursement	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND (((((((payment system) OR payment systems) OR payment design) OR payment designs) OR payment model) OR payment models) OR payment studies) OR payment study) AND (((reimbursement) OR reimbursement design) OR reimbursement study)
• Bundled payment / bundles / health care	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND (((health care) OR healthcare) OR value-based healthcare)
• Bundled payment / bundles / payment system / risk adjustment	((bundled payment) AND bundled payments) AND ((((bundle) OR bundles) OR bundled) OR bundling) AND (((((((payment system) OR payment systems) OR payment design) OR payment designs) OR payment model) OR payment models) OR payment studies) OR payment study) AND (((risk adjustment) OR risk-adjusted) OR risk-adjust)
Voids	(n= 28)
• Bundled payment / bundles / health care / payment system / reimbursement / risk adjustment	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘health care’ OR ‘healthcare‘ OR ‘value-based healthcare) AND (‘Payment system*’ OR ‘payment design*’ OR ‘payment model*’ OR ‘payment study’ OR ‘payment studies’) AND

	(‘reimbursement’ OR ‘reimbursement design’ OR ‘reimbursement study’) AND (‘risk adjustment’ OR ‘risk adjusted’ OR ‘risk adjust’)
• Bundled payment / bundles / health care / payment system	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘health care’ OR ‘healthcare‘ OR ‘value-based healthcare) AND (‘Payment system*’ OR ‘payment design*’ OR ‘payment model*’ OR ‘payment study’ OR ‘payment studies’)
• Bundled payment / bundles / payment system / reimbursement	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘Payment system*’ OR ‘payment design*’ OR ‘payment model*’ OR ‘payment study’ OR ‘payment studies’) AND (‘reimbursement’ OR ‘reimbursement design’ OR ‘reimbursement study’)
• Bundled payment / bundles / health care	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘health care’ OR ‘healthcare‘ OR ‘value based healthcare’)
• Bundled payment / bundles / payment system / risk adjustment	‘bundled payment*’ AND (‘bundle*’ OR ‘bundling’) AND (‘Payment system*’ OR ‘payment design*’ OR ‘payment model*’ OR ‘payment study’ OR ‘payment studies’) AND (‘risk adjustment’ OR ‘risk adjusted’ OR ‘risk adjust’)
Science Direct	(n=4409)
• Bundled payment / bundles / health care / payment system / reimbursement / risk adjustment	(“bundled payment” OR “bundled payments”)) AND (“bundle” OR “bundling” OR “bundled” OR “bundles”) AND (“health care” OR “healthcare” OR “value-based healthcare”) AND (“payment system” OR “payment systems” OR “payment design” OR “payment designs” OR “payment model” OR “payment models” OR “payment study” OR “payment studies”) AND (“reimbursement” OR “reimbursement design” OR “reimbursement study”) AND (“risk adjustment” OR “risk adjusted” OR “risk-adjust”)
• Bundled payment / bundles / health care / payment system	(“bundled payment” OR “bundled payments”)) AND (“bundle” OR “bundling” OR “bundled” OR “bundles”) AND (“health care” OR “healthcare” OR “value based healthcare”) AND (“payment system” OR “payment systems” OR “payment design” OR “payment designs” OR “payment model” OR “payment models” OR “payment study” OR “payment studies”)
• Bundled payment / bundles / payment system / reimbursement	(“bundled payment” OR “bundled payments”)) AND (“bundle” OR “bundling” OR “bundled” OR “bundles”) AND (“payment system” OR “payment systems” OR “payment design” OR “payment designs” OR “payment model” OR “payment models” OR “payment study” OR “payment studies”) AND (“reimbursement” OR “reimbursement design” OR “reimbursement study”)
• Bundled payment / bundles / health care	(“bundled payment” OR “bundled payments”)) AND (“bundle” OR “bundling” OR “bundled” OR “bundles”) AND (“health care” OR “healthcare” OR “value based healthcare”)
• Bundled payment / bundles / payment system / risk adjustment	(“bundled payment” OR “bundled payments”)) AND (“bundle” OR “bundling” OR “bundled” OR “bundles”) AND (“payment system” OR “payment systems” OR “payment design” OR “payment designs” OR “payment model” OR “payment models” OR “payment study” OR “payment studies”) AND (“risk adjustment” OR “risk adjusted” OR “risk-adjust”)

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