PALLIATIVE CARE FOR CANCER PATIENTS IN RESOURCE-LIMITED SETTINGS OF KAZAKHSTAN: IMPLICATIONS FOR COST-EFFECTIVENESS AND HEALTH POLICY

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LIST OF ABBREVIATIONS

CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CHF: Swiss Franc
CNS: Central Nervous System
CRC: Colorectal Cancer
ECOG: Eastern Cooperative Oncology Group
HIC: High-Income Countries
HIV: Human Immunodeficiency Virus
ICER: Incremental cost-effectiveness ratio
ICU: Intensive Care Unit
KAPC: Kazakhstan Association of Palliative Care
KZT: Kazakhstan Tenge
LS: Lynch Syndrome
LMICs: Lower-Middle-Income Countries
NGO: Non-Governmental Organization
PICU: Pediatric Intensive Care Unit
POS: Palliative Outcome Scale
QALY: Quality-Adjusted Life Year
UHC: Universal Health Coverage
USD: United States dollar
WHO: World Health Organization
ZBI: Zarit Burden Interview

ABSTRACT

Introduction: About 60 million people need palliative care worldwide, and nearly 80% of them live in low-to middle- income countries (LMICs) where only 12% of patients who require palliative services have access to them. As a Central Asian LMIC with a transitional economy and a reforming healthcare system, Kazakhstan has recently taken on the task of integrating palliative care into the general healthcare system to meet its national needs and international standards. Although palliative care services in Kazakhstan have significantly improved care for persons nearing the end of life, patients needing these services still suffer from pain, lack of access, and high out-of-pocket expenditures. Palliative care in Kazakhstan is provided by hospices, cancer centers, general hospitals, and mobile teams. More than 100,000 people need palliative care in Kazakhstan; however, as one or more family members are usually involved in the care of a terminal patient, more than 200,000 people would benefit from high-quality palliative care services in this country. Considering that cancer is a primary illness necessitating palliative care, there is a need for a comprehensive understanding of how strategies aimed at preventing cancer could reshape the demand and delivery of the spectrum of cancer care services, including palliative care.

Objectives of this study include:

- Present a detailed analysis of palliative care in Kazakhstan, including funding, policy, workforce, education, infrastructure, etc., providing an evidence base for future assessments and research of palliative care in Kazakhstan and in other LMICs.
- Assess the cost-effectiveness of hospice-based palliative care for cancer patients compared to the current standard of care provided in cancer centers across the country.
- Explore the challenges faced by palliative care stakeholders in resource-limited settings, and to offer evidence-based recommendations for policymakers to facilitate the advancement of palliative care in Kazakhstan and other LMICs.
- Asses the cost-effectiveness of genetic testing for Lynch syndrome provided to patients newly diagnosed with colorectal cancer, followed by cascade genetic screening of biological relatives from the perspective of the Swiss healthcare system.

Methods: The authors assessed the nation's palliative care landscape using data from the Ministry of Health, regional healthcare centers, and NGOs (Study 1). This comprehensive evaluation involved soliciting information through official correspondence and engaging with key stakeholders.

For the cost-effectiveness analysis, a total of 182 family caregivers were recruited, 104 from three hospices and 78 from three palliative care units of cancer centers (Study 2). Patients' state of health and family caregivers' burden were assessed with the Palliative Outcome Scale (POS) and the Zarit Burden Inventory (ZBI). Direct medical and non-medical costs, and family caregivers' out-of-pocket expenses associated with palliative care were collected. One-way and probabilistic sensitivity analysis was conducted by generating 1,000 resamples using bootstrapping with Monte-Carlo simulation.

To assess challenges of palliative care stakeholders, we conducted 29 semi-structured interviews with palliative stakeholders (family caregivers n=12, healthcare professionals =12, administrators n= 5) across five regions (Study 3). Verbatim transcripts were analyzed using content analysis to identify challenges of palliative stakeholders in resource-limited settings. Recognizing that these findings mirror the well-documented challenges faced by palliative care stakeholders, we converted these insights into evidence-based recommendations, specifically designed for the resource-constrained contexts of LMICs, and in congruence with the latest body of literature on palliative care and family caregiving.

Additionally, we used decision trees with Markov models to conduct a cost-effectiveness analysis of universal genetic testing for Lynch syndrome of all patients newly diagnosed with colorectal cancer, and compared it with the current tumour-based testing with immunohistochemistry techniques followed by DNA sequencing that examines for germline pathogenic variants associated with Lynch syndrome.

Results: The authors obtained the necessary data through official responses from the Ministry of Health, regional centers of healthcare and NGOs. These responses were accompanied by supplementary materials that fulfilled the authors' requests. Overall, the findings of the assessment provide a thorough understanding of the current state of palliative care in Kazakhstan presented in this study along with areas that require attention for future development.

Cost-effectiveness analysis revealed that after 14 days of inpatient palliative care, patients' median POS score was 5 points better in the hospice group compared to the cancer center group. Family caregiver burden was also 2.5 points lower in favour of the hospice group. The median cost of palliative care per patient over 14 days was $31 lower for the hospice group. There was a statistically significant correlation between the cost of palliative care and patients'

quality of life (r = 0.58). Probabilistic sensitivity analysis showed that hospice-based care has better outcomes and lower costs than care provided in cancer centers in 80% of tested scenarios. Discovering the challenges of palliative care stakeholders, our analysis identified seven main themes that were initially brought forward by different groups of stakeholders. The most common challenges highlighted by family caregivers were high out-of-pocket expenditures; the lack of mobile palliative care services; and shortages of opioids to prevent pain suffering. Health professionals highlighted poor palliative care education and lack of medication, especially opioids for pain relief as the major challenges they encounter in their daily practice. Major challenges for administrators included lack of societal awareness about palliative care, and lack of financial support from the State.

Within the analysis of the universal genetinc testing for Lynch syndrome, the incremental cost-effectiveness ratio of this strategy was CHF65,058 per QALY saved, which is cost-effective in the Swiss context. Moreover, the universal testing correctly identifies all colorectal cancer patients with Lynch syndrome, prevents 17 deaths and prevents 19 colorectal cancer cases compared to the currently applied tumor-based testing.

Conclusion: Despite recent progress, Kazakhstan faces ongoing challenges such as restricted opioid availability, insufficient education, and low public awareness about palliative care services. Hospice-based palliative care can be a cost-effective alternative in resource-limited settings of Kazakhstan. Implementation of further national palliative care strategies and policies require a large-scale coordinated involvement of all stakeholders. Family caregivers play a crucial role in providing palliative care, yet, they have been completely unsupported by they system in their tasks. Our recommendations are based on the idea that coordinated targeted and tailored stakeholder engagement is preferred to a one-size-fits-all strategy.

In the Swiss healthcare context, universal genetic testing has demonstrated both cost-effectiveness and significant health advantages. However, the ICER of CHF 65,058 (USD 70,000) surpasses the cost-effectiveness threshold of most low-to middle-income countries, including Kazakhstan where the GDP per capita is USD 11,000. Hence, the authors underline the critical necessity for locally viable, low-cost cancer screening options in resource-restricted settings. The introduction of more affordable cancer preventive measures, such as mammography, Pap smear test, and fecal occult blood test, among others, could be considered as more financially viable options for population-based cancer screening.

CHAPTER I

INTRODUCTION

1.1 Palliative care needs worldwide

WHO defines palliative care as an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification, assessment, and treatment of pain and other physical, psychosocial and spiritual problems.[1] This approach is intended to enhance the quality of life for patients by addressing their overall well-being, rather than just managing specific medical conditions. The comprehensive nature of palliative care underscores the importance of attending to all aspects of a patient's life when treating life-threatening illnesses [1]. By incorporating various dimensions of care, such as psychological, social, and spiritual support, palliative care can significantly improve the overall quality of life for patients.[1] Palliative care also supports the family members of terminal patients by helping them cope with the significant stress and burden of illness.[1] This type of care can be administered in multiple settings, including hospitals, hospices, and at home. [1,2] By providing support to both patients and their families, palliative care can greatly enhance the overall quality of life for everyone affected by a life-threatening illness.[1,2] About 40 million people need palliative care worldwide and nearly 80% of them live in low-middle-income countries (LMICs), where access to such services is severely limited. [2] By 2060, the need for palliative care worldwide will nearly double with the highest increase in LMICs. [3] WHO estimates that only 14% of patients needing palliative care worldwide has access to such services, primarily in economically developed countries. [3] As the demographic shift continues in LMICs, aging and palliative care needs will become increasingly linked [4].

1.2 Demographic Shifts and Health Challenges in LMICs.

Substantial reduction of mortality from communicable diseases in LMICs has resulted in an increase in global life expectancy, from 67 to 73 years between 2000 and 2019. [5] However, the number of years of living with poor health have also increased from 8 to 10 years, further challenging healthcare systems, since the demographic shifts in LMICs continue. [4,6] By 2050, the percentage of the world’s population over 60 years of age is expected to double to two billion, while the population over 80 years of age is expected to triple, reaching 426 million.[4,7] Within just 30 years, 64 countries are expected to parallel Japan, with an older population of more than 30%.[8] Moreover, by that same year, 80% of older people will be living in LMICs.[9] In addition, more than five million children, globally, are affected by serious health suffering, with more than 98% of them living in LMICs. [4] More than 2 million children die in a state of severe health suffering, accounting for 10% of all deaths globally. [4,7] The challenge of promoting healthy aging across all population segments is a major concern for health systems, especially given the ongoing demographic transitions in LMICs, where the growing need for long-term palliative care will make these services more closely linked and increasingly essential. [4]

1.3 Demographics of the Republic of Kazakhstan

Kazakhstan has a population of around 19 million people living in an area of 2.7 million km^2, resulting in one of the lowest population densities globally, with only seven individuals per km^2.[10] The dispersed population in Kazakhstan presents significant challenges in accessing health services, especially for the 50% of the population residing in rural areas. [11] Life expectancy in Kazakhstan is expected to rise from 73 years in 2021 to 77 years in 2050, with women reaching an average lifespan of nearly 85 years and men reaching an average of 75 years. [12,13] The demographic shift in Kazakhstan is characterized by a doubling of the proportion of the elderly over the age of 65 by 2050. At the same time, the ratio of people 65 and older to the working age population will reach almost 40% in 2050, leading to a greater burden on healthcare funding. Despite being a relatively young nation, Kazakhstan needs to anticipate these trends, and the consequences and problems caused by the rise of chronic non-communicable diseases such as cancer, diabetes, and cardiovascular disease. [8,14] Therefore, developing high-quality palliative care services must be prioritized by the Ministry of Health to ensure higher quality-of-life and end-of-life care among people with terminal diseases.

1.4 Overview of Palliative Care in Kazakhstan

The World Atlas of Palliative Care characterized palliative care in Kazakhstan, a LMIC in central Asia, as being at the preliminary stage of integration into the healthcare system, while the Quality of Death Index ranked Kazakhstan 50th out of 80 countries assessed. [2] According to the assessment conducted by the World Hospice Palliative Care Alliance, approximately 107,000 people needed palliative care in Kazakhstan in 2021 and more than 100,000 family caregivers would have benefited from such services. [2] Moreover, about 190,000 people have been diagnosed with cancer, of whom 4,000 were registered as terminally ill in 2021. [2] Such developments and demographic shifts pose new medical and economic challenges for

Kazakhstan and other LMICs. As a country with a transitional economy and a recently established social health insurance system, Kazakhstan is looking for a cost-effective allocation of limited resources for end-of-life care.

1.5 Cost-Effectiveness of Palliative care

The need for cost-effectiveness analysis of palliative care services in LMICs has been previously emphasized. [2] As a LMIC with limited resources, Kazakhstan is exploring cost-effective allocation strategies for palliative care, which underscores the significance of conducting an analysis on the cost-effectiveness of such care in this setting. Currently, palliative care in Kazakhstan is provided by four different types of healthcare organizations: hospices, palliative units of cancer centers, palliative beds in general hospitals, and mobile palliative teams. Due to the high heterogeneity in the approach and the wide spectrum of care in the last two models, we focus on comparing hospice-based palliative care services to cancer center-based palliative care. Moreover, mobile teams are sporadically distributed across rural areas of the country, making data collection rather inexpedient. Although palliative care is associated with a wide range of chronic conditions, we focus on cancer, as it is the most common illness associated with palliative care. [2]

1.6 Role of Palliative Stakeholders

Although palliative care is a holistic family-centered approach, which includes multidisciplinary teams, the roles and challenges faced by palliative care stakeholders, particularly in LMICs, remain poorly understood. [15] LMICs typically lack the data collection systems needed to evaluate how palliative care is provided, how much it costs, and how well it works. [7] Furthermore, stakeholders such as NGOs, health professionals, and family caregivers have not been involved in recent initiatives and developments in palliative care, such as the National Palliative Strategy in Kazakhstan. [16] Therefore, it is essential to perform a formal stakeholder analysis to systematically collect and analyze information to better understand the interests and priorities of all stakeholders, including policymakers, healthcare providers and informal caregivers. [17] Formal stakeholder analysis methods are well-suited to guide policy and program development and implementation. [18] To our knowledge, no comprehensive analysis of the needs of palliative care stakeholders has been carried out in Central Asia; therefore, by demonstrating the needs and challenges which palliative stakeholders encounter in limited-resource settings, it is our hope that this study will help other LMICs in their efforts to reform their palliative care systems.

1.7 Understanding the Cost-Effectiveness of Preventive Measures

In addition to assessing the cost-effectiveness of palliative care in Kazakhstan, this study also seeks to understand the health economics of preemptive measures in cancer management. To that end, we explored the cost-effectiveness of universal screening for Lynch syndrome, a hereditary condition associated with a high risk of cancer, in patients newly diagnosed with colorectal cancer followed by cascade genetic testing of relatives. This analysis, conducted in the Swiss context, offers valuable insights into the economic and health implications of such a preventive approach. While this study is conducted in a high-income country, its findings provide a useful comparative perspective and lay groundwork for considering how preventive strategies could be incorporated into resource-limited settings like Kazakhstan. By reducing the incidence of cancer, preventive measures could, in the long term, alleviate some of the burden on palliative care services, creating a more sustainable healthcare system.

CHAPTER II

OBJECTIVES

The overall purpose of this study is to generate an evidence-based evaluation of palliative care services in Kazakhstan, and, consequently, provide recommendations for policymakers to guide future development of these services in the country. Specific objectives include:

Objective I

To comprehensively examine the current state of palliative care services in Kazakhstan, its needs, funding, healthcare policy, education, workforce, infrastructure, and needs, with the goal of providing valuable insights to researchers, policymakers in LMICs, and key organizations involved in palliative care, such as the Global Atlas of Palliative Care and Quality of Death Index. In the recently published Quality of Death and Dying Index, Kazakhstan was not included due to a shortage of palliative care specialists and insufficient data on the status of palliative care in the country. [19,20]

Objective II

To evaluate the cost-effectiveness of hospice-based palliative care compared to cancer center-based palliative care for terminal cancer patients. Currently, palliative care in Kazakhstan is provided by four different types of healthcare organizations: hospices, palliative units of cancer centers, palliative beds in general hospitals, and mobile palliative teams. Due to the high heterogeneity in the approach and the wide spectrum of care in the last two models, we focus on comparing hospice-based palliative care services to cancer center-based palliative care. Moreover, mobile teams are sporadically distributed across rural areas of the country, making data collection rather inexpedient. Although palliative care is associated with a wide range of chronic conditions, we focus on cancer, as it is the most common illness associated with palliative care. [4]

Objective III

To obtain a comprehensive understanding of the challenges encountered by key palliative care stakeholders and develop policy recommendations tailored to resource-limited settings. To do this, we aim to gather data from a diverse array of palliative care stakeholders including health professionals, administrators, and family caregivers, employing interviews as our primary tool, across different settings. Moreover, we aim to convert these challenges into tailored and context-specific health policy recommendations to assist LMICs beyond Kazakhstan to initiate dialogue among different stakeholders, drive action, and facilitate much-needed changes in palliative care provision.

Objective IV

To conduct a Swiss-based cost-effectiveness analysis of genetic screening for Lynch syndrome provided to patients newly diagnosed with colorectal cancer, followed by cascade genetic screening of their biological relatives. This objective provides a comparative perspective to better understand the economic implications and benefits of preventive measures in cancer care, by opening the discussion on the value and feasibility of incorporating preventive strategies in resource-limited settings. Also, this objective helps to assess how cancer prevention could alleviate the burden of overall cancer care, including palliative care in the long term. By preventing and indentifiyng cancer at earlier stages, the demand for palliative care services may decrease, leading to more available resources for those in need.

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CHAPTER III

CHALLENGES FOR DEVELOPING PALLIATIVE CARE SERVICES IN RESOURCE- LIMITED SETTINGS OF KAZAKHSTAN

First Article

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ABSTRACT

Background: Approximately 40 million people in need of palliative care worldwide, while 80% of them live in low- and middle-income countries. Kazakhstan, a low- to middle-income country with a reforming healthcare system, is committed to improving quality and accessibility of care for its 100,000 terminal patients in need of palliative care.

Policy Options and Recommendations: To join the group of countries where palliative care is available, accessible, and affordable, Kazakhstan must integrate palliative services into the mainstream healthcare system at all levels, from primary healthcare to hospices, and from major cities to remote villages. Based on the evidence thoroughly collected directly from the Ministry of Health, authors propose a feasible set of recommendations regarding palliative policy, paint relief, infrastructure, workforce, and education, which could be implemented in LMICs beyond Kazakhstan.

Conclusions: This study presents an analysis of challenges, recent developments, and needs of palliative care in Kazakhstan, including funding, policy, workforce, education, and infrastructure, providing an evidence base and recommendations for future development of palliative care in Kazakhstan and in other LMICs.

Background

According to WHO, of the 40 million people who require palliative care worldwide, only 12% receive it, most of whom live in high-income countries.(1) With a population of approximately 19 million living in an area of 2.7 million km^2, Kazakhstan has one of the lowest population densities worldwide, with only seven people per km^2.(2) According to the 2nd edition of the Global Atlas of Palliative Care, currently 107,430 patients in Kazakhstan require palliative care, including 4,900 children.(3) In 2021, there were about 35,000 newly diagnosed cancer cases and approximately 190,000 people living with cancer in Kazakhstan, while more than 14,000 people died from the disease.(4) In addition, Kazakhstan has a total incidence of 60 tuberculosis cases per 100,000, where the registration of 50 cases per 100,000 is considered an epidemic. (5)This places Kazakhstan among the to 30 countries worldwide with the highest burden of multidrug-resistant tuberculosis.(5) The dispersed population poses serious challenges for accessing health services, especially for half the population in Kazakhstan who live in rural areas.(6) Despite being a relatively young nation, Kazakhstan needs to anticipate these trends, and the consequences and problems caused by the rise of chronic non-communicable diseases such as cancer, diabetes, and cardiovascular disease. (7,8) As the demographic shift continues in LMICs, aging and palliative care needs will become increasingly linked.(9) The purpose of this policy brief is to conduct a detailed assessment and discuss the challenges of palliative care services in Kazakhstan, thereby informing researchers, LMICs policymakers, and other essential palliative care measurement initiatives, such as the Global Atlas of Palliative Care, the Lancet Commission on Palliative Care and Pain Relief, and Quality of Death and Dying Index.(1,3,10)

Evidence

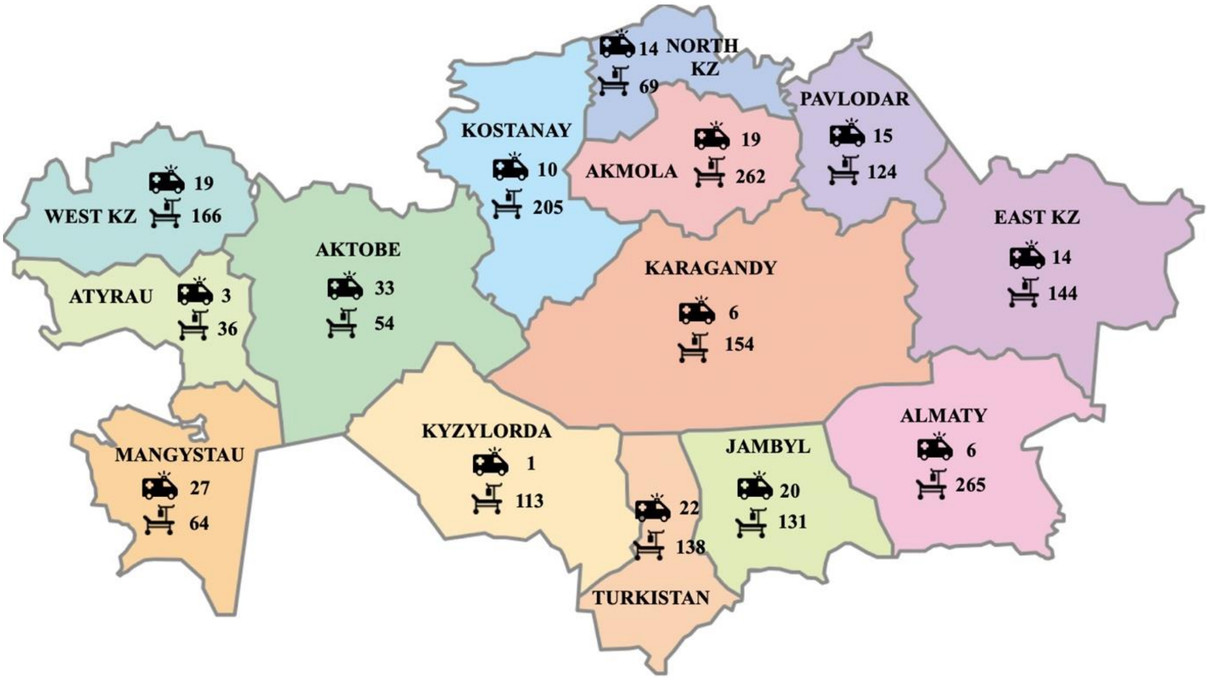
Global Perspective on Palliative Care in Kazakhstan

Target 3.8 of the Sustainable Development Goals adopted by the United Nations in 2015 indicates the necessity to achieve universal health coverage (UHC), including access to essential healthcare services and medicines, and financial risk protection for all by the year 2030.(11)According to the description of services under UHC no nation can achieve true universal health coverage without including palliative care.(9) The 2015 Quality of Death Index, which evaluates quality of palliative care worldwide, ranked Kazakhstan 50th out of 80 countries assessed. (10) Palliative care in Kazakhstan has a government-led development strategy, which represents a statement of intent but needs a clearer vision and better mechanisms in place.[12] One of the reasons for this low ranking is the rampant incidence of unrelieved pain among most patients (8 points on a 10-point scale), and the low prioritization of developing palliative care services.(10) According to the Global Atlas of Palliative Care, rankings of palliative care in Kazakhstan has improved from the level which characterizes countries with general provision of palliative care, to the level which defines palliative systems at preliminary stage of integration to the healthcare system.(3) Kazakhstan is currently classified as having a diverse workforce of palliative care providers and types of services, healthcare professionals and local communities are aware of palliative care; and a palliative care strategy is being implemented and is regularly evaluated.(3)

Policy

In 2020, the Kazakh government introduced a new National Palliative Care Standard, which now assists the integration of palliative care into the primary healthcare system, ensuring continuity of care. According to the Standard, multidisciplinary palliative teams should be created in all major medical centers, general hospitals, and specialized clinics of the republican level. As part of the National Cancer Control Plan, terminal cancer patients across the country have access to mobile teams that provide in-home palliative care.(12) Moreover, 17 essential medicines, including 3 opioids, have been included into the free palliative package.(13,14) As a United Nations member state working with WHO, Kazakhstan has committed to integrating palliative care into the healthcare system by signing the wide range of international initiatives in the field of health and human rights.(15–17) The Kazakhstan Palliative Care Association (KPCA) has a leading role in palliative care advocacy, education, training, and government outreach, raising awareness and stimulating volunteerism. In 2018, the adoption of the first roadmap of palliative care development significantly improved care quality, knowledge, coverage, and awareness. The Ministry of Health updated the roadmap in 2022, with goals to enhance legal and regulatory frameworks, expand medication and equipment coverage, improve opioid accessibility, and establish better monitoring indicators.

Figure 1. Distribution of palliative mobile teams and in-patient palliative beds across 14 regions of Kazakhstan (National Research Center for Health Development) (Astana, Kazakhstan. 2021)



Infrastructure

Currently, in-patient palliative care in Kazakhstan is provided mainly in stand-alone hospices and palliative care units of specialized cancer centers or general hospitals (see Figure 1). There are currently 12 hospices located in largest cities while palliative care units have been established as an integral part of cancer centers, distributed across all regions of the country under the “Comprehensive Cancer Control Plan for 2018-2022”.(12) In 2018, within this plan, mobile teams were introduced for in-home palliative care for cancer patients. The only state financed specialized pediatric palliative unit is located in Shymkent with a focus on children with severe neurologic conditions. An NGO-based children’s hospice with eight beds and a home visiting service is located in Almaty. A recently opened NGO-based Center for respiratory assistance and palliative care in Almaty provides high-quality services to children with neuromuscular diseases. In the absence of specialized services, children with terminal illnesses often occupy PICU beds, although the daily cost of an ICU bed is three times higher than that of a general ward bed.(18) Acute-care hospital beds are the most expensive choice for palliative care services, and thus, they should only be utilized for people with medical conditions that necessitate that degree of care.(19) Home-based services for terminally ill children still do not exist, except for the abovementioned Almaty children's hospice. The need for establishing infrastructure for pediatric palliative care is of utmost importance. In 2021, 25,159 patients received palliative care in Kazakhstan, totaling 431,833 bed-days, or 17 bed-days per patient. There were 81 pediatric palliative care beds serving to 365 children in 2021. Table 1 summarizes the number of people with seven most common chronic diseases, their mortality, and the number of patients needing palliative care in Kazakhstan in 2021.

Table 1. Number of prevalent cases and deaths from diseases that are eligible for palliative care as well as number of patients which received palliative care in 2021 in Kazakhstan (National Research Center for Health Development) (Astana, Kazakhstan. 2021)

Disease	**Prevalence (n)**	**Number of deaths (adults) (n)**	**Number of patients who received palliative care (adults)**		**Number of deaths (children)**	**Number of patients who received palliative care (children)**	
			n	**%***	**n**	**n**	**%***
Diabetes	417 328	6 522	555	9%	16	1	6%
Cancer	190 159	14 049	3 180	23%	327	35	11%
Cardiovascular	177 182	42 768	1 271	3%	337	14	4%
Respiratory	87 006	20 242	870	4%	457	3	1%
Liver	79 114	9 218	264	3%	37	1	3%
CNS	37 196	29 246	231	8%	610	267	44%
HIV	29 331	198	271	137%	5	N/A	N/A
Total	1 017 316	122 243	6 642	5%	1 789	321	18%

* Percentage of patients who received palliative care from the total number of deaths from the corresponding disease.

Workforce

Currently there are 101 nurses and 45 physicians providing in-patient palliative care in hospices across Kazakhstan. The ratio of hospice physicians to palliative patients is 1:2,000, while the WHO recommends a ratio of 1 physician per 1,000 people in the general population.(20) In total, there are approximately 1,925 palliative beds in Kazakhstan, corresponding to national and international standards of 10 palliative beds per 100,000 people. However, 60% of all palliative beds are scattered throughout the vast country as single beds in regional hospitals, while, according to suggested standards, 80% of palliative beds should be in hospices.(21) Correcting the balance of hospice beds is critical for meeting the requirements of patients who cannot be cared for or who do not want to die at home.(22) To meet international standards, Kazakhstan should reorganize the wide distribution of single palliative beds in favor of local hospices or palliative units, which will contribute to the homogeneity of the quality of care and a smoother implementation of reforms in palliative care. It is worth mentioning that family caregivers represent a very important workforce in palliative care in Kazakhstan, especially in rural and remote settings. Family caregivers' active participation in providing care, even in inpatient settings, helps support patients' quality-of-life and reduces the overall burden on medical staff and limited resources. Therefore, the reorganization of palliative care in Kazakhstan should consider how to better integrate family caregivers into palliative practice, providing educational programs and support to families of palliative patients.

Funding

Healthcare in Kazakhstan is funded by the Obligatory Social Health Insurance and by the guaranteed Statutory Free Medical Assistance. The total palliative care budget amounted to approximately $6 million in 2020, $10 million in 2021, $15 million in 2022, and is projected to reach $22 million in 2023. Despite the substantial increase in the annual funding, it is important to ensure that the allocated budget is used efficiently and effectively to meet patients' needs. Funding for palliative care is based on bed-day reimbursement, i.e., the length of stay of each patient, without considering actual costs of inpatient care. Table 2 shows available palliative infrastructure in different settings in Kazakhstan.

Table 2. Nationally available palliative infrastructure (National Research Center for Health Development) (Astana, Kazakhstan. 2021)

	Settings	Number of facilities	Total number of beds
1	**Hospices**	12	596
2	**Palliative units**	22	182
3	**General hospitals***	217	1,147

4	**Mobile teams**	209	N/A

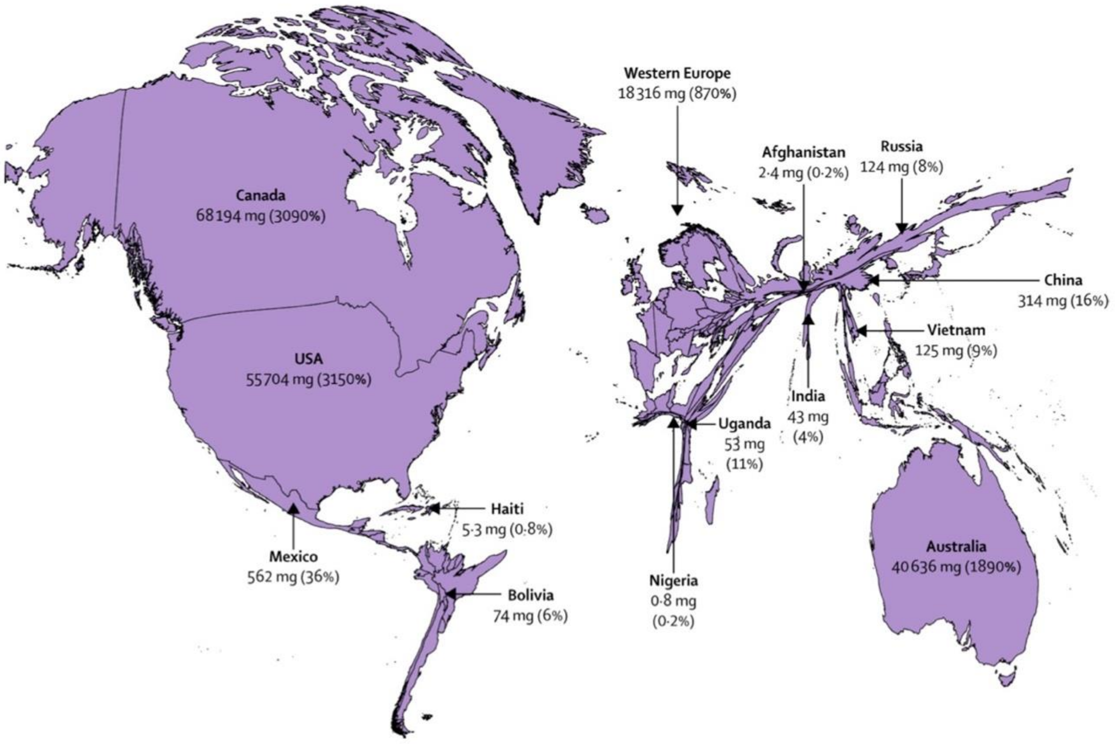
*Has at least one palliative bed per hospital

**Depends on the budget and location of each hospital

Essential palliative care medicines

The need and access to opioids is a tracer of overall availability of palliative care and pain relief.(9) Pain relief, a pillar of palliative care, was found to be the most lacking and inequitably distributed health intervention in the world, as 90% of the world population consumes only 11% of available opioids.(9,23) Only 1% of 380 metric tons of morphine-equivalent opioids is distributed to low-income countries.(24) Figure 2 represents the world distribution of morphine-equivalent opioids (mg/patient), and percentage of pain relief needs that were met.(9) In 2018, the Worldwide Hospice Palliative Care Alliance estimated that the deficit of morphine-equivalent opioids in Kazakhstan was approximately 178 kgs. (3) At the same time, the Lancet Commission ranked Kazakhstan assessed that Kazakhstan covers 10% of needs for morphine, which is consistent an analysis conducted by KAPC which showed that up to 95% of deceased cancer patients in Kazakhstan died without receiving adequate pain management.[2] Moreover, the use of opioids for children in Kazakhstan is avoided, while adequate pain relief for one child costs less than $1/day.(9) In 2021, the Lancet Commission and the International Narcotics Control Board, ranked Kazakhstan 95th and 132nd country in opioid usage, respectively, with an average consumption of 1.31 mg/person, compared to 480.28 mg/person in Germany and 201.85 mg in Switzerland.(23,24) By comparison, Kazakhstan consumes 15,000 and 68,000 times less morphine than in Belarus and in Canada, respectively.(1,9) The state covers only 17 medications related to palliative care, while the list of necessary medicines of the International Association for Hospice and Palliative Care includes 33 medicines to control various symptoms such as depression, insomnia, pain, vomiting, etc.(13) However, between January and June of 2022, out of the 14,000 patients experiencing severe pain, only 7% were prescribed fentanyl patches, 10% morphine injections, and 83% tramadol. In Kazakhstan, like in many LMICs, patients who need morphine often have to seek admission to an in-patient facility in order to receive opioid pain relief. (9)

Figure 2. World distribution of morphine-equivalent opioids and the percentage of covered needs for pain relief (9). License number: 5320150276782. Provided by the Elsevier and Copyright Clearance Center. (USA. 2018)



Education

Currently, there is no recognized specialty in palliative care for physicians and nurses in Kazakhstan. The only existing advanced training course (specialization), termed "hospice and palliative care", is available solely for physicians, although nurses represent the main workforce in palliative care. In 2020, elective palliative care courses were introduced into educational programs for physicians, nurses, and paramedics for both undergraduate and postgraduate studies. However, the content, scope, and structure of such courses are non-standardized and often they are inconsistent with international requirements. While high-quality education requires trained faculty, there are no palliative care specialists who can provide such training.

Recommendations

Recent developments have undoubtedly improved the image of Kazakhstan's healthcare, however, to join the group of countries where palliative care is available, accessible, and affordable, Kazakhstan must integrate palliative services into the mainstream healthcare system at all levels throughout the country, from primary healthcare to hospices, and from major cities to remote villages.(3) Based on the existing evidence authors suggest that the palliative policy in Kazakhstan as well as other LMICs in similar settings should prioritize and focus on the following affordable steps:

- Establish continuous and transparent mechanisms of quantitative monitoring of quality of palliative care services and its outcomes.
- Establish registry of patients in need of palliative care, which is necessary for effective healthcare systems.(1)
- Reorganize the distribution of palliative beds across regions in favor of established hospices and palliative care units.
- Remove system barriers to availability of opioids and close the gap between needs and actual consumption of opioids by expanding the list of available pain medication beyond injectable morphine and fentanyl patches.
- Establish regular courses for physicians on pain and symptom management and safe use of opioids.
- Provide educational opportunities for all healthcare providers and establishing palliative care specialization for nurses. The training required for healthcare providers to implement palliative care at each level of healthcare has been recommended by WHO and described in the literature.(25)
- Establish mobile palliative care teams to improve access to palliative care in remote areas, where half of the population lives without access to palliative care.(6)
- Examine perspectives and challenges of key stakeholders in palliative care (patients, families, healthcare professionals, providers, and policymakers) to identify and address gaps.
- Encourage awareness-building campaigns and public education regarding palliative care and pain relief, which is key to expanding access. (9)
- Establish mobile teams for home-based care for patients whose palliative care needs could be met in their place of residence even after discharge. Should these patients require specialized inpatient care, they can be referred to a local hospice or palliative care unit.
- Prioritize oral forms of morphine over injections. Immediate-release oral morphine

represents an effective, essential, and inexpensive intervention which is unjustifiably denied to most patients in need in LMICs.

- Integrate family caregivers into palliative care as they represent a major workforce and are crucially needed in LMICs settings. Empowering and utilizing them could improve the quality of care and reduce the burden on the resource-limited system.
- Participate in international agenda and collaborate with international stakeholders, such as the World Hospice Palliative Care Alliance and the International Palliative Care Association, which frequently offer programs and grants designed for LMICs facing similar challenges.
- Establish a cohort of palliative care specialists with advanced knowledge and skills to deliver high-quality palliative care services and provide training to others.(1)
- Develop free online and onsite educational resources on palliative care for family caregivers can be an additional effective measure to improve the quality of life of patients and their families in resource-limited settings, whereas a wide range of medical staff should also have access to basic palliative training to make palliative literacy ubiquitous in all settings.(26)

While goals of extending life are well-prioritized and well-funded, they need to be followed by goals to reduce suffering by offering adequate pain relief and symptom management at the end-of-life. Therefore, developing high-quality palliative care services must be prioritized by the Ministry of Health to ensure higher quality-of-life and end-of-life care among people with terminal diseases.

Conclusions

In conclusion, the development of palliative care, in addition to the "ethical imperative" of eliminating the suffering of people with life-threatening illnesses, has several benefits for the state: it saves healthcare budgets by freeing up hospital beds, it reduces the number of hospitalizations and medical interventions, it reduces social tension and frees economically active family members, and improves society as a whole.(27) Being at the core of the universal health coverage, palliative care might be the least costly among all its components. (1)The COVID-19 pandemic set new obstacles for palliative care providers worldwide; however, patients cannot wait for proper changes to take place. Well-designed and appropriately financed palliative care relieves pressures on other parts of the health system and reduces overall costs.(9)

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Competing interests Statement

The authors declare no competing interests.

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CHAPTER IV

COST-EFFECTIVENESS OF HOSPICE PALLIATIVE CARE FOR CANCER PATIENTS AND FAMILY CAREGIVERS: A MULTI- CENTER STUDY IN KAZAKHSTAN

Second article

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ABSTRACT

Background: In Kazakhstan, palliative care is offered through hospices, cancer centers, general hospitals, and mobile teams to about 107,000 patients in need. As a country with a transitional economy and a newly implemented social healthcare insurance system, Kazakhstan seeks a cost-effective allocation of limited resources for end-of-life care.

Objective: To assess cost-effectiveness of hospice-based palliative care for cancer patients compared to the current standard of care provided in cancer centers across the country, and thereby, provide a better understanding for policy making regarding palliative care.

Methods: A total of 182 family caregivers were recruited, 104 from three hospices and 78 from three palliative care units of cancer centers. Patients' state of health and family caregivers' burden were assessed with the Palliative Outcome Scale (POS) and the Zarit Burden Inventory (ZBI). Direct medical and non-medical costs, and family caregivers' out-of-pocket expenses associated with palliative care were collected. One-way and probabilistic sensitivity analysis was conducted by generating 1,000 resamples using bootstrapping with Monte-Carlo simulation.

Results: Cost-effectiveness analysis revealed that after 14 days of inpatient palliative care, patients' median POS score was 5 points better in the hospice group compared to the cancer center group. Family caregiver burden was 2.5 points better in the hospice group. The median cost of palliative care per patient over 14 days was $31 lower for the hospice group. There was a statistically significant correlation between the total cost of treatment and patients' quality of life (r = 0.58). Probabilistic sensitivity analysis showed that hospice-based care has better outcomes and lower costs than care provided in cancer centers in 80% of tested scenarios.

Conclusion: Hospice-based palliative care is cost-effective compared to the care provided in palliative units of cancer centers in resource-limited settings in Kazakhstan.

Introduction

Palliative care can improve the quality of life of patients at the end of life and can help their families cope with issues associated with terminal illness by preventing and alleviating physical and mental suffering. [1] About 40 million people need palliative care worldwide and nearly 80% of them live in LMICs, where access to such services is severely limited. [1] WHO estimates that only 14% of patients needing palliative care worldwide has access to such services, primarily in countries with more robust economies. [2] By 2060, the need for palliative care worldwide will nearly double with the highest increase in LMICs. [2]

The World Atlas of Palliative Care characterized palliative care in Kazakhstan, a LMIC in central Asia, as being at the preliminary stage of integration into the healthcare system, while the Quality of Death Index ranked Kazakhstan 50th out of 80 countries assessed. [3,4] According to the assessment conducted by the World Hospice Palliative Care Alliance, approximately 107,000 people needed palliative care in Kazakhstan in 2021 and more than 100,000 family caregivers would have benefited from such services. [4,5] Moreover, about 190,000 people have been diagnosed with cancer, of whom 4,000 were registered as terminally ill in 2021. [6] Such developments and demographic shifts pose new medical and economic challenges for Kazakhstan and other LMICs. As a country with a transitional economy and a recently established social healthcare insurance system, Kazakhstan is looking for a cost-effective allocation of limited resources for end-of-life care.

The need for cost-effectiveness analysis of palliative care services in LMICs has been previously emphasized. [4,7] The overall purpose of this study is to generate an evidence-based evaluation of palliative care services in Kazakhstan, and, consequently, provide recommendations for policymakers to guide future development of these services in the country. Currently, palliative care in Kazakhstan is provided by four different types of healthcare organizations: hospices, palliative units of cancer centers, palliative beds in general hospitals, and mobile palliative teams. Due to the high heterogeneity in the approach and the wide spectrum of care in the last two models, we focus on comparing hospice-based palliative care services to cancer center-based palliative care. Moreover, mobile teams are sporadically distributed across rural areas of the country, making data collection rather inexpedient. Although palliative care is associated with a wide range of chronic conditions, we focus on cancer, as it is the most common illness associated with palliative care. [7] The primary aim of this study is to evaluate the cost-effectiveness of hospice-based palliative care compared to cancer center-based palliative care for terminal cancer patients, therefore, provide evidence for further policymaking. A secondary aim is to understand the societal cost of palliative care, i.e., the physical, mental, and financial burden of family caregiving for terminal cancer patients.

Methods

This cost-effectiveness analysis was based on the updated Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 statement.[8] The cost-effectiveness of medical interventions is usually measured as the ratio of cost per one quality-adjusted life-year saved (QALY), which considers expectancy and quality of life. [9,10] However, given the short life expectancy of terminal cancer patients and potential gains only in quality, QALY may not be well-suited to analyze the effectiveness of palliative care. [10] Palliative care provides physical, psychological, and social help, improving the lives of terminally ill patients to a more humane and satisfactory conclusion, adding value to life, which represents a crucial benefit that cannot be captured by the measurement of QALYs saved. [10] However, most published cost-effectiveness analyses of palliative care used cost per patient, cost per day, or per service as an outcome, which does not correspond to the definition of cost-effectiveness analysis. [11] Thus, we replaced the QALY maximization approach by a more holistic concept, where the outcome of palliative care is represented by better quality of life for patients and lower burden for their family caregivers.

Table 1 shows the key criteria used to design the cost-effectiveness analysis. Costs are represented by medical and non-medical costs incurred by social health insurance, as well as by out-of-pocket expenditures of family caregivers. Outcomes of palliative care were assessed as the quality of life of patients and the burden on their family caregivers. The health-economics analysis is provided in the supplementary materials and is expressed in 2021 US dollars converted from Kazakhstani tenge (KZ) at the exchange rate of $1 = KZ435.09. The national average salary in Kazakhstan is $450 and the purchasing power parity is $28,600. [12]

Table 1. Key design criteria of the cost-effectiveness analysis

Population	Family caregivers of patients with terminal cancer receiving palliative care
Intervention	Hospice-based palliative care
Control	Cancer center-based palliative care
Outcome	Quality of life of patients and burden of family caregivers (both assessed by family caregivers)
Costs	Direct medical and non-medical costs
Type of analysis	Cost-effectiveness analysis One-way and probabilistic sensitivity analyses with Monte-Carlo simulation and bootstrapping
Time horizon	14 days of inpatient palliative care
Perspective	Social health care system and out-of-pocket payer perspective
Discount rate	Not applicable due to short time horizon
Currency	2021 US dollars ($) converted from KZT tenge

Palliative care models

Hospices represent separate independent organizations providing palliative care to patients with a wide range of conditions, such as cancer, stroke, cerebral palsy, HIV, etc., with an average of 80 beds per hospice. [13] Hospice care focuses on the comfort of patients at the end of life rather than on performing tests and providing treatments to diagnose and cure disease. Therefore, providing a home-like environment and full access to family caregivers is paramount. Cancer center-based palliative care provides care to patients who received cancer treatment in the corresponding cancer center but have been referred to the palliative unit. Care in these units is provided by trained oncologists as they represent a structural part of cancer centers.

Settings, Sample, and Procedures

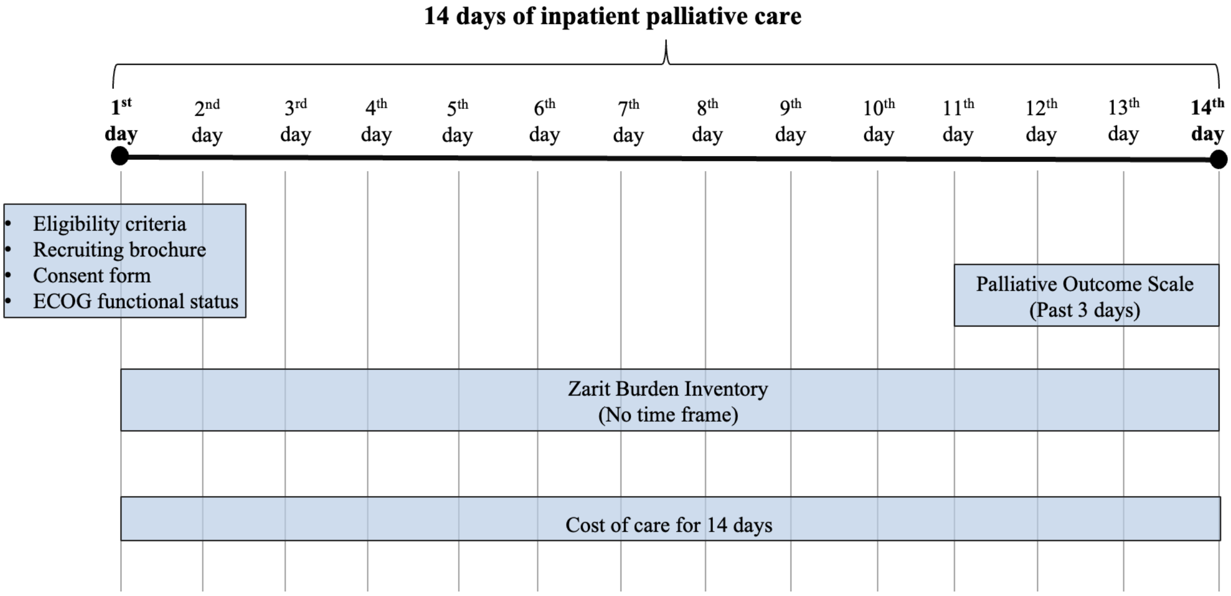
Ethical approval for this study was obtained from the Nazarbayev University Institutional Research Ethics Committee on June 15th, 2021 (IREC № 413/24052021). Three hospices and three cancer centers located in five regions of Kazakhstan were approached by the research group. The following criteria were applied for the selection of appropriate settings: 1) hospices with 60 or more beds for patients with terminal cancer; 2) cancer centers with designated palliative care units with at least 20 beds for patients with terminal cancer; 3) the facility enables active participation of family caregivers as part of palliative care. Table 2 provides detailed characteristics of the study facilities.

Table 2. Characteristics of the study facilities

	Three hospices	Three cancer centers
Region	Pavlodar Astana Almaty	Astana Semey Kostanay
Number of physicians	19	5
Number of nurses	35	17
Services	Pain management Symptom management Psychological support Social support	Pain management Symptom management Psychological support At the request of patients or family caregivers: Palliative chemotherapy Palliative radiation Palliative surgery
Number of beds	347	75
Eligibility of patients	Terminal stage of cancer HIV/AIDS Terminal organ failure Stroke Terminal tuberculosis Neurodegenerative diseases	Terminal stage of cancer
Involvement of family caregivers	Desirable	With the permission of the administration
Funding	Free	Free

Eligible participants were adult (18+) family caregivers of cancer patients, who have not received palliative care previously, and have been admitted to inpatient palliative care settings in one of the selected hospices or cancer centers. Excluded were family caregivers of patients with neurodegenerative disorders (e.g., Parkinson's, Alzheimer's). Potential participants were identified by medical staff and were first contacted by head doctors. At a second step, a researcher explained the study, provided a recruitment brochure, and obtained written consent. Family caregivers were provided a self-administered survey. The survey took approximately 15 minutes to complete, and family caregivers could complete it on site. No incentives were provided for participating in the study. Overall, data collection occurred between August 2021 and April 2022. Figure 1 illustrates the chronology of the study procedures.

Figure 1. Study procedures: patients were recruited, and their functional status was assessed on day 1, while outcomes and costs were evaluated on day 14 of inpatient palliative care.



Measures

The self-administered survey was available in Russian and included 47 questions that assessed demographics, patients' quality of life, and caregiver burden. Gains in patients' quality of life were assessed with the Palliative Outcome Scale (POS), a validated instrument with 12 items assessing patients' physical and mental symptoms and support needs the past three days. POS is scored from 0 to 40, where a higher score represents worse quality of life. [14] We applied a version of POS designed for family caregivers to measure patients' quality of life (Supplementary material). [14] The Cronbach's alpha of the scale was 0.81 in this sample.

Family caregivers' burden was assessed with the Zarit Burden Interview (ZBI), a 22-item self-administered instrument which assesses physical and mental burden associated with family caregiving without a set time frame. Scores range from 0 to 88, where a higher score represents higher physical and mental burden. [15] Cronbach's alpha of the scale was 0.84 in this sample.

The self-administered survey also included questions about patients' and family caregivers' demographics and clinical data. Data on performance status at admission were collected with the Eastern Cooperative Oncology Group (ECOG) to test the homogeneity of patients between both groups at baseline. [16] ECOG was scored by nursing personnel upon admission, measuring patients' functional status from 0 to 5, where "0" represents fully active patients, "3" indicates patients confined to bed, and "5" represents death.

Costs

We used a combined healthcare system and societal perspective for the cost-effectiveness analysis, based on the cost of incremental improvement of quality of life of patients assessed with POS, and the cost of incremental decline of family caregiver burden assessed with ZBI. All medical and non-medical costs in hospices and cancer centers during a period of 14 days of palliative care were collected from respective accounting departments (see supplementary materials). Direct medical costs included medical materials, consumables, and services provided by health professionals. Indirect medical costs included utilities, food, and non-medical items. To calculate the out-of-pocket expenses, we collected data on expenditures by family caregivers for purchasing medicines, food, and medical materials, e.g., painkillers, diapers, etc.

Analysis

Cost-effectiveness analysis was conducted by combining data on differences between total costs of 14 days of palliative care with data on differences between POS and ZBI scores between hospices and cancer centers. Given the abnormal distribution of data, Wilcoxon-Mann-Whitney-Test was used to test the differences between POS and ZBI scores in the two groups. We also calculated differences between the total cost of care in both groups, including medical expenses and out-of-pocket expenditures. We applied a time horizon of 14 days of inpatient treatment to allow adequate "exposure" of patients and family caregivers to palliative care. Using Lehr’s formula, a sample of 180 family caregivers was estimated to provide 80% power to detect a difference of >2 in quality of life of palliative patients between the two groups.

Sensitivity analyses

A deterministic one-way sensitivity analysis was used to estimate the effects of 30% variations in costs and outcomes on overall cost-effectiveness of hospice-based palliative care. Probabilistic sensitivity analyses tested the robustness of our calculations and assessed the overall probability that the hospice-based palliative care is cost-effective compared to cancer center-based palliative care. Probabilistic sensitivity analysis tested 1,000 scenarios, varying costs, and outcome parameters, such as quality of life of patients and family caregiver burden using Monte-Carlo simulations. We generated 1,000 resamples of each observation using bootstrapping and computing the mean difference in costs and outcomes (see supplementary materials). Given the existing correlation between costs and outcomes, the probabilistic sensitivity analysis was conducted based on joint distributions in these parameters. [17,18] We plotted mean differences in costs along with corresponding mean differences in outcomes for all 1,000 resamples on a cost-effectiveness plane. This method graphically demonstrates the proportion of resamples in four different scenarios: the upper-right quadrant shows better outcomes at higher costs, the lower-right quadrant shows better outcomes at lower costs, the upper-left quadrant represents worse outcomes at higher costs, and the lower-left quadrant shows worse outcomes at lower costs. Statistical analyses were conducted using statistical software SPSS 26.0 (IBM SPSS), while cost-effectiveness analyses were carried out using MS Excel 2020 (Microsoft Corporation).

Results

Data were collected from 182 family caregivers of patients with terminal cancer receiving inpatient palliative care within two alternative models (1:1 ratio of family caregiver to cancer patient). Among them, 104 (57.1%) were family caregivers of patients who received hospice-based palliative care, while the remaining 78 (42.9%) were family caregivers of patients who received cancer center-based palliative care. Table 3 and Table 4 present baseline characteristics of patients and family caregivers.

Table 3. Baseline characteristics of patients

		Hospice (treatment) n=104	**Cancer Centers (control) n=78**	**Total (%) n=182**
Age (mean, SD)		62 (12.6)	65 (10.2)	
Sex	Female	37	43	80 (44)
	Male	67	35	102 (56)
Education	High school degree or equivalent	18	8	26 (14)
	Some college but no degree	49	44	93 (51)
	Higher and postgraduate degree	37	26	63 (35)
Type of cancer	Breast	8	15	23 (13)
	Bowel	23	7	30 (16)
	Lung	27	17	44 (24)
	Uterus	9	12	21 (12)
	Prostate	21	9	30 (16)
	Other type	16	18	34 (19)
Living conditions	Lives alone	32	29	61 (34)
	Lives with family caregiver	72	49	121 (66)
Time since diagnosis	1–3 months	16	7	23 (12)
	>3–6 months	5	16	21 (12)
	>6–12 months	25	22	47 (26)
	> 12 months	58	33	91 (50)

Table 4. Baseline characteristics of family caregivers

	Hospice (treatment) n=104	**Cancer Centers (control) n=78**	**Total (%) n=182**
Age (mean, SD)	47 (12.6)	48 (13.2)	

Family size (mean, SD)		3 (1)	3 (1.1)	
Monthly income (mean, SD)		473 (174.1)	427 (180.9)	
Sex	Female	61	58	119 (65)
	Male	43	20	63 (35)
Education	High school degree or equivalent	4	9	13 (7)
	Some college but no degree	31	22	53 (29)
	Higher and postgraduate degree	69	47	116 (64)
Employment	Full time job	54	33	87 (48)
	Part-time job	22	18	40 (22)
	Not employed	16	15	31 (17)
	Retired	12	7	19 (10)
	Disabled, not able to work	0	5	5 (3)

Outcomes

Table 5 presents median scores of outcomes in the two groups. The difference in patients' ECOG performance status on the day of admission was not statistically significant implying homogeneity of patients' physical status in both groups. The median ECOG score was "3" for each group, indicating limited self-care and patients that are confined to bed or a chair for more than 50% of waking hours. Patients' quality of life over 14 days of inpatient care, as measured with POS, was 5 points better for hospice patients compared to patients treated in cancer centers, implying better quality of life for hospice patients.

Table 5. Median (IQR) Outcome Scores after 14 days of inpatient palliative care

Measure and group	Scoring	Time	Hospice-based care	Cancer center - based care	Median difference	p-value

ECOG performance status (Patients)	0-best 5-worst	Admission	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0	0,06
Palliative Outcome Scale (Patients)	0-best 40-worst	Day 14	24.5 (20.0–29.0)	29.5 (20.0–34.0)	-5	0,01
Zarit Burden Inventory (Family Caregivers)	0-best 88-worst	Day 14	48.0 (39.0–59.5)	50.5 (41.0–65.0)	-2,5	0,4

Overall, family caregivers in the hospice group had mild to moderate burden, while most family caregivers in the cancer center-based group had moderate to severe burden. Family caregiver burden, as measured with ZBI, were 2.5 points lower in the hospice group compared to the cancer center group, implying less burden for family caregivers in hospices.

Costs

Table 6 shows itemized, the main expenses per one patient incurred by hospices and cancer centers within a period of 14 days of inpatient care. The total cost of palliative care per one patient over 14 days was $31 higher in the cancer center-based group compared to the hospice-based group. Similarly, out-of-pocket expenditures incurred by family caregivers over the time of inpatient treatment were $18 higher in the cancer center-based group compared to hospice-based care. In contrast, the staff salary was $41 lower in the hospice-based group compared to the cancer center-based group. Overall, on the 14th day of inpatient care, hospice care showed to be $31 cheaper providing better quality-of-life for patients according to POS, and lower burden for family caregivers according to ZBI.

Table 6. Median (IQR) costs ($) per one patient for 14 days of inpatient palliative care

Costs	Hospices	Cancer Centers	Median difference
Medical costs			
- **Food**	36.3 (33.7–40.1)	31.8 (26.6–36.8)	4.5
- **Utilities**	16.3 (13.4–20.1)	15.5 (11.5–19.1)	0.8
- **Salaries and taxes**	164.9 (148.3–181.5)	205.9 (177.3–231.5)	-41

- **Non-medical consumables**	39.6 (34.5–45.1)	43.3 (37.8–48.1)	-3.7
- **Building rent**	23.6 (22.1–25.4)	-	23.6
- **Painkillers**	9.8 (6.1–13.7)	7.2 (4.7–9.9)	2.6
Out-of-pocket expenditures	172.06 (145.4–198.7)	189.9 (163.9–241.9)	-17.8
Total cost of treatment	462.7 (436.1–489.3)	493.6 (454.6–532.6)	-30.9

Sensitivity analysis

All observations shown on cost-effectiveness planes have been tested using probabilistic sensitivity analysis. Figure 2a represents graphically the cost-effectiveness plane with 1,000 replications, 80% of which were in the lower-right quadrant, indicating that hospice-based palliative care had better outcomes and lower costs than the cancer care-based care. Findings also showed that 10% were in the upper-right quadrant, indicating better outcomes at higher costs. Similarly, based on the family caregiver burden (ZBI) (Figure 2b), around 80% of replications were in the lower-right quadrant showing lower costs and better outcomes, and 10% in the upper-right quadrant showing higher costs and better outcomes.

Using Spearman correlation, the correlation coefficient between the patients' quality of life and family caregivers' burden was estimated to be 0.60 ($p<0.001$), meaning significant correlation according to the Cheddok's scale. At the same time, the correlation between the cost of treatment and the POS score was estimated to be 0.58 ($p<0.001$).

Figure 2a

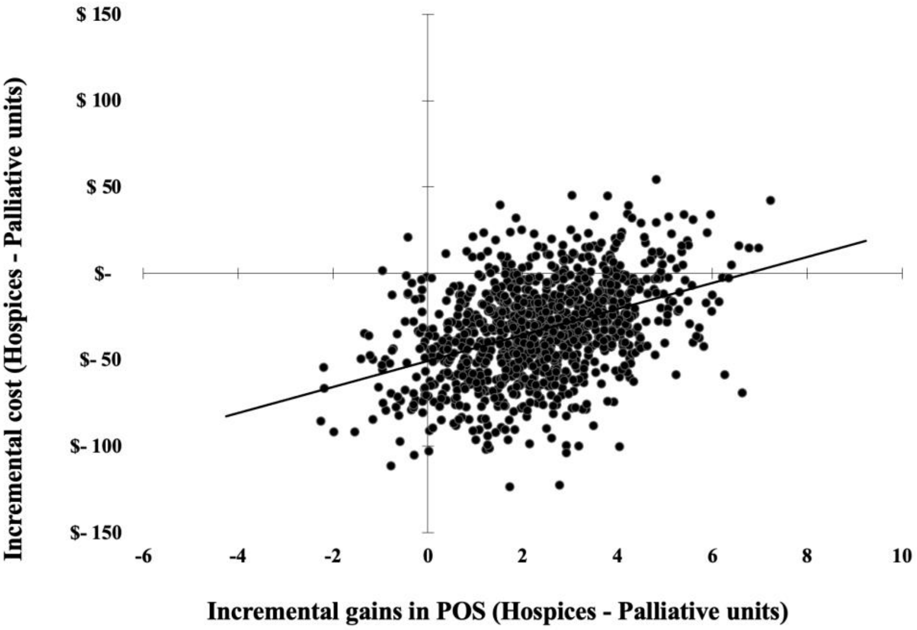


Figure 2b

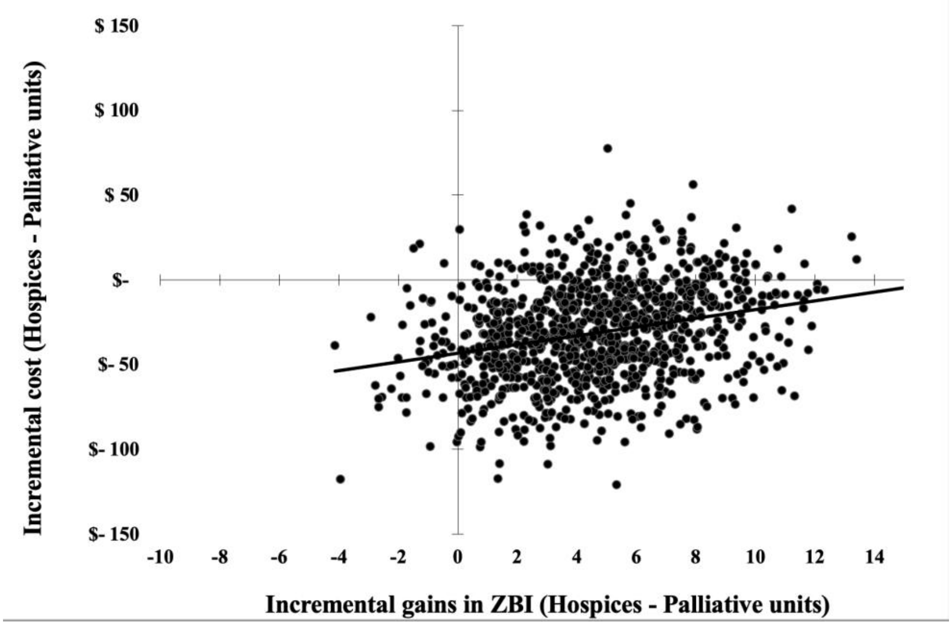


Figure 2. Probabilistic sensitivity analysis of hospice-based palliative care for terminal cancer patients compared to cancer center-based palliative care: The horizontal x-axis of the cost-effectiveness plane represents the mean differences in POS (a) and ZBI (b), while the vertical y-axis indicates differences in the mean cost of treatment between both groups. Dots to the right of the vertical axis indicate better outcomes in hospices; dots below the horizontal axis show lower costs in hospices. Therefore, dots in the lower right quadrant show both improved outcomes and lower costs, and those in the upper left quadrant show worse outcomes and higher costs.

Discussion

The aim of our study was to compare cost-effectiveness of two different models of palliative care, namely hospice-based versus cancer center-based palliative care. This is a strength of our study, since most cost-effectiveness analyses of palliative care either do not have a control group or apply usual hospital care as a comparator. [11,19] Our cost-effectiveness analysis indicates that hospice-based palliative care for patients with terminal cancer is cost-saving compared to palliative care provided in designated palliative units of cancer centers. Findings suggest that hospice-based care for people with terminal cancer may improve patient experience and quality of life, which in turn may reduce the burden of their family caregivers and decrease costs for healthcare services. The results show that hospice-based palliative care is cost-saving and more effective in maintaining quality of life of patients and family caregivers in 80% of scenarios. Our findings are consistent with previous reviews and other studies. [11,19] A cost-effectiveness analysis of three different palliative care models for cancer patients in Turkey showed that cancer center-based palliative care is the most expensive, while home-based palliative care services are the most cost-effective strategy in Turkey and in Australia. [20,21]

Outcome assessments showed a median difference of 5 and 2.5 on POS and ZBI scores, respectively, in favor of hospice care, meaning milder symptoms for patients and less burden for their family caregivers. The main causes for cost savings in hospice care are related to lower staff salaries and higher out-of-pocket costs for family caregivers in palliative care units at cancer centers. Hospices assume higher spending on care-related consumables and drugs by hospices, which reduces the out-of-pocket of families for these materials. This finding has significant implications given the 4,000 terminal cancer cases that were newly registered in 2021. [6] Even if the hospice-based palliative care produced cost-savings for only 14 days, this results in total savings of almost $124,000 annually. If these savings were extended from 14 days to one month, cost savings would also likely double. These cost-savings are of great importance in LMICs with limited resources, such as Kazakhstan. Our study showed that personnel salaries and taxes represent around 60% of the total expenses for palliative care, while the average daily cost of medicines was only $0.6. At the same time, given a wide range of other terminal chronic conditions, i.e., cardiovascular, and neurodegenerative conditions, this evaluation may underestimate the actual number of family caregivers and households who would benefit from palliative care services and associated cost-benefits.

Our analysis supports previous findings, which recommend that majority of palliative care beds should be in hospices. [22] A Lancet commission report suggests that universal, public funding of basic low-cost palliative care components reduces the risk of catastrophic healthcare expenditures as a main cause of impoverishment in LMICs. [23,24] Healthcare in Kazakhstan is funded by the Social Health Insurance and the Statutory Free Medical Assistance. [25] Introduced in 2020 the insurance system implies shared responsibility of the state, employers, and citizens, which pay three percent of their salaries as a monthly contribution towards health insurance. [25] Free medical assistance is limited and includes ambulance services, vaccination, screening programs, HIV treatment, and palliative care. Moreover, there are substantial out-of-pocket expenditures for patients and their families above the monthly insurance contributions. [25]

Our analysis showed that, one bed-day of palliative care in Kazakhstan costs on average $21, while the cost of one day of hospice-based care in the US ranges from $143 - $1,500 and around $50 in Russia. [26] With a mean monthly income of $453, family caregivers spent, on average, $185 for expenses associated with palliative care, which corresponds to 41% of their monthly income, exceeding the 40% threshold of the catastrophic health expenses defined by WHO. [27] Representing a major health and economic threat to LMIC societies, catastrophic health expenses exacerbate the poverty level by bringing the highest financial burden to households with the lowest financial resources. [27,28] Having proven the effectiveness of hospice-based palliative care, even in such resource-restricted settings, the need for funding palliative care is emphasized to ensure further improvement of the quality of life of patients and their families in Kazakhstan, and possibly in other LMICs.

In this study we also considered burden of family caregivers, which are described as the invisible workforce of healthcare systems while they are at increased risk of physical, social, and psychological distress. [29,30] In 2017, 41 million family caregivers provided 34 billion hours of care in the US, corresponding to an economic value of $470 billion. [29] Palliative care in Kazakhstan relies heavily on family caregivers, who provide palliative care to most of the 107,000 people in need, including those living in remote rural areas. [4] Therefore, further development of palliative care should include support and training of family caregivers, which may be an effective and affordable measure in LMICs. [29,31]

To date, palliative care in Kazakhstan is not included in the social insurance system but, as with emergency care, it is provided free of charge. However, this funding mechanism is very scarce and insufficient to meet patients' and family caregivers' needs. Indonesia, also a LMIC, has successfully used social health insurance schemes to achieve universal health coverage for the most vulnerable populations, while providing effective national risk-pooling. [32] We emphasize the importance of comprehensive state support of palliative care since progress is almost impossible solely through the efforts of charitable and nongovernmental organizations. The experience of wealthy countries has shown that private hospices are not the solution, as they provide much poorer care and, in pursuit of profit, focus on accepting patients with less-severe conditions. [26] As a key component of universal health coverage, palliative care improves the quality of life of dying patients and protects households from catastrophic health expenditures. [7] Therefore, to achieve sustainability and risk-pooling in palliative care, the recently introduced social insurance could be a viable option to contribute to universal health coverage in Kazakhstan. [33] Close coordination of various stakeholders, such as palliative care clinicians, advocates, and policymakers of the Ministry of Health, is necessary to achieve these goals.

Our study has several limitations. First, data are cross-sectional, while the effects of palliative care would be better reflected in a longitudinal time frame. The cross-sectional design was dictated by contextual factors, such as life expectancy of patients with cancer and/or their willingness to discontinue impatient care; and data collection took place in 2021 when the COVID-19 pandemic reached Kazakhstan and when access to frail palliative patients was highly restricted. A second limitation is that we did not distinguish between different types of out-of-pocket expenses incurred by family caregivers, but rather recorded them as a single overall expenditure figure.

Conclusion

We demonstrated that hospice-based palliative care for patients with terminal cancer, while being more cost-effective, is also more beneficial to the Kazakh healthcare system and to society. Support for palliative patients and their family caregivers is necessary to promote dignity at the end of life and to ensure that households do not sacrifice their basic needs, or are driven into poverty, while caring for loved ones. We highlight opportunities for cost-savings by improving access to hospice-based palliative care services to meet sustainable development goals, and to ensure good health and well-being for all. Further investigation of various palliative care stakeholders' views is necessary to guide decision-makers and determine allocation in resource-limited settings of Kazakhstan.

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CHAPTER V

IMPROVING PALLIATIVE CARE OUTCOMES IN REMOTE AND RURAL AREAS OF LMICs THROUGH FAMILY CAREGIVERS: LESSONS FROM KAZAKHSTAN

Third article

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ABSTRACT

Almost half of the 19 million population of Kazakhstan lives in rural areas where access to healthcare services, particularly palliative care, is scarce. Family caregivers play a major role in providing home-based palliative care. To understand challenges and propose tailored solutions, 29 key stakeholders, including family caregivers, health professionals, and palliative care administrators were identified in five regions of Kazakhstan. The main challenges encountered by family caregivers included lack of palliative care skills, the need for home-based care from mobile services, and high out-of-pocket expenditures. Challenges highlighted by healthcare providers and administrators were the lack of formal education in palliative care, shortage of opioids, and limited societal awareness and state support.

This Perspective advocates against replicating strategies implemented in high-income countries. Family caregivers play a critical role in implementing affordable and efficient palliative care solutions in resource-limited settings. Enhancing their competencies through digital training and increasing access to palliative care services through mobile teams are tailored and localized solutions that address specific challenges unique to LMICs. Additional considerations are the establishment of comprehensive palliative care services with affordable access to pain management and societal awareness.

Introduction

About 60 million people needed palliative care worldwide in 2020, and nearly 80% of them lived in low- and middle- income countries (LMICs). [1,2] Palliative care is a crucial aspect of healthcare, aiming to alleviate suffering and to enhance quality of life for individuals with serious illnesses and their families. [1,3] Despite growing demand, access to palliative care in LMICs remains limited. [1–3] The demand for palliative care in LMICs is projected to double by 2060, yet these countries lack the necessary infrastructure for establishing and distributing these services, especially in rural and remote areas. [3,4] According to the United Nations, 3 billion people worldwide who live in rural and remote areas face significant challenges, such as poverty and limited access to healthcare and education, creating critical challenges for policymakers and development organizations.[5] The Lancet Commission on the Value of Death suggested that strengthening palliative care services in LMICs requires comprehensive approaches that consider the unique challenges faced by communities in these settings and leverages innovative solutions to improve access to care. [1]

Investing in palliative care in LMICs has the potential to improve health equity worldwide. [1,2] WHO estimates that only 14% of patients worldwide who need palliative care has access to such services, primarily in countries with more robust economies. [6] This leads to an unequal distribution of suffering among patients and their families, especially for those who are economically disadvantaged, socially excluded, or reside in remote and rural regions. Palliative care in LMICs can improve quality of life for patients and their family caregivers by increasing access to essential medications for pain and symptom management. [7,8] Studies in Kenya, India, and Bangladesh found that introducing palliative care services in rural districts led to long-term cost-savings, as patients receive home- and community-based care, reducing the need for costly hospitalizations and other healthcare services. [3,9] Palliative care services can contribute to health equity by addressing underlying social determinants of health, such as poverty, lack of access to services, and discrimination.[5,10] As the demand for palliative care in LMICs increases, it is important to identify tailored local solutions. Adopting the strategies and approaches of high-income countries is neither feasible nor sustainable due to limited resources and lack of healthcare infrastructure in LMICs.

Palliative care in Kazakhstan

Kazakhstan is a LMIC in Central Asia with a population of approximately 19 million living in an area of 2.7 million km^2. The country has one of the lowest population densities worldwide, with only seven people per km^2. The disperse population poses serious challenges for accessing health services, especially for half of the population who live in remote and rural areas. [11] Kazakhstan's demographic shift is characterized by a doubling of the proportion of the older adults over the age of 65 by 2050, a trend that is consistent with other LMICs.[12] There are currently 107,000 people needing palliative care services in the country. [13] With only 45 physicians and 101 nurses serving 1,925 palliative care beds in the entire country, the Quality of Death Index ranked Kazakhstan 50th out of 80 countries investigated. [3,14] According to the World Hospice Palliative Care Alliance, Kazakhstan's palliative care is at the preliminary stage of integration into the healthcare system and seeks to develop palliative care services that meet its national needs and international standards. [3,14]

This Perspective examines challenges of developing palliative care services in Kazakhstan as an example of developing such services in LMICs that are searching for affordable solutions to transform their own healthcare system. According to the Lancet Commission Report, lack of data hinders the evaluation of palliative care services in LMICs.[1] Addressing this challenge requires research on stakeholder needs, i.e., family caregivers of terminal patients, healthcare providers, and policy makers.[15,16] This Perspective presents a comprehensive synthesis of challenges faced by key stakeholders in palliative care in Kazakhstan, and offers suggestions for improving palliative care outcomes in resource-limited and remote and rural settings. Our suggestions could be relevant for other LMICs in Central Asia beyond Kazakhstan.

Challenges of palliative care stakeholders in Kazakhstan

We identified 29 key palliative care stakeholders in Kazakhstan between August 2021 and April 2022, and we assessed their needs regarding palliative care services and challenges they encountered. Stakeholders were identified from hospices or cancer centers located in five urban or remote regions of Kazakhstan. Their needs and challenges were assessed with semi-structured interviews conducted in Russian. Procedures followed the Medical Research Council good research practice guidelines. [17] Approval was obtained from the Nazarbayev University Institutional Research Ethics Committee (IREC413/24052021).

Key stakeholders included 12 adult family caregivers, 12 healthcare providers, and 5 administrators of palliative care services. Family caregivers provided help with palliative procedures (massage, hygiene, prevention of bedsores, etc.) to terminally ill cancer patients receiving inpatient palliative care for at least 14 days. Healthcare providers (5 physicians, 5 nurses, and 2 psychologists) had a minimum of 3 years' experience in palliative care. Administrators were employed by Non-Governmental Organizations (NGOs), were often involved in communications with the Ministry of Health and policymaking and had a minimum of 5 years' experience in palliative care services. Figure 1 summarizes positive and negative factors related to patients' and families' decisions to receive palliative care. Reflecting on the Road Map of Palliative Care Development in Kazakhstan, we describe specific challenges to providing palliative care in the country, and we provide recommendations to address these challenges. [13]

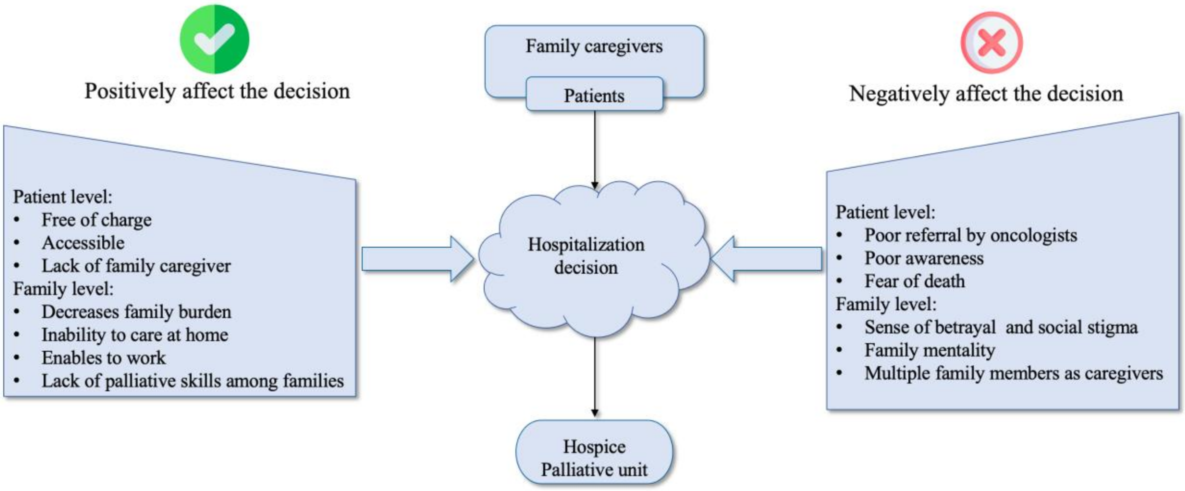

Figure 1. Factors associated with the decision to receive inpatient palliative care.

Lack of caregiving skills, mobile palliative care services for home-based care, and loss of income and high out-of-pocket expenditures

Palliative care services in Kazakhstan, both in inpatient and outpatient settings, rely heavily on family caregivers and especially in remote and rural areas, where half of the population resides. However, most family caregivers lack knowledge and practical skills related to patient care. Although nursing staff provide demonstrations of basic procedures in inpatient settings, this is very unsystematic. A terminal cancer diagnosis and family caregiving often result in loss of income for the entire family, either due to patients' inability to work or due to family caregivers leaving their job to provide care. Most family caregivers favor home-based care and the support of mobile teams over inpatient palliative care services. Home-based care would enable many of them, especially in remote and rural areas, to minimize long distance travel to inpatient services, retain their job, and minimize the loss of income for the entire family. However, mobile teams are largely unavailable. For example, there is only one mobile team that covers palliative care needs of the city of Almaty with a population of two million. The lack of sufficient state funding and universal health coverage results in high out-of-pocket medical expenses that consume a large portion of the family income. This financial burden further exacerbates catastrophic health expenditures for families living in remote and rural areas, and increases inequalities, with some families being able to afford more expensive treatments, equipment, and consumables than others.

Poor formal education and shortage of opioids for pain management

Formal education of healthcare providers in palliative care is inadequate due to lack of academics and other teaching personnel with expertise in palliative care. Few physicians and other healthcare providers have been trained abroad under a state-funded educational program. Most of the training occurs “on the job”, which translates to poor understanding of the nature of palliative care. This especially impacts the nursing workforce, where the heavy workload and unmet expectations lead to burnout and high turnover of new nurses. Remote and rural areas are affected disproportionately, because trained specialists prefer to seek employment in larger cities rather than rural areas. [2,18]

Lack of formal education of healthcare providers in palliative care often leads to opiophobia and reluctance to prescribe opioids among physicians and oncologists. [19,20] In Kazakhstan, 95% of terminally ill patients experience severe pain at the end of life and do not have access to opioids. [13] The problem is exacerbated by increased governmental control in the attempt to combat drug trafficking. There are few medications available for pain control, including only weak opioids and small amounts of oral morphine, making access to pain medication difficult in remote and rural areas. This leads to many avoidable hospitalizations, as patients are forced to be admitted to a hospice or palliative unit to receive opioids.

Lack of societal awareness and State support

Lack of awareness about palliative care among the general population is another barrier to developing and delivering effective services. Lack of understanding of the role of palliative care creates false expectations that patients will be receiving curative treatment. Unmet expectations lead to stigmatization of palliative care services and generate anger and hostility towards healthcare providers. This is magnified in remote and rural areas, with lower levels of healthcare awareness. The absence of strong and comprehensive policies and regulations regarding palliative care in Kazakhstan resulted in these services developing without active participation of governmental organizations. Thus, palliative care is often not integrated into existing healthcare systems, leading to lack of accountability, insufficient quality control, and limited availability and accessibility to palliative services.[6] Stakeholders suggested that the key to further developing palliative care is better cooperation between stakeholders and the government, and increasing support from governmental organizations.

Recommendations

Establishing and expanding palliative care in Kazakhstan can be addressed by implementing a horizontal and a vertical integration of existing services (Figure 2). Horizontal integration involves the standardization and consistency of palliative care delivery across various settings, such as mobile teams, hospices, and palliative care units. Vertical integration involves the coordination and collaboration between government, NGOs, and sponsors in providing comprehensive and effective palliative care services. Family caregivers are at the center of this model, both as care providers and care recipients. The horizontal and vertical integration of palliative care services is crucial in promoting a uniform approach to palliative care and guaranteeing consistent implementation of reforms across all settings, which is especially important in LMICs.

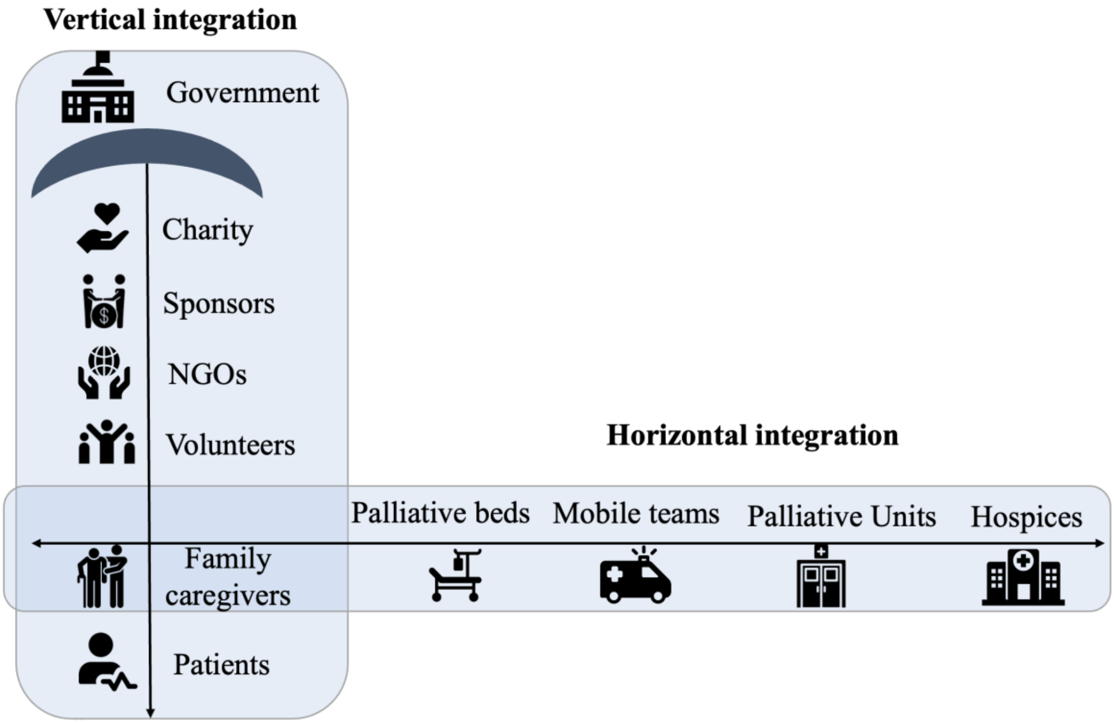

Figure 2. Vertical and horizontal integration of palliative care services.

Enhance competencies of family caregivers through training and increase access to palliative care through home-based mobile services

Providing training to family caregivers and increasing the number of mobile teams can be financially feasible and cost-effective for remote and rural areas of Kazakhstan, and possibly other LMICs. Home-based care is less expensive than inpatient care, as it improves patient outcomes by increasing access to essential care, and reduces healthcare costs by reducing hospitalizations.[21] Increasing the number of mobile teams would also help address disparities in accessing these services in remote and rural areas, where traditional healthcare facilities may be absent or limited.[8,21,22] Given that the majority of palliative patients in Kazakhstan are cared for by their families, training of family caregivers can help support families in providing high-quality, home-based care. This can reduce the burden and financial strain associated with terminal disease, while it ensures the best use of limited resources at the family and societal levels.[23] Training courses can focus on increasing caregivers' knowledge and self-efficacy about basic palliative care procedures, such hygiene and feeding, and provide resources to support them psychologically and address caregiver burden [24,25]. Under the guidance of mobile teams, trained caregivers will be better equipped to manage pain and other symptoms, and to provide basic care for preventing bed sores. Taking advantage of the explosion of digital technologies in the post-Covid-19 era, online and m-Health courses could reach family caregivers in remote and rural areas of Kazakhstan and other LMICs.[26,27]

Establish a comprehensive palliative care system and increase awareness of palliative care in remote and rural areas

Increased opportunities for educating healthcare providers and access to pain medication are interconnected key components of the horizontal integration of palliative services, promoting a consistent approach to care delivery in different contexts of remote and rural regions.[28] Training in palliative care would help minimize variations in care provision, and enable a uniform approach to effective use of medication for pain management and symptom control, and psychosocial support across all settings. By integrating pain management into the horizontal axis of palliative care services, healthcare providers can ensure that patients receive the care they need, regardless of their geographic location or socioeconomic status. This means that bureaucratic procedures related to the import and distribution of pain medications should be streamlined to reduce delays and ensure availability.

Local production of various pain medications could reduce the cost of medication and mitigate the disproportionate economic impact of fluctuating exchange rates on LMICs. The 2003 successful implementation of strategies for affordable local morphine production in Uganda, exemplifies the importance of addressing the challenge of promoting local production of pain medication, as it has a significant impact on the quality of life of patients and family caregivers, and is also affordable for LMICs.[29] The cost of 110 days of pain management with oral morphine in Uganda is equivalent to the price of a loaf of bread, which allows providing necessary pain relief and maintaining a satisfactory quality of life of all palliative patients until death. [29] The Kazakhstan Association of Palliative Care successfully engaged the Ministry of Health and the Police Department, to facilitate a five-fold increase in the availability of fentanyl patches. This is a noteworthy accomplishment that highlights the importance of advocacy and collaboration in addressing the palliative care needs in the country. Awareness-raising campaigns organized annually by the Kazakhstan Association of Palliative Care with the support of hospices and hospital units, physician organizations, and NGOs attract hundreds of volunteers and social media, advocate for an integrated approach to palliative care, and highlight its long-term benefits for society. [30] The goal of these campaigns is to increase public support and engagement in the development and implementation of sustainable palliative care systems in Kazakhstan and other LMICs.

Conclusion

Based on the challenges and needs of LMICs, our recommendations focus on efficient use of available resources to achieve the desired goals. In this Perspective, we argue that a universal approach which involves copying expensive strategies of high-income countries is neither sustainable nor advisable. Instead, more nuanced, tailored, and context-specific approaches should be adopted. The lessons learned from current developments in palliative care in Kazakhstan provide valuable insights into the challenges and opportunities for developing such services in other LMICs and demonstrate the importance of identifying local solutions for meeting the unique needs of these populations. At the center of these solutions, especially for LMICs are family caregivers, who need to be supported in their tasks.

Target 3.8 of the United Nations Sustainable Development Goals points to the need for achieving universal health coverage by 2030, including access to essential health services and financial risk protection. [31] However, no country can achieve universal health coverage without including palliative care. By highlighting key challenges and providing recommendations, our Perspective provides guidance to health authorities and policymakers in LMICs who are looking to improve palliative care in their communities. Shifting care to the community can reduce healthcare costs, improve access to care for patients who might otherwise not receive it, and enhance overall well-being and quality of life for remote and rural communities in LMICs.

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CHAPTER VI

SWISS COST-EFFECTIVENESS ANALYSIS OF UNIVERSAL SCREENING FOR LYNCH SYNDROME OF PATIENTS WITH COLORECTAL CANCER FOLLOWED BY CASCADE GENETIC TESTING OF RELATIVES

Fourth article

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Swiss cost-effectiveness analysis of universal screening for Lynch syndrome of patients with colorectal cancer followed by cascade genetic testing of relatives

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ABSTRACT

Background We estimated the cost-effectiveness of universal DNA screening for Lynch syndrome (LS) among newly diagnosed patients with colorectal cancer (CRC) followed by cascade screening of relatives from the Swiss healthcare system perspective.

Methods We integrated decision trees with Markov models to calculate incremental cost per quality-adjusted life-year saved by screening all patients with CRC (alternative strategy) compared with CRC tumour-based testing followed by DNA sequencing (current strategy).

Results The alternative strategy has an incremental cost-effectiveness ratio of CHF65 058 compared with the current strategy, which is cost-effective according to Swiss standards. Based on annual incidence of CRC in Switzerland, universal DNA screening correctly identifies all 123 patients with CRC with LS, prevents 17 LS deaths and avoids 19 CRC cases, while the current strategy leads to 32 false negative results and 253 LS cases lost to follow-up. One way and probabilistic sensitivity analyses showed that universal DNA testing is cost-effective in around 80% of scenarios, and that the cost of DNA testing and the number of invited relatives per LS case determine the cost-effectiveness ratio.

Conclusion Results can inform policymakers, healthcare providers and insurance companies about the costs and benefits associated with universal screening for LS and cascade genetic testing of relatives.

INTRODUCTION

Lynch syndrome (LS) is a cancer predisposition syndrome that confers a 12%–52% lifetime risk for colorectal cancer (CRC), and a 13%–60% lifetime risk for endometrial cancer, while the corresponding risks in the general population are 5%–6% and 2%–3%, respectively.[1] LS is also associated with glioblastomas and with gastric, ovarian, small bowel, pancreatic and urothelial cancers.[2] Germline pathogenic variants in mismatch repair (MMR) genes (ie, MLH1, MSH2, MSH6 or PMS2) or deletions in the 3'end of the EPCAM gene predispose to LS.[3] Pathogenic variants are inherited in an autosomal-dominant manner; for every LS case, there are multiple blood relatives with the same pathogenic variant. First-degree and second-degree relatives (FDR, SDR) have 50% and 25% probability, respectively, of inheriting the pathogenic variant.[4]

LS is a common cancer predisposition condition with an estimated population frequency 1:279.[5] However, LS remains largely undetected due to different associated cancer types and the lack of clear diagnostic criteria. The Amsterdam II and revised Bethesda guidelines that have been traditionally used to identify individuals at risk for LS can miss 23%–50% of cases.[6–8] Moreover, LS often occurs before screening recommendations apply, resulting in late identification of cases.[9] Due to these limitations, only a fraction of LS cases is referred for genetic evaluation and less than 10% receive genetic testing.[10] Underdiagnosis of LS results in a significant number of patients and blood relatives not receiving appropriate care and in unnecessary and preventable morbidity and mortality.[11] LS cases with CRC can benefit from treatment with monoclonal antibodies or immune check-point inhibitors in combination with adjuvant chemotherapy.[12] Colonoscopy decreases CRC morbidity and mortality by detecting the disease at earlier stages and can also be preventive by allowing for endoscopic removal of preneoplastic lesions/polyps.[13 14] Additional prevention and screening methods, such as daily aspirin, upper gastrointestinal endoscopy and prophylactic surgery can be tailored to individual needs of LS cases.[15]

This study presents a Swiss-based cost-effectiveness analysis of genetic screening for LS provided to all newly diagnosed patients with CRC, followed by cascade genetic screening of blood relatives. Although LS cases may present with different forms of cancer, we focus on CRC because it is the most common cancer associated with the syndrome. Screening for LS among all newly diagnosed CRC cases, irrespective of age and family history, followed by cascade testing of blood relatives, has been embraced by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group.[16] Blood relatives of LS cases can be tested inexpensively and with 100% accuracy, and those who test negative are excluded from early screening and preventive interventions.[17] Diagnosis of LS with this protocol has 85% sensitivity and 90% specificity.

Table 1 Key design criteria of the analysis

Population	Individuals newly diagnosed with CRC and FDR and SDR
Intervention	DNA sequencing of all newly diagnosed CRC cases and cascade genetic testing of four or more FDR and SDR of identified LS cases
Comparator	Current strategy with IHC, BRAF V600E and DNA sequencing for a proportion of newly diagnosed CRC cases and cascade testing of four FDR and/or SDR
Outcome	QALYs saved
Model type	Decision trees integrated with Markov models
Time horizon	Lifetime/50 years
Perspective	Swiss healthcare system
Costs	Swiss francs (CHF)
Discounting	3% per year
Cost-effectiveness threshold	CHF100000 per QALY

CRC, colorectal cancer; FDR, first-degree relative; IHC, immunohistochemistry; LS, Lynch syndrome; QALYs, quality-adjusted life years; SDR, second-degree relative.

We compared two strategies: the current strategy implemented in Switzerland involves preliminary tumour testing with immunohistochemistry (IHC), BRAF V600E and germline DNA sequencing of a fraction of patients with CRC and inviting four FDR and/or SDR per every identified LS case for cascade testing. The alternative strategy involves DNA sequencing of all newly diagnosed patients with CRC, and inviting four FDR and/or SDR per every identified LS case for cascade testing. The alternative strategy does not include preliminary tumour testing but focuses on germline genetic testing of patients with CRC followed by cascade testing of relatives. The study examines whether the alternative strategy for identifying LS cases is economically reasonable, considering the perspective of the Swiss healthcare system.

MATERIALS AND METHODS

We developed an analytic model combining decision trees with Markov modelling to estimate the cost-effectiveness of universal screening for LS for all newly diagnosed patients with CRC followed by cascade testing. We estimated costs of tumour testing, DNA sequencing, colonoscopy and treatment. Decision trees represent the structure of LS screening, modelling possible decisions and outcomes and displaying the algorithm behind the processes leading to genetic testing. The integration of Markov modelling helped conduct probabilistic forecasting and predictive modelling of future events to calculate costs and outcomes (number of CRC cases, deaths, CRC avoided) associated with genetic testing over the period of 50 years. Each Markov model is associated with a corresponding end node of the decision tree. To find incremental cost-effectiveness ratio (ICER), we calculated differences in total costs and number of gained quality-adjusted life years (QALYs) for each strategy (table 1).

Model inputs

Data on costs have been obtained from the University Hospital Basel, the Geneva University Hospitals and published literature.[10] Costs applied in modelling include detection of LS cases among patients with CRC and relatives; colonoscopy; CRC treatment. Costs associated with detection of LS cases among CRC incident cases include genetic consultations; tumour-based testing (IHC for the four MMR proteins and BRAF V600E) and germline screening. In Switzerland, germline screening for LS diagnosis is conducted in two steps: sequencing of two to four MMR genes by next generation sequencing (NGS); Sanger sequencing of selected exons and gene dosage analysis by multiplex ligation-dependent probe amplification conducted to confirm NGS findings. Costs of LS screening for relatives include genetic consultations and carrier testing for the identified pathogenic variant (cascade testing). All costs applied in modelling are provided in the supplementary materials and are expressed in 2020 Swiss Francs (CHF).

Parameters used in decision trees and Markov modelling are based on an EGAPP review.[16] All financial, epidemiological, and clinical model inputs, including sensitivity and specificity of IHC, BRAF V600E and DNA sequencing are literature-based[10] (see online supplemental materials). For IHC and BRAF V600E, we applied sensitivity of 83.0% and 69.0%, respectively, and specificity of 88.8% and 99.0% respectively. We assumed 99.5% sensitivity and 99.9% specificity of DNA sequencing. We also assumed that 79% of relatives testing positive for LS would accept increased surveillance. Transition probabilities between states (Healthy, CRC, mCRC, Death) and stage distributions of CRC in screened and unscreened populations are literature-based and were used to calculate costs of treatment of the corresponding CRC stage.[10 18] Risks associated with colonoscopy, such as perforation, bleeding and death, have also been incorporated into the model.[19 20] To separate CRC-related deaths and deaths from other causes, we used annual crude death rate in Switzerland equal to 0 0079 in both strategies.[21] Based on current Swiss practices, we assume that identified LS cases will invite four CRC-free FDR and/or SDR for cascade testing. Among relatives who agree to genetic testing, those who test positive for LS are offered biennial colonoscopy, starting at 25 years old.[22] The probability of identifying the familial pathogenic variant among FDR is 45% and decreases to around 25% in SDR. The probability to identify LS cases with cascade testing in both FDR and SDR is around 35%.[10] Both strategies were ranked according to costs in CHF and effects in QALYs. We calculated ICER of net costs per QALYs saved. The cost-effectiveness analysis was conducted based on the Consolidated Health Economic Evaluation Reporting Standards statement.[23]

Decision trees

Decision trees represent the detailed structure of events and outcomes associated with each of the two strategies based on epidemiological data and Swiss clinical parameters for CRC and LS (see online supplemental materials). For the current strategy, we calculated the number of false negative and false positive results associated with IHC and BRAF V600 testing and we assessed the number of patients with CRC lost-to-follow up. For the alternative strategy, the decision tree allowed us to calculate the number of patients with CRC and relatives with pathogenic variants in MMR genes and to evaluate the number of individuals who develop CRC (figure 1).

The current strategy consists of three phases: identifying carriers of pathogenic variants in MMR genes among newly diagnosed patients with CRC by screening tumour tissue with IHC, BRAF V600E and DNA sequencing; offering carrier testing to FDR and/or SDR of identified LS cases; using colonoscopy for early detection of CRC among relatives with LS. IHC is conducted routinely in Switzerland and patients with loss of MLH1 expression undergo testing for BRAF V600E, while patients whose tumours demonstrate loss of MSH2, MSH6 or PMS2 expression undergo germline DNA sequencing directly after IHC. Cases identified with LS receive recommendations to notify their blood relatives for cascade testing. The cost of carrier

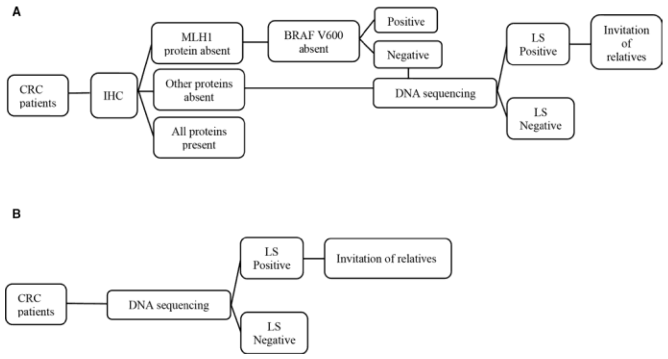

Figure 1 Schematic representation of compared testing strategies for LS for patients newly diagnosed with CRC. (A) Strategy 1 represents current screening for LS including two tumour analyses (IHC and BRAF V600), followed by DNA sequencing for suspicious cases. (B) Strategy 2 represents alternative universal DNA sequencing for all CRC cases followed by cascade genetic testing of relatives of mutation carriers. CRC, colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome.

testing for relatives is substantially lower because the location of the pathogenic variant is known (ie, CHF3500 for patients with CRC vs CHF400 for relatives). This cost is covered only for FDR in the Swiss healthcare system. The alternative strategy assumes universal germline testing for all newly-diagnosed CRC cases followed by cascade testing of four FDR and/or SDR of LS cases. The alternative strategy has high sensitivity and specificity to detect LS and is consistent with evidence-based recommendations for cascade screening for 'actionable' hereditary cancer syndromes.[4,18]

Markov modelling

Markov modelling estimated the long-term costs and the number of annually gained QALYs in both strategies. Markov models were based on four states: healthy, CRC, metachronous CRC (mCRC) and death. Once a person is diagnosed with CRC, the disease could progress to mCRC or death. Markov models used 1 year cycle length and were continued for 50 years, assuming that all cohort participants will be dead by the end of this time frame. We modelled annual transition probability from CRC to mCRC of around 1%, based on the risk of mCRC depending on the affected MMR gene and considering a time frame ranging from 6 months to 12 years post initial CRC diagnosis.[24–26] We modelled risk of developing cancer (mCRC) among screened and unscreened populations according to evidence of frequency of colonoscopy and its CRC/mCRC risk reduction.[13,26] Modelling assumptions are conservative, therefore, intentionally made unfavourable for the cost-effectiveness of the alternative strategy. Analyses were performed using Microsoft Excel 2016 (Microsoft) with a discount rate of 3% for both costs and effects (see online supplemental materials).

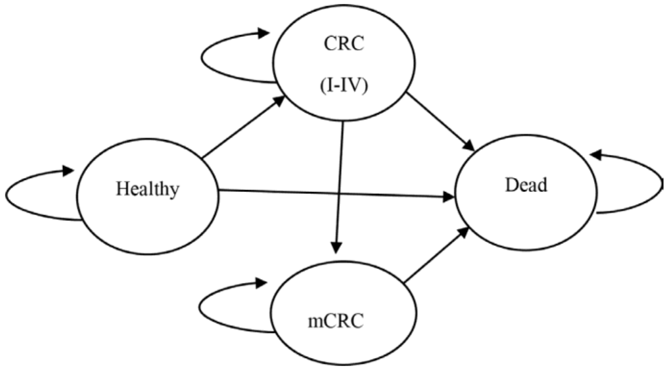

Figure 2 Markov model with the modelled transition probabilities between health states: healthy, CRC, metachronous CRC and death. CRC, colorectal cancer.

Sensitivity analysis

A deterministic one-way sensitivity analysis estimated the effects of variations in each input parameter on overall cost-effectiveness of the alternative strategy. Probabilistic sensitivity analysis tested the robustness of our modelling and assessed the overall likelihood of the alternative strategy to be not cost-effective. Probabilistic sensitivity analysis tested 1000 scenarios varying different parameters, such as number of CRC cases accepting germline genetic testing, number of relatives accepting carrier testing, probability to develop cancer among relatives positive for LS, compliance with colonoscopy and lost-to-follow up rate.

RESULTS

Decision trees

Modelling of the two LS screening strategies begins with a cohort of 4100 newly diagnosed patients with CRC, based on the annual number of CRC incident cases in Switzerland.[27] Assuming that 3% of all newly diagnosed patients with CRC are affected by LS, there are 123 LS cases with CRC.[28] With the current strategy, all 4100 newly diagnosed patients with CRC are offered tumour-based testing. Among them, 32 cases have false negative results, while 33 patients with CRC are correctly identified with LS, counselled and invite relatives for cascade testing. With the current strategy, 253 patients with CRC are lost to follow-up before DNA sequencing. Using a conservative approach, we assumed that only 50% of relatives accept cascade testing, while only 79% of relatives identified with LS undergo biennial colonoscopy. With the alternative strategy, all 123 of 4100 newly diagnosed patients with CRC are identified as LS cases, and 492 relatives are invited for cascade testing (see online supplemental materials). CRC stages are classified according to the Duke's Classification.[29]

Markov modelling

Figure 2 shows the Markov models with transitions between the four disease states. The Markov models account for costs associated with colonoscopy and CRC treatment over 50 years. Each cancer-free relative diagnosed with LS is recommended to undergo biennial colonoscopy, starting at the age of 25. We assumed that colonoscopy decreases the lifetime risk of CRC by 67%; therefore, more LS cases tend to stay healthy during each following year compared with those who do not undergo colonoscopy. While colonoscopy is associated with higher costs of surveillance, it reduces overall treatment costs, due to early detection of CRC and mCRC while also having a favourable effect on stage distribution of CRC. Swiss anecdotal data suggest that a proportion of relatives who refuse cascade testing may still elect to have a colonoscopy every 3 years. We assumed that this frequency of colonoscopy also decreases the risk of CRC but only by 25%. Relatives testing negative for LS are assumed to have a population-level risk of CRC; therefore, they are offered colonoscopy screening every 10 years, starting at the age of 50 (see online supplemental materials).

Total screening costs for patients with CRC and relatives ranged between CHF136 966 947 with the current strategy and CHF150 691 700 with the alternative strategy. ICER of

Table 2 Costs associated with genetic testing for LS

Costs for cohort (CHF)	Current strategy	Alternative strategy
IHC	1 476 000	0
BRAF V600E	50 809	0
DNA sequencing	497 808	14 350 000
DNA sequencing for relatives	29 442	110 700
Colonoscopy and treatment	134 912 887	136 231 000
Total	136 966 947	150 691 700
QALYs gained	361 147	361 358
Cost difference	13 724 753	
QALYs difference	211	
ICER	65 058	

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; LS, Lynch syndrome; QALYs, quality-adjusted life years.

universal LS screening with cascade testing of four relatives is CHF65 058 per QALY gained. This is cost-effective in Swiss healthcare settings, where the cost-effectiveness threshold is assumed to be CHF100 000 per QALY saved. The expected discounted gained QALYs ranged between CHF361 147 with the current strategy and CHF361 358 in the alternative strategy. Universal LS screening gained 211 more QALYs at the additional cost of CHF13 724 753 compared with the current strategy (table 2). LS is associated with high rates of secondary CRC; therefore, mCRC was incorporated into our model to calculate associated costs and mortality. According to our model, the alternative strategy prevents 17 deaths at the cost of CHF785 645 per death avoided. Moreover, the alternative strategy avoids 18 cases of CRC and one case of mCRC, compared with the current strategy (table 3).

Sensitivity analyses

Figure 3 shows results of one-way sensitivity analysis using 11 parameters in descending importance. This analysis revealed that the number of invited relatives and cost of germline DNA sequencing for patients with CRC had a major impact on the outcome. Decreasing the cost of DNA sequencing from CHF3500 to CHF2500 reduces the ICER of the alternative strategy to CHF49 947. Costs of tumour tests and carrier testing for relatives did not have a substantial effect on the overall cost-effectiveness of the alternative strategy. In cases when only two relatives per LS case are invited for cascade testing, the alternative strategy costs CHF123 483 per QALY and is not cost-effective. Reducing the risk of CRC in relatives diagnosed with LS to 25% increases the cost of the programme to CHF103 385 per QALY, exceeding the cost-effectiveness threshold.

Table 3 Health outcomes associated with compared screening strategies

Health outcome (N)	Current strategy	Alternative strategy	Difference
QALYs gained	361 147	361 358	211
Relatives with CRC	814	795	−18
Relatives with mCRC	33	32	−1
Deaths	5612	5595	−17
Patients with CRC with LS identified	33	123	90
Relatives with LS identified	29	111	81

CRC, colorectal cancer; LS, Lynch syndrome; QALYs, quality-adjusted life years.

Probabilistic sensitivity analysis was conducted using five parameters, that is, patients with CRC lost-to-follow up, number of invited relatives per LS case, proportion of tested relatives and compliance with biennial colonoscopy. Results of probabilistic sensitivity analysis suggest that the number of invited relatives per LS case is the most influential factor affecting the overall cost-effectiveness of the alternative strategy. In a Monte-Carlo simulation of 5000 scenarios, the ICER of the alternative strategy varied between CHF33 075 and CHF316 010, with a mean of CHF73 792. Increasing the number of invited relatives from four to seven decreases the ICER from CHF65 058 to about CHF45 000. Given 50% acceptance rate among relatives, increasing the number of invited relatives by one per LS case decreases the ICER on average by CHF5000. Including SDR reduces the ICER from CHF65 058 to CHF32 886. Finally, increasing the frequency of colonoscopy from biennial to annual increases the ICER from CHF65 058 to CHF70 536 per QALY gained. The universal strategy has a probability of 80% to be cost-effective given the threshold of CHF100 000 per QALY. We assumed normal distribution in epidemiological and clinical parameters and gamma distribution in costs.

DISCUSSION

We estimated the cost-effectiveness of universal screening for LS among all newly diagnosed patients with CRC with cascade testing of relatives as a measure of identifying LS cases. Our cost-effectiveness analysis incorporated costs of carrier testing of relatives, an aspect that is often omitted from cost-effectiveness analyses of genetic testing technologies.[30] Universal LS screening with cascade testing of relatives is cost-effective in around 80% of scenarios. The alternative strategy prevents 17 deaths at the cost of CHF785 645 per death avoided, with ICER of CHF65 058 per QALY saved and below the acceptable Swiss cost-effectiveness threshold of CHF100 000. Since the risk of death from other causes was equal in both strategies, the observed difference of 17 deaths is associated with CRC. The number of prevented deaths is associated with annual transitions from Healthy to CRC, and from CRC to death, which are substantially lower in tested and screened populations.[13]

The current strategy for LS screening in Switzerland involves two tumour-based tests (IHC and BRAF V600) followed by DNA sequencing. It is possible that anticipating results from three sequential tests, including tumour biopsy, causes discomfort to patients and their families, resulting in 64% lost-to-follow-up rate among patients with CRC.[31] Germline DNA screening has almost 100% validity and, therefore, identifies all LS cases and eliminates false negative and false positive diagnoses. This may result in modification of CRC treatment with better patient outcomes.[12] It also prevents patients with CRC from being lost-to-follow-up and deaths of undiagnosed LS cases and identifies a higher number of cancer-free relatives and new CRC cases at early stages through colonoscopy screening. The advantages of universal LS screening are to simplify the process of identifying LS cases, possibly provide personalised treatment to those with CRC and to identify cancer-free relatives with LS who can benefit from colonoscopy screening starting at a younger age. Despite wide application of the Bethesda and Amsterdam guidelines for initiating LS screening, they are not routinely applied in Switzerland because they can miss up to 50% of LS cases due to poor data quality, small family size or lack of awareness of cancer cases in the family.[6] Implementing these criteria is also associated with more costs and burden of data collection, interpretation and quality assurance.

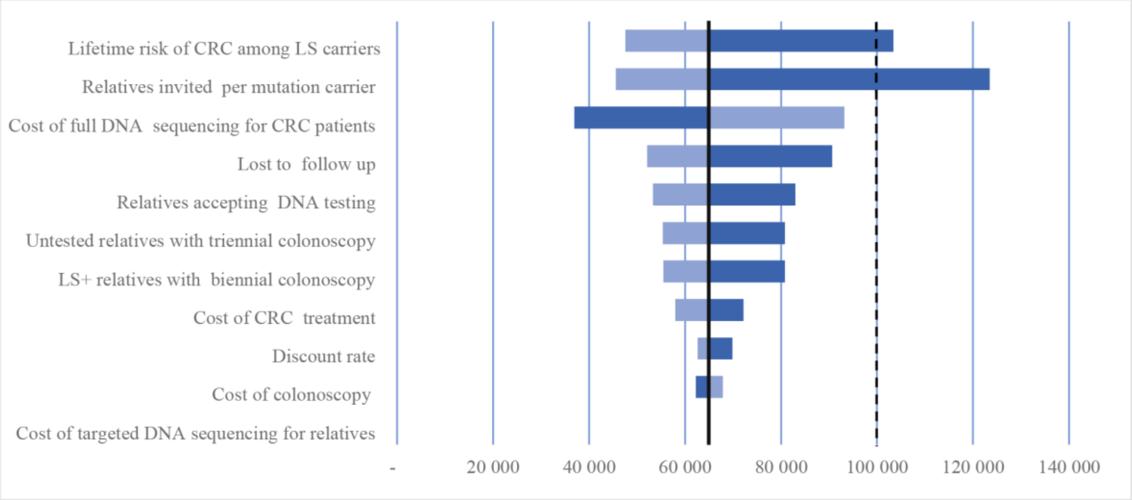

Figure 3 Tornado diagram. One-way sensitivity analysis for universal DNA sequencing (Strategy 2). The Y axis shows tested parameters and the X axis shows cost per QALY saved. The change in cost-effectiveness associated with 50% decrease in each parameter is depicted by the darker bars, which indicate higher cost per QALY saved (ie, less cost-effective), the change associated with 50% increase in each parameter is depicted by the lighter bars, which indicate lower cost per QALY saved (ie, more cost-effective). The solid vertical line represents the default cost-effectiveness ratio of CHF 65 058 per QALY saved. The dotted vertical lines indicate cost-effectiveness threshold of CHF 100 000 in Switzerland. CRC, colorectal cancer; LS, Lynch syndrome; QALY, quality-adjusted life years.

Despite the significant cost associated with offering DNA testing to all patients with CRC, universal LS screening improves the overall utility of genetic testing at a reasonable cost. Probabilistic sensitivity analysis revealed that universal LS screening is cost-effective in around 80% of scenarios, while one-way sensitivity analysis showed that it is cost-effective in the majority of possible scenarios. Our model was limited to LS and germline sequencing to either two or four MMR genes, while NGS-panel testing is highly advisable for all CRC cases because it can identify several other cancer syndromes.[32] Identification of non-LS-associated CRC cases would likely increase the cost-effectiveness of universal LS screening as more families with inherited predisposition to cancer would be identified and provided with risk reducing strategies.

One scenario that was unfavourable for universal LS screening was to decrease the number of invited relatives to two per LS case. This scenario increases the ICER to about CHF123 000, which is unfavourable for the Swiss healthcare system. Although our models assumed testing of four relatives per LS case, Swiss data demonstrate that four LS cases invited more than 50 relatives for cascade testing.[31] Implementing strategies to facilitate cascade testing, for example, mailing of saliva kits and family-based telephone or web-based counselling, holds promise to enhance the cost-effectiveness of universal LS screening.[33 34] Expanding insurance coverage to SDR, who are currently not covered for carrier testing in the Swiss healthcare system, will increase identification of an underdiagnosed syndrome at the population level and significantly reduce the time needed to detect LS predisposing variants.[35] Moreover, although the cost of targeted testing is significantly lower (CHF400 vs CHF3500), lack of insurance coverage for cascade testing may be a significant barrier accessing specialised genetic services for segments of the population and further contributes to healthcare disparities.[36]

Another unfavourable scenario for universal LS screening was to reduce the risk of CRC among relatives diagnosed with LS to 25%, which increased the cost of the programme to CHF103 385 per QALY above the cost-effectiveness threshold. Cumulative risks of LS-associated cancers depend on sex and distribution of MMR gene pathogenic variants.[2] MLH1 and MSH2 pathogenic variants raise the lifetime risk of CRC to around 50%,[37] while PMS2 variants raise the lifetime risk of CRC up to 12% and 13% for endometrial cancer.[2 32] Given that PMS2 pathogenic variants are less frequent, we consider that a 40% CRC risk among relatives identified with LS through cascade testing is a realistic assumption, consistent with the German-based model (42% risk of CRC among LS cases by age 80 years) and with EGAAPP consensus.[5 18 20]

Finally, the cost of carrier testing for relatives and the cost of colonoscopy do not have substantial effects on ICER. Our model assumed 79% compliance with biannual colonoscopy.[10] Other studies reported colonoscopy compliance ranging from 67% to 97%.[20 38 39] Using one-way sensitivity analysis and probabilistic sensitivity analysis, we varied compliance rates between 58% and 100%. Decreasing colonoscopy compliance to 58% increased the cost-effectiveness ratio to almost CHF 81 000 which is still below the cost-effectiveness threshold.

Our findings and parameters are compatible with cost-effectiveness analyses of LS screening conducted in the USA and in Australia. The US-based model demonstrated the cost-effectiveness of a strategy including IHC, BRAF and DNA sequencing with cascade testing of 12 relatives per LS case and ICER of $50 000 per life-year saved.[10] Based on a second US-based model, using a predictive model to stratify individuals into different levels of cancer risk, followed by IHC and germline DNA testing resulted in ICER of $35 143 per life-year saved with the age cut-off at 25–35 years.[40] The Australian-based model showed a cost-effectiveness ratio of $61 235 per life-year saved with annual colonoscopy and with no age limit.[19] Our findings are conflicting with a German-based model, reporting that the ICER of universal LS screening is €4 188 036, and it is not cost-effective compared with tumour-based screening.[18] This substantial difference in costs between the German and our model might be explained by several reasons. The German model assumed higher costs of DNA sequencing, lower number of tested relatives per LS case, and lower proportion of cancer-free relatives participating in colonoscopy screening. In our model, one-way sensitivity analysis revealed that the number of tested relatives per LS case and the cost of germline DNA testing had the highest impact on overall cost-effectiveness ratio. In most studies, the number of tested relatives per LS case had the highest impact on results, despite substantial differences in input parameters.

The first limitation of our study is that we evaluated the cost-effectiveness of universal LS screening based solely on patients with CRC, while LS is also associated with other types of cancer, including endometrial cancer. We focused on CRC because it is commonly associated with the syndrome and affects both women and men. Including screening for endometrial cancer will probably increase the cost-effectiveness of universal LS screening, given strategies for early prevention and risk-reducing surgery.[41] International groups further emphasise the importance of genetic testing of women with endometrial cancer for early identification of healthy LS cases.[42] We also assumed that 50% of relatives who refused cascade testing might undergo frequent colonoscopy screening. The exact proportion of relatives undergoing frequent colonoscopies is unknown and our analyses may not be accurate regarding the potential benefits of universal LS screening. Our model did not account for the proportion of CRC cases identified with variants of unknown significance (VUS). VUS rate is reportedly 6% for MLH1/MSH2/MSH6/EPCAM genes and 4% for PMS2,[43] while Swiss lab experience indicates 10% frequency of VUS. Although these cases will not yield downstream cascade testing, they are managed with increased frequency of colonoscopy,[44] which may yield changes in surveillance among relatives. Nevertheless, we acknowledge that VUS cases will likely decrease the cost-effectiveness of universal genetic screening in real-world settings. Finally, in real-world settings, it is unlikely to obtain consent for germline genetic testing from 100% of CRC cases, which may have an effect on cost-effectiveness of universal LS screening. A Swiss-based single-centre study reported approximately 14% refusal rate of germline testing among patients with CRC.[31] Our one- way sensitivity analyses showed that when only 50% of patients with new CRC accept germline testing, the overall cost of the alternative strategy increases to almost CHF78 000 per QALY saved, still below the cost-effectiveness threshold.

We demonstrate that universal LS screening with cascade testing of relatives results in substantial benefits for the Swiss healthcare system at a reasonable cost. Our findings provide evidence needed to inform policymakers, healthcare providers and insurance companies about the costs and health benefits associated with universal LS screening and cascade testing of relatives as a public health intervention, supporting NICE guidelines.[45] The overall cost-effectiveness of this approach depends on the costs of DNA sequencing and the willingness of patients and relatives to be tested. The cost of DNA sequencing depends on how many genetic variations are analysed; during the past 15 years, this cost has dramatically decreased, and it is foreseen that this trend will continue.[46] Close coordination of different stakeholders, such as primary care providers, specialists, genetic clinicians and laboratories is crucial to encourage and educate the public about the importance of screening for LS. Further research needs to examine the cost-benefit ratio of universal LS screening, since individual preferences for genetic testing should be elicited and used in shared decision-making.[47]

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CHAPTER VII

DISCUSSION

The first objective of this study was to conduct a comprehensive examination of palliative care in Kazakhstan, encompassing aspects such as financing, policy, human resources, education, and infrastructure. This investigation aimed to generate a robust evidence foundation for subsequent evaluations and research concerning palliative care in Kazakhstan. Additionally, the study sought to perform a cost-effectiveness analysis comparing various palliative care settings, while also exploring the experiences and challenges encountered by stakeholders in the palliative care domain. The ultimate goal was to formulate context-specific and tailored recommendations for policy-making that effectively address the needs of the stakeholders. It should be noted that the authors did not describe the history of palliative care development in Kazakhstan, as it has been extensively discussed elsewhere. [1]

6.1 Kazakhstan's Palliative Care Landscape

Our first article presents an exhaustive analysis of the current status of palliative care in Kazakhstan by procuring extensive and comprehensive data on all facets of palliative care, including financing, workforce, infrastructure, number of patients in need, policy framework, and Kazakhstan's position in the global context. This evaluation is particularly crucial for resource-constrained settings, which frequently lack transparent data collection mechanisms for future assessments.[2] Moreover, the data amassed in this study may prove beneficial for future evaluations conducted by the Global Atlas of Palliative Care and the Quality of Death Index, potentially informing their appraisals. [3,4] The 2021 Quality of Death and Dying Index excluded Kazakhstan due to the absence of data collection mechanisms and reliable statistics for evaluating the country's palliative care status. In contrast, other post-Soviet LMICs, such as Georgia, Ukraine, Armenia, and Russia, have been assessed. [4] This exclusion underscores the significance of studies like this one, which endeavor to provide a comprehensive analysis of the current state of palliative care in Kazakhstan and contribute to the establishment of dependable data collection mechanisms.

6.2 Cost-Effectiveness of Hospice-Based Care

Our second article examines the costs and outcomes of palliative care in different settings, specifically hospices and cancer centers. Considering the funding constraints within Kazakhstan's healthcare system, it is essential to allocate resources in a cost-effective manner. The results of this study indicate that hospice-based palliative care offers an enhanced quality of life for patients and reduced burden for their families at lower costs. Hospices in Kazakhstan furnish a homelike atmosphere for patients and their families, enabling family caregivers to be near their loved ones, while cancer centers focus on delivering supplementary specialized treatment procedures and medications in adherence to treatment protocols.[5] These findings underscore that cancer centers following treatment protocols become of lesser importance in palliative care, while fostering a homelike environment, which can improve the quality of care and support for patients and their families, is of paramount importance in resource-limited settings, such as Kazakhstan.

Upon completing interviews with family caregivers, it became apparent that mobile teams can provide a substantial service to remote and rural areas, where palliative services are largely unavailable. For some patients and their family caregivers, support by mobile teams would be the only available option. However, we did not evaluate the cost-effectiveness of mobile teams first because we were not aware of the large preference of family caregivers for home-based care, and second because data on cost-effectiveness of mobile teams were not available. A future study should focus on evaluating the cost-effectivess of mobile teams as a viable solution for providing palliative care in remote and rural areas of Kazakhstan, where 45% of the 19 million of Kazakh population resides, and for other LMICs.

6.3 Insights of Palliative Care Stakeholders

In contrast to conventional evaluations of health services, which primarily rely on statistical and numerical data, the third article of this study collected narrative data to explore the challenges faced by individuals directly engaged in palliative care, encompassing family caregivers, palliative health professionals, and palliative administrators. By delving deeper and looking beyond the surface level of statistical data, this study aimed to gain a better understanding of the human aspects of palliative care and provide context-specific health policy recommendations that take into account the unique challenges of stakeholders in resource-limited settings.

At the same time, our study does not advocate for the widespread construction of hospices throughout Kazakhstan; instead, it emphasizes the importance of concentrating efforts on providing homelike and home-based environments, which, according to the collected narrative data from various stakeholders, are the preferred settings for palliative care. By adopting this cost-effective approach, policymakers and healthcare providers can better address the needs and preferences of patients and their families in the local context, ultimately enhancing the quality of life for those facing life-limiting illnesses.[6,7]

6.4 The Value of Family Caregivers and Home Care

Within the context of Kazakhstan, an advantageous aspect of the Kazakh society that can be capitalized upon is the presence of family caregivers willing to provide palliative care to their loved ones, predominantly in home-based settings and hospices. This advantage is underpinned by the local mentality, robust familial cohesion, religious beliefs, larger family units, and greater number of children within families. These factors endow Kazakhstan with a distinctive trait, where family structures and caregiving responsibilities are readily assumed by family members.[8,9] By leveraging the existing large network of family caregivers in Kazakhstan, the palliative care system in the country has the potential to greatly expand its reach and impact, ultimately improving outcomes and quality of life for patients and whole families facing end-of-life issues.

As articulated in our third article and illustrated in its Figure 2, family caregivers constitute a fundamental pillar of palliative care, functioning simultaneously as care providers and care recipients. The provision of support and training for family caregivers is essential not only to enhance the caregiving experience and improve patients' quality of life but also to elevate the overall quality of palliative care.[10] By addressing the needs of family caregivers through targeted interventions, the palliative care system can foster more effective and compassionate care for patients facing life-limiting conditions.

An additional compelling argument in favor of supporting and training of family caregivers is determined by the geography and demographics of the Republic of Kazakhstan. As the 9th largest country, Kazakhstan has one of the lowest population densities globally, with approximately 9 million of its population residing in remote and rural areas where health services are scarcely accessible. [11] The broad support of family caregivers may facilitate better palliative care in remote rural regions and extend the impact of palliative care beyond large cities, which already possess the requisite infrastructure and access to health services and education. By prioritizing home-based care and empowering family caregivers, the palliative care system in Kazakhstan can more effectively address the unique challenges posed by its vast geography and the diverse needs of its population.[6,12]

6.5 Addressing Opioid Shortage for Pain Relief

Despite the significance and necessity of the aforementioned reforms, the most pressing concern is the lack of opioids for pain relief among palliative patients in Kazakhstan. According to the unpublished KAPC estimate, 95% of all deceased palliative patients in the country endured severe pain. In contrast, the example of Uganda demonstrates that pain management with oral morphine for 110 days is as affordable as a loaf of bread, indicating its feasibility even in resource-limited settings.[13] The authors advocate for the local production of opioids and other pain management medication in Kazakhstan, which would likely yield short-term benefits, alleviate the burden on families, and improve the quality of life for patients. By addressing the crucial issue of pain relief through the increased availability and accessibility of opioids, the palliative care system in Kazakhstan can more effectively support patients facing life-limiting illnesses and their families.

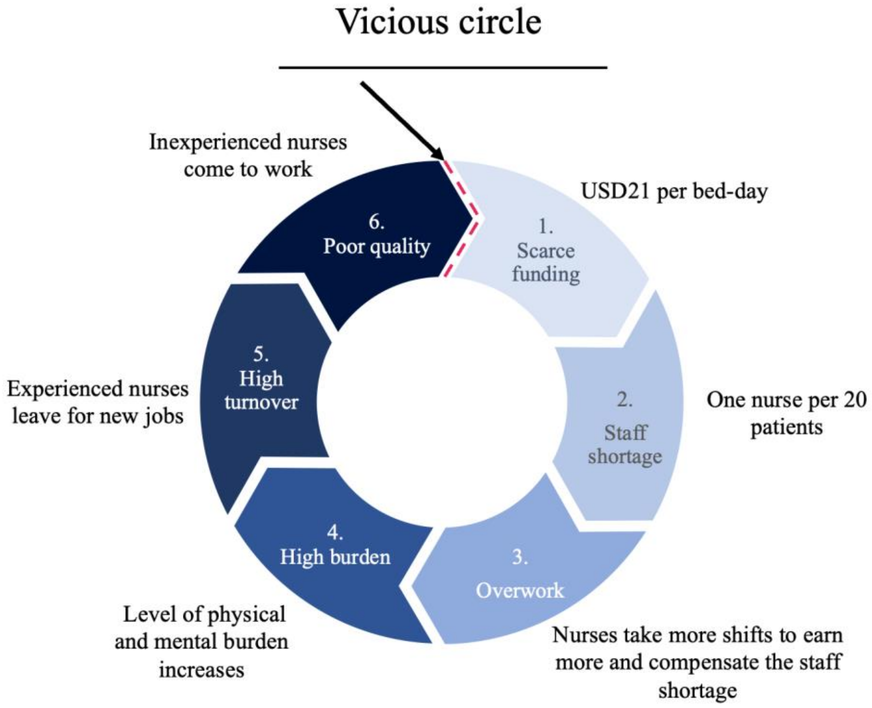

Figure 1. Vicious cycle representing cause and effect links between the funding, staff burden, and quality of care.

6.6 Incentivizing Quality in Palliative Care Policy

Last, the current policy on performance in palliative care is centered around punitive measures rather than incentives. As reported by numerous stakeholders, underperformance by hospices results in funding cuts for the subsequent year, leading to even poorer performance as experienced staff members leave and are replaced by inexperienced personnel. Figure 1 in this

Discussion illustrates the cause-and-effect relationships among funding, staff burden, and high staff turnover in palliative care in Kazakhstan. The authors argue that this policy could be revised in favor of more transparent mechanisms through which the quality of palliative care can be incentivized rather than penalized. Reduced funding inevitably contributes to a decline in patients' quality of life; therefore, adopting a more supportive and constructive approach to performance improvement is crucial for enhancing palliative care outcomes in Kazakhstan. Stable and sustainable funding for palliative care services plays even more crucial role in LMICs as it allows for long-term planning of services and sustainable development of palliative care.[14,15]

6.7 Bridging Prevention and Palliative Care

This research undertook an exploration of critical components within the cancer care continuum, including prevention, treatment, and palliative care. Within this context we conducted the cost-effectiveness analysis of universal screening for Lynch syndrome of patients newly diagnosed with colorectal cancer and promote cascade genetic testing as means to prevent cancer among their biological relatives. This investigation facilitated an in-depth study into the initial stages of the cancer care spectrum, predominantly emphasizing prevention and early detection and provided insights into strategies that could help better organization of healthcare services that are geared towards prevention and early detection, potentially changing the trajectory of cancer care. Such an approach has the potential to significantly inform research on palliative care, providing a comprehensive view of the cancer care continuum.

While the context of these studies is different, the approach and its implications are fundamentally linked. Both cost-effectiveness studies address the overarching question of ensuring optimal allocation of limited resources. Additionally, juxtaposing a high-income country's preventative approach with a middle-income country's palliative care strategies broadens the discussion on global disparities in healthcare provision. The insights drawn from this comparison enable a deeper understanding of the multifaceted challenges of cancer care across different socio-economic contexts. In essence, this dissertation captures the spectrum of cancer care, from the preventive strategies applied in Switzerland to the palliative care approaches utilized in Kazakhstan. By studying both ends of this spectrum, the PhD thesis offers a comprehensive analysis of the cost-effectiveness of cancer care.

We found that the universal genetic screening for Lynch syndrome among newly diagnosed colorectal cancer patients costs more than CHF 65,000 (about USD 70,000) per QALY saved, which is considered cost-effective in a high-income country, such as Switzerland. However, such cost is prohibitively high and not affordable for countries like Kazakhstan, with a GDP per capita of about USD 11,000. At the same time, the high cost of genetic testing in Switzerland does not necessarily suggest that cancer preventive strategies are not feasible in resource-limited settings. Given the economic disparities, it is crucial to explore less sophisticated, but still effective, cancer prevention strategies suitable for LMICs. These strategies could include population-based screenings such as mammography for breast cancer, Pap-smear tests for cervical cancer, and fecal oocult blood tests for CRC. These interventions are significantly less expensive than genetic testing and may be more appropriate and feasible for many LMICs, including Kazakhstan. Therefore, the Swiss study serves as a critical comparative point and helps emphasize the importance of context-specific, cost-effective cancer prevention strategies. Our findings reinforce the argument for the continued development and implementation of local preventive strategies in resource-limited settings. In fact, in 2016, Kazakhstan started the implementation of a population-based screening program for several types of cancer, including breast, lung, ovarian, colorectal, and prostate, indicating a commitment to preventive care in oncology. Moreoever, despite the current economic barriers precluding the implementation of genetic testing in Kazakhstan, future cost reductions of genetic and genomic technologies might render this approach more affordable.

6.8 Contrasting Measures of Value between Prevention and Palliative Care

A common measure of effectiveness in healthcare is the number of QALY saved, which combines both quantity and quality of life gained from an intervention. However, QALY is suited to interventions that seek to extend life, like genetic testing for Lynch syndrome in Switzerland. By identifying individuals at higher risk, this approach aims to prevent or detect cancers early, thus, extending lives of individuals with disease-causing variants. Palliative care, on the other hand, seeks not to extend life, but to improve its quality, particularly for terminally-ill patients and their families. The goal is to alleviate symptoms and improve comfort, rather than to prevent or cure the disease. As such, the QALY measure, which heavily weights life extension, may not be suitable for assessing the value of palliative care. Therefore, our study examining cost-effectiveness of palliative care refrained from employing cost per QALY as the outcome measure. Instead, specific tools designed to assess the unique benefits of palliative care were applied, namely POS which measures quality of life of patients, and ZBI which evaluates burden of their family caregivers. By comparing the outcomes used in the preventive and palliative care studies, we illustrate how the objectives and nature of a healthcare intervention determine the most suitable measures of cost-effectiveness. This shift in evaluative measures underlines the distinct value of palliative care and challenges traditional healthcare metrics. Our study thus underscores the importance of aligning evaluation tools with specific intervention objectives for a more comprehensive assessment of healthcare impacts.

CHAPTER VIII

CONCLUSION

The idea that runs as a read thread through this study is the notion that LMICs are advised to develop tailored and context-specific solutions rather than emulating strategies employed by HICs. This argument stems from the recognition that LMICs often face unique challenges, resource constraints, and cultural contexts that differ significantly from those in HICs.[16] Adopting context-specific solutions enables LMICs to address their distinctive needs more effectively and efficiently. By taking into consideration factors such as cultural values, economic constraints, demographic patterns, and local infrastructure, LMICs can design and implement palliative care strategies that are better suited to their specific circumstances. Furthermore, tailored solutions are more likely to be accepted and adopted by the local population, as they align with local beliefs, customs, and preferences, fostering a sense of ownership and empowerment among stakeholders. In contrast, replicating HIC strategies may not only be less effective in addressing the unique challenges faced by LMICs but may also be economically inefficient and culturally inappropriate.[17] Such an approach could result in the misallocation of limited resources and the implementation of policies that do not resonate with local populations, ultimately hindering the development and improvement of palliative care services in LMICs.[16,17]

Based on the findings of this study, future research in palliative care in Kazakhstan and other LMICs could focus on the following areas:

- Accessibility and quality of home-based palliative care: Investigate the feasibility and cost-effectiveness of implementing home-based palliative care services and mobile teams, particularly in remote or rural areas.
- Opioid accessibility and management: Conduct research on the barriers to accessing opioids for pain relief in palliative care, and explore ways to improve access without increasing the risk of substance misuse.
- Education and training programs: Evaluate the effectiveness of targeted education and training initiatives for health professionals and family caregivers in improving palliative care knowledge and skills, with a focus on practical aspects of care provision.
- Public awareness campaigns: Assess the impact of public awareness campaigns on societal perceptions of palliative care, including the role of cultural and religious factors in shaping attitudes and preferences.
- Financial support mechanisms: Explore innovative financing models for stable funding

  of services to enable sustainable planning of services. Reduce out-of-pocket expenditures for patients and families, such as government subsidies, insurance coverage, or community-based funding schemes, to diminish catastrophic health expenditures.

- Evaluating the feasibility and cost-effectiveness of affordable cancer screening strategies. Such studies are crucial to bridge the gap between advanced and resource-limited settings, and to potentially democratize preventative healthcare across diverse socioeconomic landscapes.
- Monitoring and evaluation frameworks: Develop and implement robust monitoring and evaluation frameworks to track the progress of palliative care services in Kazakhstan and other LMICs, and to identify areas for continuous improvement.
- While this cross-sectional study provides a foundation for understanding the current state of palliative care in Kazakhstan, longitudinal studies will provide in-depth understanding of the effects of palliative care on patients and their families.

Although constrained by limited resources, Kazakhstan remains dedicated to the development of its palliative care services to enhance the quality of life for citizens confronting terminal illnesses. Over the past decade, significant progress has been made in palliative care in Kazakhstan, encompassing increased funding, an expanded list of palliative medications, a more robust policy framework, and better engagement with the international agenda. [1] Despite these advancements, palliative patients in Kazakhstan continue to endure avoidable pain and often suffer from poor quality of life. While considerable strides have been taken, further efforts are required to guarantee that all patients facing life-limiting illnesses in Kazakhstan can access high-quality palliative care. This emphasizes the necessity for ongoing investment in palliative care infrastructure, training, and education, as well as initiatives to raise public awareness and foster increased engagement with the international palliative care community.

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Contributions By The PhD Student

During my PhD, I spent 14 months (March 2021 - May 2022) in Kazakhstan, collecting data for the study. This period allowed me to collaborate with numerous stakeholders and co-authors in the design, execution, and analysis of the research projects that form the basis of my dissertation. My contributions to the thesis content include designing the three reported studies, developing statistical analysis plans, interpreting results, and writing and critically revising manuscripts.

Study I:

I drafted official letters, endorsed by Gulnara Kunirova, the President of the Kazakhstan Association of Palliative Care, and Dr. Byron Crape, my second supervisor and Assistant Professor at Nazarbayev University, to request data for the manuscript. I maintained correspondence with variety of stakeholders, including the Ministry of Health and regional departments of healthcare in different regions of Kazakshtan. After obtaining the necessary data, I've analyzed it and written the draft. Dr Maria Katapodi as well as all co-authors contributed to the manuscript's writing.

Study II:

I secured Institutional Review Board (IRB) approval and liaised with the administrations of study facilities in five regions of Kazakhstan to collect data. I executed data acquisition, analysis, and interpretation under the guidance of Prof. Dr. Simon Wieser.

Study III:

I conducted semi-structured interviews, transcribed, and analyzed the narrative data. Prof. Dr. Maria Katapodi participated in the interpretation of stakeholder challenges into policy recommendations. All co-authors reviewed the manuscripts before submission.

Study IV:

I designed and analyzed the research under the close supervision of Prof. Dr. Simon Wieser and Prof. Dr. Dr. Karl Heinimann. The manuscript was written with the guidance and review of Prof. Dr. Maria Katapodi.

SUPPLEMENTARY MATERIALS

Supplementary material 1

CHEERS 2022 Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	
Setting and location	6	Provide relevant contextual information that may influence findings.	
Comparators	7	Describe the interventions or strategies being compared and why chosen.	
Perspective	8	State the perspective(s) adopted by the study and why chosen.	
Time horizon	9	State the time horizon for the study and why appropriate.	
Discount rate	10	Report the discount rate(s) and reason chosen.	
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	
Valuation of outcomes	13	Describe the population and methods used	

		to measure and value outcomes.	
Measurement and valuation of resources and costs	14	Describe how costs were valued.	
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	
	RESULTS		
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	
	DISCUSSION		

Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	

Supplementary material 2

Patient Outcome Scale

CARER QUESTIONNAIRE (version 2)

www.pos-pal.org

Patient number: ……………………………………….. Assessment date: ....

Date of birth: ..…………………………..………………...

Care setting: ………………………………………………

Please answer the following questions by ticking the box next to the answer that you think most accurately describes how the person you care for has been feeling.
Thank you.

1 Over the past 3 days, has s/he been affected by pain?

☐ 0 Not at all, no effect
☐ 1 Slightly - but not bothered to be rid of it
☐ 2 Moderately - pain limits some activity
☐ 3 Severely - activities or concentration markedly affected
☐ 4 Overwhelmingly - unable to think of anything else

2 Over the past 3 days, have other symptoms e.g. nausea, coughing or constipation seemed to be affectinghow s/he feels?

☐ 0 No, not at all
☐ 1 Slightly
☐ 2 Moderately
☐ 3 Severely
☐ 4 Overwhelmingly

3 Over the past 3 days, has s/he been feeling anxious or worried about their illness or treatment?

☐ 0 No, not at all
☐ 1 Occasionally
☐ 2 Sometimes - affects their concentration now and then
☐ 3 Most of the time - often affects their concentration
☐ 4 The patient does not seem to think of anything else - completely pre-occupied by worry and anxiety

4 Over the past 3 days, have any of his/her family or friends been anxious or worried about the patient?

- ☐ 0 No, not at all
- ☐ 1 Occasionally
- ☐ 2 Sometimes – it seems to affect their concentration
- ☐ 3 Most of the time
- ☐ 4 Yes, they always seem preoccupied with worry

5 Over the past 3 days, how much information has been given to him/her, you and his/her family orfriends?

- ☐ 0 Full information or as much as wanted – always feel free to ask
- ☐ 1 Information given but hard to understand
- ☐ 2 Information given on request but would have liked more
- ☐ 3 Very little given and some questions were avoided
- ☐ 4 None at all – when we wanted information

6 Over the past 3 days, has s/he been able to share how they are feeling with his/her family or friends?

- ☐ 0 Yes, as much as they wanted to
- ☐ 1 Most of the time
- ☐ 2 Sometimes
- ☐ 3 Occasionally
- ☐ 4 No, not at all with anyone

7 Over the past 3 days, do you think s/he has been feeling depressed?

- ☐ 0 No, not at all
- ☐ 1 Occasionally
- ☐ 2 Sometimes
- ☐ 3 Most of the time
- ☐ 4 Yes, all the time

8 Over the past 3 days, do you think s/he has felt good about themselves?

- ☐ 0 Yes, all the time
- ☐ 1 Most of the time
- ☐ 2 Sometimes
- ☐ 3 Occasionally
- ☐ 4 No, not at all

9 Over the past 3 days, how much time do you feel has been wasted on appointments relating to thehealthcare of this patient, e.g. waiting around for transport or repeating tests?

- ☐ 0 None at all
- ☐ 2 Up to half a day wasted
- ☐ 4 More than half a day wasted

10 Over the past 3 days, have any practical matters resulting from his/her illness, either financial orpersonal, been addressed?

- ☐ 0 Practical problems have been addressed and their affairs are as up to date as they would wish
- ☐ 2 Practical problems are in the process of being addressed
- ☐ 4 Practical problems exist which were not addressed
- ☐ 0 The patient has had no practical problems

11 If any, what have been his/her main problems in the last 3 days?

1

2.

12 Please tick which of the following best describes the person you care for:

- ☐ 0 Fully active
- ☐ 1 Restricted
- ☐ 2 Ambulatory
- ☐ 3 Limited self care
- ☐ 4 Completely disabled

Supplementary materials 3

Patient number: ……………………………………….. Assessment date: ....

Date of birth: ..………………………….………………...

Care setting: ………………………………………………

ZARIT BURDEN INTERVIEW

INSTRUCTIONS: The following is a list of statements, which reflect how people sometimes feel when taking care of another person. After each statement, indicate how often you feel that way; never, rarely, sometimes, quite frequently, or nearly always. There are no right or wrong answers.

1. **Do you feel that your relative asks for more help than he/she needs?**

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

2. **Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?**

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

3. **Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?**

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

4. **Do you feel embarrassed over your relative's behavior?**

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

5. **Do you feel angry when you are around your relative?**

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

6. **Do you feel that your relative currently affects your relationship with other family members or friends in a negative way?**

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

7. **Are you afraid what the future holds for your relative?**

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

8. **Do you feel your relative is dependent upon you?**

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

9. **Do you feel strained when you are around your relative?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

10. **Do you feel your health has suffered because of your involvement with your relative?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

11. **Do you feel that you don’t have as much privacy as you would like, because of your relative?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

12. **Do you feel that your social life has suffered because you are caring for your relative?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

13. **Do you feel uncomfortable about having friends over, because of your relative?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

14. **Do you feel that your relative seems to expect you to take care of him/her, as if you were the only one he/she could depend on?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

15. **Do you feel that you don’t have enough money to care for your relative, in addition to the rest of your expenses?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

16. **Do you feel that you will be unable to take care of your relative much longer?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

17. **Do you feel you have lost control of your life since your relative’s illness?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

18. **Do you wish you could just leave the care of your relative to someone else?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

19. **Do you feel uncertain about what to do about your relative?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

20. **Do you feel you should be doing more for your relative?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

21. **Do you feel you could do a better job in caring for your relative?**

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

22. **Overall, how burdened do you feel in caring for your relative?**

0. Not at all 1. A little 2. Moderately 3. Quite a bit 4. Extremely

Supplementary materials 4
Interview guides for Family caregivers

	Theme	Aim	Questions / probes
1	Start of the caregiving process	Rapport building. Understand initial experience with palliative care.	1) What relationship do you have with the person, to whom you provide care to? 2) Tell me about one of your days, starting from the morning, for example on Monday... • What kind of care do you conduct on daily basis? • How much time do you spend on these caregiving activities on a typical day? • Do you have someone from your family/friends who helps you with caregiving on a regular or irregular basis? Who is this person? 3) Do your remember when it started? At what occasion and how it happened? • When did you start to provide the care • How the state of health of “name” has changed since then? • What help are you able to provide easily?

			• What help is hard for you to provide? Why is it so? 4) How was it decided that you are the one in your family taking over these tasks?
2	Identifying work-life balance of family caregiver	Discover the burden of family caregiving	1) How do you balance providing care and your personal life? • Which feelings do you experience providing care? • Do you feel stress? If yes how do you deal with it ? • How much time do you dedicate to your work, leisure time, and sleep while being a caregiver? • Has it changed since becoming a caregiver? How? 2) Do you communicate with others about your current situation as a caregiver of “name”? 3) What do you tell them? Can you speak to somebody if you have difficulties? • Do others enquire about your wellbeing? Who? 4) What would make you stop providing care to your relative?
3	Identifying facilitators and difficulties	Identify difficulties that influence caregiving process	1) Going back to the care you are now giving, what are the difficulties?

		and strategies for improvements	• What should be improved according to you? 2) What can people from your family and social network do to help you to improve the situation? • How your relationships with your relatives and friends changed since you became a caregiver? 3) How the care affects your financial condition? • How much money do you spend out-of-pocket?
4	Relationships between family caregiver and patient	Identify perceived effects and outcomes of caregiving and coordination	1) How do you think your presence affects the care? • How relationships with the patient changed after becoming the caregiver? • Who do you think should contribute more to the care: hospice staff or family?
5	Communication with the hospice staff	Assess the quality of communication between staff and family caregivers	1) How would you assess your relationships with hospice doctors/nurses that treat “name”? • Can you describe the quality of communication with hospice staff? • How do they help and support you? • Are you satisfied with the hospice care?

			2) How do you seek information when you need help? - Are you satisfied with the given information? 3) Have you been taught providing palliative care? - If yes, What kind of teaching or training you received?
6	Closing questions	Views and opinions	1) Is there anything else you would like to share on this topic?

Interview guide for Doctors

	Theme	**Aim**	**Questions / probes**
1	Personal experience	Rapport building General views and opinions of palliative care.	1) Tell me please about your position / role - How long have you been working in palliative care? - How did you decide to work in palliative care? 2) How changes/reforms in the past affected patients and PC workers?
2	Involvement of family caregivers into palliative care	To discover the current involvement and burden of family caregivers in the PC process	1) To what extent family members are involved in caregiving in your hospice? - Are all patients treated by family caregivers in your hospice? If they are not, how does it happen?

			2) How would you evaluate the effect of caregiving on mental health of a family? • If it is stressful, how do you help them to cope with stress? 3) Does the hospice staff provide training to family caregivers? • If yes, can you describe me how and how long? 4) What are the different tasks/activities that family caregivers carry? • Do you think that some tasks are more appropriate for family member to do than for a professional? • Do you have experiences with some caregivers who carry out tasks that are not up to them ? For example ? • If you encounter difficulties what are common problems you have with family caregivers?
3	Communication with family caregivers	Understand the quality of communication between doctors and family caregivers	2) Do you try to involve more families into caregiving process? if yes, how… • Is it easy to promote open communication ? If no .. What are the difficulties ? How do you manage this?

			• If yes, how do you seek to promote open communication, mutual support and teamwork? 3) Do patients and caregivers share their concerns, emotions and thoughts with your staff? 4) Is it possible to provide knowledge of palliative care to potential patients and caregivers? How do you do this ? • Ok now with patients in need of palliative care from countryside, do you change something in your discourses? Perhaps communicate in a different way or adapt information? How do you communicate with patients in need of palliative care from countryside?
4	Identifying status quo in palliative care in Kazakhstan	Assess current quality and scope of palliative care services in the country	Now more general questions about the situation of palliative care in Kazakhstan: 1) How would you assess the quality of palliative care services in Kazakhstan? • How would you assess the funding of palliative care in Kazakhstan? • How would you assess the role of the government and its support?

			• What are the common difficulties in this work? And in the everyday work ? and at the hospice? • What should be improved? • At a large scale (government)? • In daily work in your hospice? • with the family caregivers (customs, uses)
5	Closing questions	Views and opinions	2) How satisfied are you by your job? 3) Is there anything else you would like to share on the topic?

Interview guide for Health Managers

	Theme	Aim	Questions / probes
1	Status quo	Discover perspectives of health administration of current state of PC	1) Tell me please about your position / role 2) How long do you work in palliative care management? 3) How did you decide to work in PC? 4) Tell me please about your education/ training in PC? 5) Could you please describe your tasks and organization with PC practitioners/ hospice staff? 6) How do you collaborate / communicate with PC practitioners / hospices staff? 7) How do you manage the coordination of the work with physicians / nurses/ family caregivers?

			• What is average salary of PC practitioners (doctors, nurses) • How many people work in PC in KZ? What is staff turnover in KZ? Its reasons and ways to reduce? 8) How trainings / educational programs and courses are organized for PC practitioners? If yes, can you please describe them? 9) How palliative care is funded in KZ? And usually elsewhere?
2	Development of palliative care in independent Kazakhstan	Discover which strategies were successful in the past and plans for the future	1) Can you describe how PC has been developed since Kazakhstan became independent in 1991? • What are the most significant milestones? • How it affected patients and PC workers? 2) How would you describe current state / quality of PC in KZ? • What are achievements? • What are difficulties? • What remains to be improved? 3) Are you perhaps involved in some international discussions or meeting, congress of PC? • How often do you participate in conferences/meetings/congresses?

			• You told me about international standards (or first what the international standards ?) • Is it possible to follow these standards ? why not
3	Identifying caregiver burden	To discover the current involvement and burden of family caregivers in the PC process	5) How do you think the involvement of family caregivers affects palliative care? • How they can help improve patients' experience? • To what extent are they involved in the care?
4	Supplement	To identify important aspects in the provision of palliative care that have not been discussed yet.	1) In your opinion, does the government provide enough contribution to make PC in KZ better? Why do you think so? 2) What are plans of your organization for the future? • Vision and strategy 3) Can you describe the future of family caregiving in KZ? Either your hopes or fears for the future? (or both) 4) Is there anything else you would like to discuss?

Interview guide for Nurses

	Theme	Aim	Questions / probes
1	Personal experience	Rapport building General views and opinions of palliative care.	1) Tell me please about your position / role • How long do you work in palliative care? • How did you decide to work in palliative care? 2) Tell me please about your education/ training in PC? 3) Could you please describe procedures that you provide?
2	Understand experiences of formal caregivers	Discover perspectives of formal caregivers, e.g. nurses	1) How would you describe your experience as a nurse providing care to patients with cancer? 2) How do you balance working in palliative care and your personal life? • How satisfied are you by your job? • How do you cope with stress? 3) Tell me please more about your experience of working with family caregivers? • Which procedures do you delegate to family caregivers? • Are they trained? If yes, by whom and what kind of training do they have?

			• How family caregivers affect your work and care outcomes? • Which procedures do you delegate to family caregivers?
3	Supplement	Identify difficulties that influence caregiving process and strategies for improvements	1) Is there anything else you would like to discuss?