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REVIEW

Health economics evidence for medical nutrition: are these interventions value for money in integrated care?

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Background: Health care decision-makers have begun to realize that medical nutrition plays an important role in the delivery of care, and it needs to be seen as a sole category within the overall health care reimbursement system to establish the value for money. Indeed, improving health through improving patients' nutrition may contribute to the cost-effectiveness and financial sustainability of health care systems. Medical nutrition is regulated by a specific bill either in Europe or in the United States, which offers specific legislations and guidelines (as provided to patients with special nutritional needs) and indications for nutritional support. Given that the efficacy of medical nutrition has been proven, one can wonder whether the heterogeneous nature of its coverage/reimbursement across countries might be due to the lack of health-related economic evidence or value-for-money of nutritional interventions. This paper aims to address this knowledge gap by performing a systematic literature review on health economics evidence regarding medical nutrition, and by summarizing the results of these publications related to the value for money of medical nutrition interventions.

Methods: A systematic literature search was initiated and executed based on a predefined search protocol following the population, intervention, comparison, and outcomes (PICO) criteria. Following the systematic literature search of recently published literature on health economics evidence regarding medical nutrition, this study aims to summarize the results of those publications that are related to the value for money of medical nutrition interventions. The evaluations were conducted by analyzing different medical nutrition according to their indications, the economic methodology or perspective adopted, the cost source and utility measures, selected efficiency measures, as well as the incremental cost-effectiveness ratio.

Results: A total of 225 abstracts were identified for the detailed review, and the data were entered into a data extraction sheet. For the abstracts that finally met the predefined inclusion criteria (n=53), full-text publications were obtained via PubMed, subito, or directly via each journal's Webpage for further assessment. After a detailed review of the full text articles, 34 publications have been qualified for a thorough data extraction procedure. When differentiating the resulting articles in terms of their settings, 20 studies covered inpatients, whereas 14 articles covered outpatients, including patients in community centers. When reviewing the value-for-money evaluations, the indications showed that the different results were mostly impacted by the different perspectives adopted and the comparisons that were made. In order to draw comprehensive conclusions, the results were split according to the main indications and diseases.

Discussion: The systematic literature search has shown that there is not only an interest in health economics and its application in medical nutrition, but that there is a lot of ongoing research in this area. Based on the underlying systematic analysis, it has been shown that medical nutrition

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interventions offer value for money in the different health care settings, particularly for the specific disease areas that have been pointed out.

Conclusion: Based on the systematic literature search that was performed, it was shown that medical nutrition interventions offer value for money in the different health care settings. Although medical nutrition has been the topic of some health economic analyses, the usual willingness to pay threshold used in health care rarely was applied. Often, these products are either directly part of a lump sum in the financing system (for example, diagnosis-related groups), or they are covered as out-of-pocket payments by patients directly. More research would be necessary to better understand how medical nutrition interventions can be optimally funded by the health care system, given the clinical value they bring to patients in their recovery process.

Keywords: systematic review, medical nutrition, health economics

Introduction

In Europe, health authorities have started to establish incentives for efficient health care delivery by means of decentralization of the health care decision-making process and implementation of market mechanisms. Health care decision-makers have begun to realize that medical nutrition plays an important role in the delivery of care, and that nutrition needs to be seen as a sole category within the overall health care reimbursement system to establish its value for money.

Medical nutrition background

Medical nutrition is a specific nutrition category, as it either covers the specific dietary needs and/or nutrient deficiencies of patients, or it may nourish patients who are unable to eat normally. It covers energy, protein, fluid, electrolyte, mineral, micronutrient, and fiber needs. These nutrient-based needs depend on a patient's activity levels, as well as on his or her underlying clinical condition, such as catabolism, pyrexia gastrointestinal (GI) tolerance, potential metabolic instability, risk of refeeding problems, and the likely duration of nutrition support, among others. Different options for the administration of medical nutrition support exist – oral, enteral, and parenteral – by the application of special devices like infusions, tubes, probes, or perfusions. Intake of patients' medical nutrition needs by skilled health care professionals that are trained in nutritional requirements and methods of nutrition support can ensure that patients are provided with the right diagnosis and the adequate delivery of nutrition.

Indications and efficacy

Indeed, improving health through bettering patients' nutrition may contribute to the cost-effectiveness and financial sustainability of various health care systems. Moreover, medical nutrition interventions have demonstrated therapeutic efficacy in different disease areas, independent of the nutritional status of patients.[1,2] Sometimes, medical nutrition interventions are delivered within integrated care processes, such as in the enhance recovery after surgery program (http://www.erassociety.org/).[3–5] For instance, immunonutrition (IN) has been demonstrated to decrease the risk of postoperative complications and infections in GI cancer patients undergoing surgery.[6] Generally, when considering medical nutrition interventions, clinical evidence of their efficacy in supporting the recovery of patients has been demonstrated for different disease areas (for example, in critically ill patients,[7,8] pancreatitis,[9] and patients suffering from dysphagia[10]). Similarly, in pediatric Crohn's disease patients, the use of enteral nutrition during flare-ups of the disease has been shown to induce remission as effectively as corticosteroids, and even more safely.[11] Furthermore, the clinical evidence for the efficacy of medical nutrition in supporting the recovery of patients with disease-related malnutrition has been extensively documented, and it has shown a reduction in mortality, morbidity, as well as in the length of hospitalization and rehospitalizations.[12] In Alzheimer's disease, nutritional products have also shown some promise.[13]

Reimbursement, health economics, and value for money

Medical nutrition is regulated by a specific bill in both Europe or the United States, and this bill provides specific legislations and guidelines for patients with special nutritional needs and indications for nutritional support. Therefore, medical nutrition products are delivered under medical prescription and supervision by health care professionals, which is comparable to the practice in pharmaceuticals.

Although medical nutrition interventions have proven that there are clinical benefits in the recovery pathway of patients, the reimbursement status of these interventions varies widely between product categories, as well as across geographic regions. For instance, oral nutrition supplements (ONS) taken in addition to a normal diet to compensate for protein deficiencies or other nutrient gaps are covered in hospital care in Europe, and sometimes in ambulatory care as well, whereas it is not covered at all in the US. Enteral nutrition (EN), which is prescribed to replace food intake in critically ill patients, is covered in inpatient care by hospital budgets, or the cost is reimbursed to patients in outpatient care in most developed countries. However, some specialized EN or ONS formulas are sometimes reimbursed as a type of innovation, such as in France, through the submission of a "brand name" reimbursement dossier to the French Health Authority;[14] conversely, this does not occur in other markets despite submission of the same clinical evidence related to the product.

Given that these products have existed for more than two decades, the health-related economic evidence regarding medical nutrition interventions tends to be scarce. In the field of health technology research, including pharmacoeconomics, health economics is most often described through the methods used, including cost-effectiveness analysis, cost utility analysis, and budget impact analyses. Often, cost-effectiveness analyses are seen as assessing the value for money of new interventions. Judging the clinical benefit of interventions will be based on traditional clinical trial outcomes (efficacy and safety), but it may also include data on the effectiveness of the intervention and on patients' quality of life. Subsequently, the monetary (economic) criteria, as well as the clinical benefit criteria, are taken into consideration (budget impact and cost-effectiveness) in order to make a final decision. Those analyses are valued on the incremental clinical and economic benefit base of the new interventions compared with standard ones. These types of analyses are the common approach used in the United Kingdom, Canada, and Australia, among others, in order to achieve reimbursement or coverage for medical interventions. In these cases, the incremental cost-effectiveness ratios (ICERs) are then compared to a willingness-to-pay threshold, meaning that a society or health care system is willing to pay for each additional life year or quality-adjusted life year (QALY) gained due to the new intervention in comparison with the standard one.[15] In the UK, an implicit willingness-to-pay threshold of £30,000 per QALY is being applied; other countries use other thresholds.[16]

Generally we define value for money in a broader sense: if a customer accepts the price of a medical intervention with its given attributes (for example, efficacy, safety, and so on), this intervention is value for money for that specific customer. Obviously, the value for money of an intervention needs to first demonstrate its clinical value in order to convince health care professionals and payers. Hence, all therapies that are reimbursed are value for money for the health care system that is paying for it. However, this might differ in differentiating the term "customer" from a patient perspective or from a payer perspective. It can usually be assumed that new treatments lead to more costs; however, in nutrition, there might often be cost savings. The health authorities will make a trade-off between the extra clinical benefit and the impact of the health care costs of a new intervention versus the standard one.

While value for money has been extensively developed and proven for many pharmaceutical products and medical devices, it is less common in the field of medical nutrition, although these products are also prescribed to patients and are often reimbursed by health care systems.

In sum, it can be said that in Europe and North America, medical goods and services are assessed by national health authorities or private health plans in order to recommend or decide which goods and services are included in the catalogue of reimbursed health care interventions. Clinical and/or economic evidence is assessed using health technology assessment methods in order to inform pricing and coverage/reimbursement decisions. Some countries focus more on the comparative clinical benefit and the intervention's impact on the health care budget when introducing new medical interventions, whereas others consider their cost-effectiveness or cost-utility benefits for coverage decisions and negotiations on reimbursed prices. Given that the efficacy of medical nutrition has been proven, one can wonder whether the heterogeneous nature of its coverage/reimbursement across countries might be due to the lack of health economic evidence, or due to the value-for-money of nutritional interventions. This paper aims to address this knowledge gap by performing a systematic literature search regarding health economics evidence of medical nutrition, and summarizing the results of these publications as they relate to the value for money of medical nutrition interventions.

Methods

A systematic literature search was initiated and executed based on a predefined search protocol following the population, intervention, comparison, and outcomes (PICO) criteria (see also Table 1).[17] Following the systematic literature search that was published recently on the health economics evidence in medical nutrition,[18] this study aims to summarize the results of those publications that are related to the value for money of medical nutrition interventions. The research questions upon which this review was conducted can be summarized as follows: "Are medical nutrition interventions value for money in integrated care? What is the health economics evidence?"

Table 1 PICO criteria used for the systematic literature search

PICO criteria	Definition
Patient **I**ntervention	Medical nutrition/oral or enteral formulas; FSMP; medical food; ONS; oral nutrition; enteral nutrition; total EN; nutrition/nutritional intervention; support; supplements; formulas
Comparison	Patients with versus those without medical nutritionals/FSMP/medical food/ONS/PN or TPN; potentially secondary prevention
Outcomes	Cost(s), cost-effectiveness, cost per QALY, cost saving, cost of illness, cost minimization, health economics; willingness to pay; (re)-hospitalization; morbidity and mortality; complications; utility

Abbreviations: PICO, patient, intervention, comparison, and outcomes; FSMP, food for special medical purposes; ONS, oral nutrition supplements; EN, enteral nutrition; PN, parenteral nutrition; TPN, total parenteral nutrition; QALY, quality-adjusted life year.

In order to answer the specific research questions, the standard literature databases such as PubMed (National Center for Biotechnology, US National Library of Medicine, Bethesda, MD, USA), the Health Technology Assessment Database (The Cochrane Collaboration, Oxford, UK), and the NHS Economic Evaluation Database (The Cochrane Collaboration) have been searched. Additionally, a free search in Google (Google Inc., Mountain View, CA, USA) was conducted using the search terms that were utilized in the systematic literature search. This search was solely focused on the health economic data in nutritional economics; thus, publications without a health economic component/analysis were not covered within this search. For the abstracts that met the predefined inclusion criteria, publications (full text) were obtained. The abstracts not meeting the search criteria were excluded. Based on these full-text reports, it was decided whether each study met the selection criteria; the identified, relevant data were recorded in a data extraction sheet. An analysis of the clinical background, health economic design, and results of the selected articles was performed and, finally, the quality of the studies was validated upon application of the Drummond checklist for health economic modeling studies and the application of the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist for published systematic reviews. Based on the literature search results and the basic analysis of the clinical background, health economic design, and results, as well as of their quality, the articles were reviewed with respect to their value for money according to the study objective. The evaluations were conducted by analyzing different medical nutrition interventions according to their indications, the economic methodology or perspective used, the source of cost and utility measures, the selected efficiency measure, and the ICER.

Results

Results of the literature search

In total, 328 articles were excluded; 225 abstracts were identified for the detailed review, and the data were inserted into a data extraction sheet.

Following that, a narrative scrutiny of the data was performed, and further articles were excluded. All articles with a focus on primary prevention, as well as all articles solely focusing on clinical data without a health economic component/analysis were excluded. For the abstracts that finally met the predefined inclusion criteria (number [n]=53), full-text publications were obtained via PubMed, subito (subito e.v., Berlin, Germany), or directly via the journals' Webpages for further assessment. After a detailed review of the full-text articles, a further 19 articles were excluded according to the preset criteria. Consequently, 34 publications qualified for a thorough data extraction procedure, including those from the "gray literature", which were identified by a free Web search and through cross-reference searches.

When differentiating the resulting articles in terms of care settings, 63% of the manuscripts (20 studies) covered inpatients, whereas 14 articles (41% of manuscripts) covered outpatients, including patients in the community centers. When analyzing the countries where the studies were conducted, most of the articles were issued in the US and the United Kingdom (seven studies in each country; together, they accounted for 44% of all studies included). Italy and the Netherlands followed with five and four articles, respectively, even though in both countries, the same groups of researchers dominated those articles. Most other countries had only one article, except for Germany, which had three.

Results of value for money according to specific indications

When reviewing the value for money evaluations, the indications show different results mostly impacted by the different perspectives and comparisons being made (see Table 2). In order to draw comprehensive conclusions, the results were split according to the main indications and diseases, as well as the miscellaneous ones, addressed in the subject publications. The following areas were determined: malnutrition; GI surgeries (due to cancer); cow milk protein allergy (CMPA); and others.

Malnutrition

In malnutrition, the introduction of ONS has been accepted as being cost-effective, as shown by a wide range of ICERs

Table 2 Detailed overview of identified articles with respect to key study items

Authors and reference	Disease area and classification	Intervention	Model design	Health care setting and perspective	Health economic endpoints and results
Abou-Assi et al[40]	Acute pancreatitis	Initial 48-hour IV fluids and analgesics. After patients improved, they were restarted on oral feeding. The remaining patients were randomized to nasojejunal (EN group) or parenteral feeding (TPN group). Comparison: EN versus TPN	RCT in one center	Hospital perspective in the US	Average hospitalization cost: US $11,183. For the sicker patients needing nutritional support, those given enteral feeding had lower total average hospitalization costs: US $26,464 versus US $34,530 per patient. Average nutritional costs: US $394 (EN) versus US $2,756 (TPN) per patient.
Freijer and Nuijten[41]	Abdominal surgery GI surgery	ONS versus no ONS Comparison: ONS versus no ONS	Cost-effectiveness model	Hospital, national perspective	Budget impact: cost saving (in favor of ONS) of €12,986 million.
Gianotti et al[23]	Surgery in GI cancer patients GI surgery	Perioperative administration of enteral IN or standard enteral diet Comparison: ONS + EN IN versus SoC	Calculation based on RCT and cost data	Hospital perspective	Cost per patient: €347 (ONS) versus €103 (SoC). Cost per complication (for all study patients): €78,336 (ONS) versus €243,882 (SoC). Cost-effectiveness (not incremental): €1,339 (ONS) versus €3,725 (SoC).
Kruizenga et al[20]	Malnourished hospitalized patients with different diseases Malnutrition	Intervention group: patients admitted to two mixed medical and surgical wards, and who received both malnutrition screening at admission and standardized nutritional care (TF and parenteral feeding). Control group received the usual hospital clinical care. Comparison: EN versus PN	Controlled trial with a historical control group	Hospital, societal perspective	Length of stay: 11.5 days versus 14 days. Cost-effectiveness: EN more costly, less effective.
Neelemaat et al[19]	Malnourished hospitalized patients (newly admitted to the wards of general internal medicine, rheumatology, gastroenterology, dermatology, nephrology, orthopedics, traumatology, and vascular surgery) Malnutrition	Intervention group: nutritional supplementation (energy- and protein-enriched diet, ONS, calcium-vitamin D supplement, telephone counseling by a dietician) until 3 months after discharge from hospital. Patients in the control group received usual care (control). Comparison: ONS into diet protocol versus SoC	Randomized clinical trial in one center	Hospital, societal perspective (one hospital center)	Direct cost: €8,773 versus €8,332. Indirect cost: €356 versus €352. Total: €9,129 versus €8,684. ICER: €26,962/QALY.
Norman et al[21]	Malnourished hemodialysis patients Malnutrition	Oral supplementation early in the course of malnourished hemodialysis patients Comparison: ONS in mild hemodialysis patients versus ONS in moderate/severe hemodialysis patients	RCT (pilot) study	Outpatient, hemodialysis centers in the US	Length of stay: 71 days versus 107 days versus 208 days.
Wilson et al[38]	Advanced dementia Eating problems	TF versus hand-feeding nursing Comparison: TF (EN) versus SoC (including normal food intake with nurse help)	Retrospective cohort study	NH residents, long-term care facility in the US	Daily costs of NH care: US $4,219 (without feeding tubes) versus US $2,379 (with feeding tubes).
Mitchell et al[39]	Disease-related malnutrition Malnutrition	ONS (intervention) versus no ONS Comparison: ONS versus no ONS	Budget impact	Community, national perspective	Budget impact: cost savings of €12,986 million.

(*Continued*)

Table 2 (*Continued*)

Authors and reference	Disease area and classification	Intervention	Model design	Health care setting and perspective	Health economic endpoints and results
Freijer et al[27]	CVA Dysphagia	ETF in NH versus at home Comparison: ETF in different health care settings: home versus NH	Cost-utility model	Outpatient, perspective not reported	Cost/QALY (ETF at home): £12,817. Cost/QALY (in NH): £10,304–£68,064.
Elia and Stratton[42]	Acute pancreatitis	PN versus EN Comparison: PN versus EN	Randomized clinical trial	Hospital, health authority in Canada	Average cost per patient: US $1,375 (EN) versus US $2,608 (PN). Other cost categories were equivalent.
Louie et al[24]	Lower GI tract surgery GI surgery	Oral supplements (Fortisip; Nutricia Advanced Medical Nutrition Schiphol, the Netherlands) both before and after surgery. Patients were randomized to the following groups: 1) no nutritional supplements; 2) supplements both before and after surgery; 3) postoperative supplements only; 4) supplements only before surgery Comparison: ONS versus +/– ONS before/after surgery	Two-phase, randomized clinical trial	Hospital perspective	Total cost per patient: ONS pre- and postsurgery: £2,289. ONS presurgery: £2,286. ONS postsurgery: £2,324. No ONS: £2,618.
Smedley et al[29]	Patients after discharge from hospital Malnutrition	Elderly malnourished subjects were randomized to 8 weeks of supplementation (Ensure® Plus tetrapak, Abbott Laboratories, Enlive® tetrapak; Formance® Pudding; or Ensure® bars, Abbott Laboratories, Abbott Park, IL, USA) or no supplementation postdischarge, and followed up for 24 weeks Comparison: ONS versus no ONS	Multicenter prospective open label, RCT	Outpatient, NHS perspective	Cost changes within the study period: Prescriptions: £92 versus £28. Consultations: –£11 versus £16. Appointments: £28 versus £14. Hospital admissions: –£326 versus –£2,703. Hospital stays: –£326 versus –£2,703.
Edington et al[43]	1) Well-nourished surgical patients 2) Malnourished surgical patients 3) Trauma patients 4) Medical ICU patients, GI surgical and ICU patients	Immune-modulating formulations could be either: 1) Impact (Novartis AG, Basel, Switzerland), or 2) Immonaid (Braun GmbH, Kronberg, Germany) Comparison: ONS versus no ONS	Database analysis	Hospital (before/after surgery – after trauma/ICU admission) US hospital for patients covered by Medicare or Medicaid services	Cost of complications normally higher for the intervention group (ONS). Break-even infection rates calculated to define the efficiency point for ONS treatment.
Strickland et al[30]	Cancer of the stomach, pancreas, or esophagus GI surgery	Randomization into two groups receiving postoperative TPN or EEN Comparison: EN versus PN	Prospective, randomized clinical trial	Hospital, department of surgery in an Italian university hospital	Mean cost per day: $25 versus $90 (USD). Prescriptions represent 73.2% of the mean daily cost in TPN and 22% in EEN. The costs of the other variables were similar in the two groups.
Braga et al[22]	GI cancer GI surgery	1) Preoperative group receiving Oral Impact® (Nestlé SA, Canton of Vaud, Switzerland) for 5 days before surgery; 2) perioperative group receiving the same preoperative treatment plus jejunal infusion of Impact for 7 days after surgery; and 3) a conventional group Comparison: IN oral or enteral versus SoC in a pre- or perioperative regimen	Clinical study	Hospital perspective	Total cost of nutrition: €3,407 (conventional) versus €14,729 (preoperative). Cost of in-hospital routine care was similar in both groups. Mean cost of complication: €6,178 versus €4,639€. Total cost of patients with complications: €535,236 versus €334,148. Cost-effectiveness: €6,245 versus €2,985.

Braga and Gianotti[25]	GI cancer GI surgery	Preoperative IN versus no nutritional support Comparison: preoperative IN (oral) versus no ONS support	Review	Hospital, perspective NA	Cost of nutrition: €144–€347 versus €33–€103. Cost of complications: €768–€1,728 versus €2,345–€3,089. Cost-effectiveness: €1,339–€2,985 versus €3,587–€6,244.
Braga and Rocchetti[26]	GI cancer GI surgery	Oral preoperative specialized diet versus conventional treatment (no supplementation) Comparison: Preoperative IN (oral) versus no ONS support	Prospective, randomized clinical trial	Hospital, Italian university hospital	Mean cost per day per patient (without complications): €3,622 versus €3,588. Mean cost per day per patient (with complications): €10,494 versus €8,793. Mean total cost per patient: €7,092 versus €5,668.
Braga et al[26]	Critically ill patients	PN versus EN Comparison: EN versus PN	Systematic review and cost analysis	Hospital (ICU), perspective NA	Cost savings per patient (due to EN): US $2,473. Budget impact: switching 10% of PN patients to EN saves US $57 million annually.
Cangelosi et al[44]	Patients with risk of disease-related malnutrition Malnutrition	ONS versus no ONS Comparison: ONS versus no ONS	Linear decision analytic model	Hospital, perspective not reported	Total cost: €1,482 versus €1,717. Budget impact: cost savings (in favor of ONS): €603,539 million.
Nuijten and Mittendorf[45]	Malnutrition patients Malnutrition	Two groups of physicians were selected based on historical prescribing practice: group 1 with rare prescription of ONS and group 2 with frequent prescription of ONS (only an HEHP nutritional supplement that has a pharmaceutical status on the French market) Comparison: ONS versus no ONS	Observational, prospective, longitudinal, cohort study	Community, physician perspective	Length of stay: 4.3 days versus 5.6 days. Cost per patient: Oral supplementation: €565 versus €37. Hospital admissions: €1,572 versus €2,123. Nurse visits: €217 versus €362. GP visits: €32 versus €42. Total: €2,499 versus €2,694.
Arnaud-Battandier et al[6]	GI cancer GI surgery	Oral or enteral dietary supplementation with arginine, omega 3 fatty acids, and nucleotides (known as IN) Comparator: IN perioperative (EN or ONS) versus SoC	Database analysis	Hospital perspective	Cost savings per patient (in favor of IN): $3,300 (reduction in infectious complications) and $6,000 (length of hospital stay) (USD).
Mauskopf et al[28]	Disease-related malnutrition Malnutrition	ONS ONS (no comparator)	Cost review	Hospital and community perspective	Additional ONS cost for individuals: Hospital inpatients: £3,194. Long-term care: £1,646. GP visits: >£43. Hospital outpatients: >£43. Artificial nutrition and ONS in hospital: £54. Artificial nutrition and ONS in the community: £149. Total: >£5,280.
Russell[46]	Malnutrition patients Malnutrition	Disease-specific medical nutrition Comparators and treatments not specified	Database-matched analysis	Community, physician perspective	Total 6-month cost per patient: £1,003. Budget Impact: £615 million–£3,695 million.
Guest et al[32]	CMPA	Treatment data and, hence, split of patient groups according to UK market data	Computer-based budget impact model	Community, perspective not reported	Total cost of managing CMA per patient (first 12 months): £1,381. Budget impact: £25.6 million (for an annual cohort of 18,350 infants)

(*Continued*)

Table 2 (*Continued*)

Authors and reference	Disease area and classification	Intervention	Model design	Health care setting and perspective	Health economic endpoints and results
Sladkevicius et al[33]	CMPA	Soy, eHF, neocate AAF based on assumptions and the literature	Decision budget impact model	Community, KELA (health insurance), patient and society	KELA's total expenditure on clinical nutrition preparations for 1,443 new CMA sufferers is expected to fall by 34% (from €47,930–€31,666).
Guest and Valovirta[31]	CMPA	Soy, eHF, AAF	Decision budget impact model	Community, publicly funded health care system	Expected 6-monthly health care cost per CMA infant: AU $1,150.
Guest and Nagy[34]	CMPA	Soy, eHF, AAF	Decision budget impact model	Community health care insurers	Expected budget impact (4,382 new CMA sufferers up to 1 year of age): €11.28 million.
Sladkevicius and Guest[35]	CMPA	Soy, eHF, AAF	Decision budget impact model	Community, insurer, parents/carer perspective	Expected 12-monthly cost (insurance perspective): 2,430 South African (private sector) versus 1,073 R (public sector). Expected 12-month cost (parents/carers): 43,563 R (private sector) versus 24,899 R (public sector). Budget impact (annual cohort of 18,270 newly diagnosed infants): 22.1 million R for health care insurers and 489.1 million R for parents/carers.
Sladkevicius and Guest[36]	CMPA	eHF versus AAF	Decision analytic model	Community	12-month NHS cost: £1,853 and £3,161 per patient in the eHF and AAF groups, respectively. Total incremental 12-month NHS cost: £1,308 (AAf versus eHF).
Taylor et al[47]	Malnutrition patients in a gastroenterology ward Malnutrition	Nutritional support (including oral supplements, parenteral feeding, parenteral TF) Comparison: ONS; EN; and PN	G-DRG-relevant variables were prospectively collected	Inpatient, hospital perspective	Direct cost for 50 patients: ONS: €618. EN: €2,772. PN: €4,002.
Ockenga et al[37]	Pancreatitis	EN versus PN support Comparison: EN versus TPN	Retrospective review of preexisting database	Inpatient, hospital in the USA	No significant difference was found in terms of cost, even though meaningful: US $22,277 (TPN) versus US $16,724 (EN). Reason: most likely due to the small sample size.

Abbreviations: IV, intravenous; EN, enteral nutrition; TPN, total parenteral nutrition; GI, gastrointestinal; ONS, oral nutritional supplements; IN, immunonutrition; SoC, standard of care; RCT, randomized controlled trial; TF, tube feeding; PN, parenteral nutrition; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; NH, nursing homes; CVA, cerebrovascular accident; ETF, enteral tube feeding; NHS, National Health Service; ICU, intensive care unit; EEN, early enteral nutrition; NA, not applicable; HEHP, high-energy, high-protein; GP, general practitioner; CMPA, cow's milk protein allergy; CMA, cow's milk allergy; eHF, extensively hydrolyzed formula; AAF, amino acid formulas; KELA, Social Insurance Institution in Finland; AU, Australian; R, rand; G-DRG, Diagnosis-related Groups Germany.

between studies. The ICER ranged from cost-savings to a maximum, but still acceptable, ICER of €26,962/QALY.[19] Even though the introduction of ONS in comparison to a standard of care in patients' management generates acquisition costs for ONS and dietician support, different authors have shown that there are cost savings from a budget impact perspective (range: €600 million to €12 billion). Within those analyses were the inclusion of efficacy parameters, especially the length of stay, as well as hospital admissions; these appeared to be the main drivers of cost savings due to significantly shorter length of stay and fewer hospital readmissions in the ONS groups.[20,21] The article by Neelemaat et al[19] only found small differences in terms of efficacy, and the authors detected a positive ICER, which was still considered as being cost-effective when compared to the thresholds that are normally applied.

Gastrointestinal surgery (due to cancer)

GI indications mainly associated with cancer have been addressed by a good number of articles in the same manner: all articles including the total cost of treatment for oncology GI-surgery indications concluded that ONS were cost-saving. The budget impact analyses showed similar results.[6,22–26] In a few studies, cost-effectiveness results were also presented, and they were also in favor of ONS.[22,23,25] However, those results need to be interpreted with caution, as no ICERs were calculated and provided.[25] One study analyzed the cost difference between parenteral nutrition and EN and showed that EN was more costly.[22] Anyhow, this more costly approach could still be cost-effective, and it is the subject of key discussions in countries such as the UK, which are addressing whether the incremental outcomes balance the higher costs. However, this type of cost-effectiveness study has not yet been published regarding the underlying comparison. Kruizenga et al[20] have shown that severe complications were the main drivers for ONS being a cost-saving therapy. Key complications included anastomotic leak, pneumonia, and wound infections, which resulted in a cost difference of €165,546 for the entire analyzed population (n=588). Similar drivers were included by Freijer et al,[27] Braga et al,[22] and Mauskopf et al,[28] with ONS reducing mortality and complication rates. Other researchers (Smedley et al[29] Strickland et al[30]) have also reported fewer hospital stays and complications and, hence, calculated cost savings (around €300–€400 per patient). When oral or enteral IN containing arginine, among other active ingredients, were analyzed in a clinical trial (Braga et al[22]), it was found that the total cost for patients with complications was €535,236 versus €334,148 for oral nutrition versus enteral IN, respectively, and the cost-effectiveness (per patient; not incremental cost-effectiveness) was €6,245 versus €2,985, respectively.[22]

Cow milk protein allergy (CMPA)

All publications in the area of CMPA analyzed the potential introduction of CMPA coverage into the health care system and its budget impact. Long-term costs have only been included in one Finnish analysis, where it was concluded that the cost for the system would significantly decrease by 34%.[31] All other analyses have primarily focused on the status quo of the CMPA budgets and have concluded that the annual cost per patient is in the area of €1,500, independent of the country analyzed.[32–36]

Other indications

For pancreatitis, for example, two different studies were performed, which both showed that enteral feeding was cost-saving in comparison to parenteral feeding (a savings of US $1,300 and US $2,400 for the two studies, respectively).[6,37] In critically ill patients, enteral feeding was cost-saving when compared to parenteral feeding (US $2,400).[22] In the area of eating problems experienced by dementia patients, the support with feeding tubes was a cost-saving option in comparison to the standard of care (US $1,900 saving per patient).[38] In patients suffering from dysphagia, it has been shown that enteral tube feeding was cost-effective, independent on the setting (home versus nursing homes).[39] ICERs ranged between £12,817/QALY (enteral tube feeding at home) and £10,304–£68,064/QALY (in nursing homes).[27]

Discussion

This systematic literature search has shown that there is not only interest in health economics and its application in medical nutrition, but there is a lot of ongoing research in this area. Based on the underlying systematic analysis, it has been shown that medical nutrition interventions offer value for money in the different health care settings, particularly for the specific disease areas that have already been pointed out.

With GI disorders and malnutrition, the comparisons of medical nutrition interventions have always been against a standard enteral diet or nil-by-mouth. These analyses proved that medical nutrition offers value for money in these settings. Furthermore, in all studies related to IN, the standard diet was chosen as the comparator, which could be interpreted as a standard tube feeding formula (and, hence, as medical nutrition as well).[6,22,23,25,26] Most of the time, medical nutrition was more effective and cost-saving and, therefore, dominant from a health economic perspective. Among the few studies calculating an ICER, all of the calculated ICERs fell below normally acceptable cost-effectiveness thresholds applied in medical settings (Table 2).

In the other disease areas (CMPA, pancreatitis, critically ill patients, dementia, dysphagia), medical nutrition interventions were analyzed against each other. Only a few analyzed interventions were compared against a normal diet. The idea that enteral feeding is cost-saving when compared to parenteral feeding is intuitive, and has been proven in various analyses and settings (Table 2). Such arguments about cost-savings are especially important given the fact that in most countries, the budget impact/financial impact of a new medical nutrition intervention needs to be provided for reimbursement and/or inclusion in terms of funding. Cost-effectiveness has not yet gained mandatory status as a criterion for market access and reimbursement.

For CMPA, the scenarios covering an intervention for that indication a comparison was conducted versus non-coverage, analyzed by budget impact methods. However, a conclusion is hardly feasible, due to the consequent exclusion of long-term costs, especially those costs that can significantly change the results. Indeed, in most analyses that consider the short-term horizon, the budget impact was higher when a long-term horizon was applied, as shown, for example, in the case of Finland.[31] Here, cost savings have been revealed by including the impact of long-term costs. A specific feature in intensive care unit patients showed in various analyses and settings that enteral feeding is cost saving, mainly due to the much higher cost of parenteral nutrition compared to EN.

Conclusion

Based on the underlying systematic literature search, it was shown that medical nutrition interventions offer value for money in different health care settings. Although medical nutrition has been the topic of some health economic analyses, the usual willingness-to-pay threshold used in health care was rarely applied. This might be mainly due to the health care settings in which medical nutrition is distributed, and it may also be due to their market access channels at present. Often, these products are either directly part of a lump sum in the financing system (for example, diagnosis-related groups), or even directly covered as out-of-pocket payments by patients. Further, due to the current market access pathways for medical nutrition interventions, not many cost-effectiveness analyses have been generated for medical nutrition so far, especially in comparison to pharmaceuticals; hence, the willingness of the payer to pay might be different to that of the pharmaceutical environment. More research would be necessary to better understand how medical nutrition interventions can be optimally funded by the health care system, given the clinical value they bring to patients in their recovery process; however, reimbursement hurdles are becoming more rigid for medical nutrition. Furthermore, research comparing medical nutrition interventions against other therapy options ("non"-medical nutrition) is needed.

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