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POINT OF VIEW

The role and impact of health economics in the optimization of patient care in osteoarthritis: insights from a practical example

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ABSTRACT

Osteoarthritis (OA) is a degenerative joint disease with a substantial global burden, causing chronic pain and reduced quality of life. Managing OA efficiently while maximizing healthcare resources is crucial. Health economics and health technology assessment (HTA) are central tools providing a framework to evaluate the clinical, economic, and ethical aspects of healthcare technologies and interventions. This article presents some insights into the role of health economics and the HTA process in OA management. It also illustrates an example of cost-effectiveness analysis in a specific healthcare context, on the basis of a recent clinical trial involving hyaluronic acid treatment for knee OA. While HTA offers valuable insights, it faces challenges like data availability and resource constraints. Integrating health economics into decision-making can enhance patient care and allocate resources effectively in OA and other healthcare domains.

Keywords: Cost-effectiveness, Economic evaluation, Health technology assessment (HTA), Osteoarthritis (OA), Quality-adjusted life years (QALY)

Introduction

Osteoarthritis (OA) is a highly prevalent degenerative joint disease affecting over 7% of people globally (1) and causing chronic pain, reduced mobility, and decreased health-related quality of life (HR-QoL) (2-4). Environmental, biomechanical, biological, and genetic factors contribute to various clinical outcomes (5-7). Risk factors for OA include aging, genetics, trauma, obesity, and metabolic issues (6,7).

OA imposes a considerable socioeconomic burden and is a leading cause of disability in older adults (1). Between 1990 and 2019, OA cases more than doubled to 527.8 million worldwide, with rising prevalence rates, particularly in knee and hip joints (8). The knee is the most common localization of OA and contributes most to the overall burden (8,9). Unfortunately, OA management is often neglected and misunderstood, with patients' concerns disregarded by clinicians (4,10).

Despite varying OA incidence trends by region, the prevalence is expected to increase, mainly in higher-income countries, due to aging and longer life spans, and higher obesity rates (4,8,9). Elevated medical costs are related to OA, accounting for 1% to 2.5% of high-income countries' GDP (1,4,8).

The constraints of the limited healthcare budgets result in the urgent need to efficiently allocate available resources to support the effective management of OA while providing the greatest possible value to patients and society and maximizing the population's health. Healthcare resource allocation should focus on providing the best quality of healthcare to most people (11), with an equal and efficient distribution of financial resources tailored to actual needs (12). Policies for allocating scarce healthcare resources should be based on criteria relating to medical need, urgency of need, likelihood and anticipated duration of benefit, and change in quality of life of the patients. To this end, health economics and health technology assessment (HTA) are essential to support policymakers in making efficient decisions about financing and reimbursement (13,14).

This article aims to briefly review the rationale and roles of health economics in decision-making in OA. The two main methods for economic analysis, trial- and model-based

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economic evaluation, will be presented and illustrated with an example (15) of a determination of the cost-effectiveness of an intra-articular (i.a.) injection of a high- and low-molecular-weight hyaluronic acid formulation (HA-HL), for the treatment of knee OA, using individual patient data from a recent randomized, placebo-controlled trial. Finally, some limitations and challenges of HTA will be discussed.

Overview of the management of OA

Current treatment recommendations for OA combine pharmacological and non-pharmacological interventions (16,17); optimal management strategies should consider both approaches.

In addition to the use of topical, oral, or i.a. medications where appropriate, a comprehensive plan for managing OA should include supportive information and patient education, self-management, weight loss, and physical interventions such as structured exercise programs designed to maintain physical activity (16,17).

The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends the use of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) to provide symptomatic relief and potentially slow down the progression of OA (18). Analgesics, specifically oral nonsteroidal anti-inflammatory drugs (NSAIDs), remain the mainstay of pharmacological treatment, particularly in patients without comorbid conditions. Guidelines for the Osteoarthritis Research Society International (OARSI) and ESCEO support the use of oral NSAIDs for patients with knee or hip OA (16-18). Nonselective NSAIDs, preferably with the concomitant addition of a proton pump inhibitor or selective cyclooxygenase-2 (COX-2) inhibitors, may be used in individuals without comorbid conditions or with knee OA and gastrointestinal comorbidities.

Administration of i.a. corticosteroids (IACS) and i.a. HA is conditionally recommended in individuals with knee OA (19,20). IACS may provide short-term pain relief in individuals failing to respond to other conservative measures, although there are concerns about potential side effects with repeated use, whereas i.a. HA may have a beneficial effect on pain of ≥12 weeks duration, with a more favorable long-term safety profile than repeated IACS (16).

Even small to moderate effect sizes of symptomatic treatments for OA may provide clinically meaningful benefits to patients (21). Despite the many treatment options available, the heterogeneity of the disease, patient comorbidities, and individual responses to therapy may result in inadequate symptom control or adverse effects in some patients and represent a challenge for decision-making in managing OA (4). Recognizing these challenges and considering the high healthcare costs of the disease, clinicians should personalize treatment, choosing interventions in consultation with the patient that balance symptom control with low risk of harm and with a greater emphasis on HTA.

Health economics in OA

The efficient allocation of healthcare resources is critical to improving OA management; to achieve this, policymakers must be confident about the economic value of an intervention. Effective evidence-based decision-making requires rigorous evaluation of the validity, reliability, and generalizability of a medical intervention gained through trial-based empirical data and verification of the cost-effectiveness of the intervention (22,23).

Ongoing research seeks effective interventions for OA treatment, preventing disease progression, and, ideally, disease onset. The growing economic impact of OA is compounded by limited resources, with global healthcare spending projected to rise from $10 trillion in 2015 to $20 trillion in 2040 (24). Mounting tensions exist between the increasing demand for universal healthcare and new and increasingly expensive technologies such as gene therapies. A health intervention must not only be safe and effective but also cost-efficient to ensure affordable and optimal allocation of healthcare resources.

Economic evaluations provide the tools to compare and balance the costs and expected benefits of different interventions, typically in the dimensions of the difference between the interventions in societal costs against the difference in quality-adjusted life years (QALYs) (23).

Using the example of a patient with OA, QALY represents the area under the curve (AUC), combining QoL with the life years. If an intervention improves QoL but also improves life expectancy, the benefit will be a gain in QALY, which can be represented by an increase in the AUC (Fig. 1).

In OA, a common instrument for measuring the utility (a number for health status between 0—worst health state or

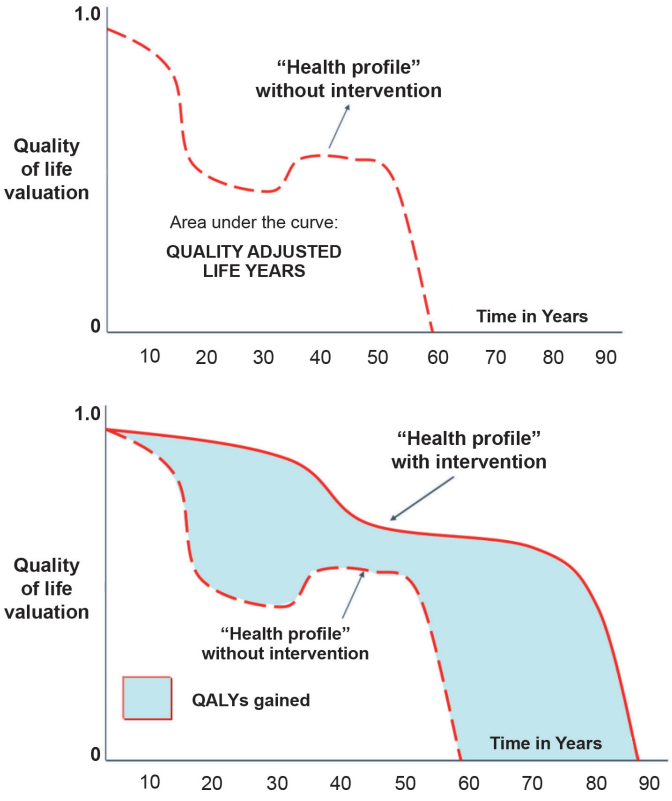

FIGURE 1 - Quality-adjusted life years gained from a health technology intervention.

death—and 1—best possible health state or full health) is the EuroQol 5-Dimension Questionnaire, a five-level health status measure (EQ-5D-5L) that measures HR-QoL (25). The EQ-5D-5L is a generic descriptive instrument that defines health in terms of the five dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression), each with five answer options and five levels of severity (none, slight, moderate, severe, extreme/unable to). Patients are asked to select the best level for each dimension. Health states calculated from the responses to the EQ-5D-5L questionnaire are converted into a single health utility score between 0 and 1, using a relevant national value set (a selection of health states). EQ-5D-5L value set is available for different countries (26-29). Over time, improvement or progression can be seen by repeating the questionnaire.

Other OA-specific QoL instruments include the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score (30), which can also be translated into a utility score (31).

Depending on the perspective of the economic evaluation, three cost types come under consideration: medical costs, patient and family costs, and productivity losses (32).

The results of a cost-effectiveness analysis can be expressed in terms of the incremental cost-effectiveness ratio (ICER) (32). The lower the ICER, the more cost-effective the intervention; an intervention should be adopted if the ICER is below the cost-effective threshold (λ). A threshold equivalent to twice the GDP has been proposed in some countries. Alternatively, the cost-effectiveness results may be represented by the cost-effectiveness plane, which plots the cost difference on the vertical axis and the effect difference on the horizontal axis (33) (Fig. 2). Within the quadrants that weigh cost vs. effectiveness, the marginal trade-off of costs and outcomes may be sufficiently high or low as to support the adoption or rejection of an intervention (23).

In an ideal situation (in the south-east quadrant of Fig. 2), the intervention can be considered to produce a better outcome and is likely to be adopted. In any case, where the ICER is below the willingness to pay threshold set by the payer, the intervention may still be considered cost-effective and be recommended when all healthcare costs are considered, including hospitalizations and other disease-related care costs.

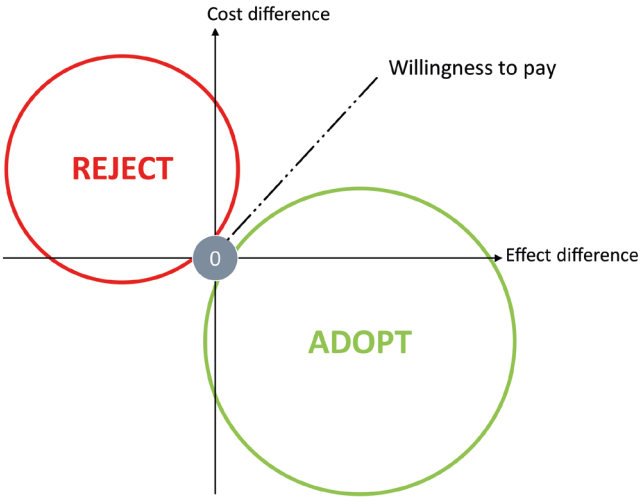

FIGURE 2 - The cost-effectiveness plane.

Economic evaluation of medical interventions in OA

There are two methods to determine the cost-effectiveness of an intervention: trial-based and model-based evaluations (34). In the case of trial-based evaluation, economic evaluation is performed in conjunction with randomized controlled trials by collecting patient-level data on costs and QALY (34). For example, in a 1-year trial with a utility questionnaire component (e.g., EQ-5D), all of the healthcare resource utilization of every patient will be collected at predetermined time points and the cost vs. QALYs gained will be averaged to determine if an intervention is cost-effective (treatment A vs. treatment B). The trial-based method has the advantage in its high validity; costs and effects are analyzed from individual patient data from the same population, with an early opportunity to produce cost-effectiveness results. However, potential disadvantages include a truncated time horizon (e.g., evaluation of data from a 1-year trial of an intervention that may have long-term benefits), a failure to consider all relevant options by restricting the comparison to the limited comparators determined by the trial design, restricted generalizability to different settings or countries, failure to incorporate all relevant evidence from different trials, and deficiencies in quantifying decision uncertainties (34,35). Trial-based economic analysis can still be appropriate, depending on whether long-term benefits and costs need to be captured or if all relevant comparators are included in a trial. In the model-based evaluation, mathematical models are used to predict an intervention's long-term health outcomes and cost consequences by extrapolating beyond the scope of available evidence. Indirect comparisons can be utilized when interventions cannot be evaluated directly, and model-based approaches allow results to be generalized to other settings or patient groups (34-36).

However, model-based analysis also has some limitations. Extrapolating accurately is difficult and subject to various uncertainties (e.g., parameter uncertainty and assumptions). To account for uncertainty and draw valid conclusions, sensitivity analyses investigate how results deviate from the base-case analysis obtained from the preferred input data set (34). Different methods of sensitivity analysis have been developed: one-way deterministic analyses using tables or tornado diagrams, bootstrapping to characterize sampling uncertainty in trial-based economic evaluation, or probabilistic sensitivity analysis for health economic models. The two last can be presented in cost-effectiveness acceptability curves. Bootstrapping is a simulation-based technique that uses the original data set and a large number of resampling assessments to generate an empirical distribution for the ICER, which can be used to prepare a cost-effectiveness acceptability curve (34).

A trial-based cost-effectiveness evaluation: one example

A recent randomized controlled trial of an innovative formulation of HA for the treatment of OA assessed the efficacy of an i.a. formulation of HA-HL (Sinovial® HL, IBSA) in the

management of moderate-to-severe symptomatic knee OA (37). Male and female subjects aged 40-80 years with primary knee OA according to American College of Rheumatology criteria, with Kellgren and Lawrence radiographic evidence of OA of grade 2-3, were enrolled in the multinational study, conducted in Belgium, Germany, Hungary, Italy, and Poland (ClinicalTrials.gov identifier NCT03200288).

The intention-to-treat and safety population of the 24-week trial consisted of 692 patients (347 in the HA-HL group and 345 in the placebo group). The study showed that a single i.a. administration of the new HA-HL formulation reduced pain much more effectively and significantly than placebo (Fig. 3), providing clinically relevant and sustained effects on pain, functionality, and HR-QoL.

However, a decision to allocate limited financial resources dictates that an intervention should be cost-effective as well as safe and effective.

Data from the clinical trial of HA-HL can be used to explore the cost-effectiveness of a single i.a. injection of HA-HL compared with placebo from a specific perspective, in this example, a Swiss healthcare perspective. Using individual patient-level data from the trial allowed a useful illustration of the value of a health economic evaluation in guiding health policy decision-making. The EQ-5D-5L 5-point verbal Likert scale was used during the trial, allowing the calculation of the health utility value and the related QALYs using the AUC method for the periods 0-1, 1-6, 6-12, 12-18, and 18-24 weeks (15,37). As no health utility value sets are available for Switzerland, the mean utility values for the five major European countries for which health utility value sets are currently available (Denmark, France, Germany, the Netherlands, and the United Kingdom) were used to calculate the exact utility value.

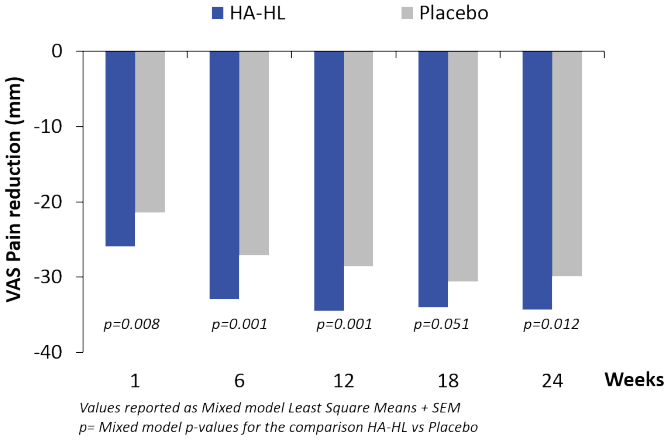

FIGURE 3 - Visual analog scale (VAS) pain reduction in patients with moderate-to-severe symptomatic knee osteoarthritis treated with a single dose of an innovative intra-articular injection of high- and low-molecular-weight hyaluronic acid (HA-HL). A repeated measures mixed-model analysis of covariance that included factors for treatment, baseline, and site (scale of 0—best to 100—worst) was used. Reproduced from Migliore (2021) (CC-BY 4.0 http://creativecommons.org/licenses/by-nc/4.0/) (37)

The ex-factory price of HA-HL in Switzerland, Swiss francs (CHF) 174.48 excluding VAT, was used for the treatment cost. Of note, HA-HL is currently not reimbursed by Swiss compulsory health insurance/compulsory basic health insurance plans. Therefore, its public price is subject to market forces. In Switzerland, the profit margin of physicians or pharmacists can be up to 80% of the ex-factory price but may be as low as around 40%. To deal with uncertainty, it is, therefore, important to incorporate sensitivity analyses into the evaluation, and the following prices were used for the calculation of the 6-month cost of treatment:

1) the total public price ("midpoint"), i.e., the ex-factory price + 40% profit margin + 7.7% VAT = CHF 263.08,
2) the lower limit of public price for sensitivity analysis, i.e., the ex-factory price + 20% profit margin + 7.7% VAT = CHF 225.50, and
3) the upper limit of public price for the sensitivity analysis, i.e., the ex-factory price + 80% profit margin + 7.7% VAT = CHF 338.25.

Although no specific threshold value for the ICERs below which an intervention is considered to be cost-effective is available, a recent review of the literature suggests a value of US $100,000 may be scientifically relevant (38). Therefore, in the analysis, a primary threshold of 91,540 CHF per QALY (corresponding to US $100,000) was considered, with secondary thresholds of 79,423 CHF per QALY (corresponding to the 2020 GDP per capita of Switzerland of 86,601.6 CHF) and 254,307 CHF per QALY (three times the GDP per capita).

When the base-case scenario for the cost of HA-HL was considered, the calculated ICER was 27,860 CHF/QALY gained, which is far below the threshold values of cost-effectiveness (Tab. I). Similar results were obtained using the bootstrap method, with an ICER of 27,212 CHF/QALY (95% confidence interval [CI] 20,135-34,289 CHF/QALY). ICERs of 23,888 and 35,815 CHF/QALY were obtained using the lower and upper limit prices in the calculations, both of which are still below the recommended international intervention thresholds (Tab. 1).

The analysis showed that, using an ICER limit of 50,000 CHF, HA-HL had an acceptable cost-effectiveness ratio compared with placebo in 99% of the cost-effectiveness pairs and was inferior in only 1% of the pairs (data not shown). However, a cost ceiling ratio is important in determining the cost-effectiveness probability of a new intervention, depending on a society's willingness to pay per gain in effectiveness. Thus, a cost-effectiveness acceptability curve for HA-HL can be calculated, given a maximum acceptable ceiling ratio between 80,000 and 90,000 CHF per QALY gained. The calculation showed that the probability that HA-HL is cost-effective compared to placebo was 95% (15).

In summary, the trial-based cost-effectiveness evaluation showed that an i.a. solution of HA-HL is cost-effective from a Swiss healthcare perspective compared to a placebo. The results support and confirm the role of HA-HL as an

TABLE 1 - Incremental cost-effectiveness ratio in patients receiving intra-articular HA-HL or placebo (n = 692)

Parameter	Value
Incremental QALYs per patient	
HA-HL group	0.0580
Placebo group	0.0486
Incremental cost per patient, CHF	
Placebo	0
HA-HL	
Base-case ("midpoint") scenario	263.08
Lower limit	225.50
Upper limit	338.25
ICER, CHF/QALY	
Base-case scenario	
Standard method	27,860
Bootstrapping	27,212 (95% CI 20, 135-34,289)
Lower limit	23,888
Upper limit	35,815

CHF = Swiss francs; CI = confidence interval; HA-HL = high- and low-molecular-weight hyaluronic acid; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.
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important therapeutic option in the management of knee OA, providing cost-effective clinical benefits that persist for at least 6 months.

Limitations and challenges of HTA

The data from the study summarized above indicate that i.a. HA was beneficial both from a clinical and pharmacoeconomic point of view. However, some limitations are worth mentioning, in light of the considerable heterogeneity in methodological approach and the variable quality and reporting standards of economic evaluation studies that limit generalizability (23). For example, the analysis focused on direct medical costs, specifically the cost of the HA-HL treatment, but it did not consider indirect costs such as productivity loss, transportation, or caregiver costs, which are important factors in the overall economic impact of a healthcare intervention. In addition, the study used mean utility values from other European countries to calculate the utility value for Switzerland. This may not accurately reflect the utility values of the Swiss population, potentially introducing bias into the results.

There remain issues with the availability and quality of evidence that forms the basis of health economic research. Research gaps for particular subgroups of patients, heterogeneity of patient populations, the need to incorporate long-term outcomes, and patient-reported outcome measures into health research are all issues that impact health economics research. These aspects are particularly relevant in such a complex, heterogeneous, multifactorial chronic disease as OA. Moreover, while clinical trial design has been refined and formalized over an extended period, designing valid models for economic evaluation is a more recent discipline that is still being established, with substantial diversity in frameworks, methodology, purposes, and roles that represent challenges for decision-makers in deciding the validity of HTA conclusions (36).

There are increasing demands placed on agencies responsible for HTA while at the same time concerns grow over fragmentation of health systems, and inadequate financial resourcing of HTA. Current methods and processes of HTA will continue to evolve to better and more precisely meet the needs of health economics and to effectively engage patients, clinicians, and other stakeholders in HTA processes (39).

Finally, the scarcity of human resources available to conduct HTA has been identified as a challenge and should not be overlooked (39). Investing in initial and ongoing staff training in health economics, collecting and analyzing real-world data, network meta-analysis, and budget impact analysis are both essential and expensive.

Conclusions

HTAs have an increasing role in the decision-making process in OA, as with other diseases, and contribute significantly to establishing quality, efficient, and sustainable healthcare systems able to allocate limited healthcare resources equitably to increasingly complex health technologies. Using the example of a recent clinical trial of an innovative i.a. HA formulation in patients with moderate-to-severe symptomatic knee OA, we have seen how a trial-based economic evaluation can augment the efficacy and safety data collected in a trial to confirm the value of an intervention as a therapeutic option (15). In this case, the value of CHF/QALY of the i.a. HA-HL formulation was substantially below the primary threshold for the ICER for which the intervention was considered to be cost-effective in the Swiss healthcare perspective and remained so when sensitivity analyses were conducted using the lower and upper limit prices in the calculations. A cost-effectiveness acceptability curve provided additional information about the distribution of the ICER estimate, demonstrating a probability of at least 95% that HA-HL was cost-effective compared with placebo over a wide range of values for the maximum acceptable ceiling ratio.

Economic considerations have become essential to inform policymakers tasked with optimizing patient care (23). Analyses able to demonstrate the economic value of advances in the management of a chronic and disabling condition such as OA are essential to ensure healthcare resources efficiently optimize patient care and reduce the considerable individual and socioeconomic burden of the disease.

As a constantly evolving discipline, HTA can be expected to play an increasingly important role in identifying optimal care strategies as key principles, best practice, and common processes for conducting economic analyses to guide resource allocation decisions continue to be developed.

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References

1. Vos T, Lim SS, Abbafati C, et al; GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-1222. CrossRef PubMed
2. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol. 2020;72(2):220-233. CrossRef PubMed
3. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol. 2014; 10(7):437-441. CrossRef PubMed
4. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019;393 (10182):1745-1759. CrossRef PubMed
5. Mobasheri A, Saarakkala S, Finnilä M, et al. Recent advances in understanding the phenotypes of osteoarthritis [version 1; peer review: 2 approved]. F1000Res 2019;8(F1000 Faculty Rev):2091. CrossRef
6. Bruyère O, Cooper C, Arden N, et al. Can we identify patients with high risk of osteoarthritis progression who will respond to treatment? A focus on epidemiology and phenotype of osteoarthritis. Drugs Aging. 2015;32(3):179-187. CrossRef PubMed
7. Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. Ann Phys Rehabil Med. 2016;59(5-6):333-339. CrossRef PubMed
8. Long H, Liu Q, Yin H, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Arthritis Rheumatol. 2022;74(7):1172-1183. CrossRef PubMed
9. Leifer VP, Katz JN, Losina E. The burden of OA-health services and economics. Osteoarthritis Cartilage. 2022;30(1):10-16. CrossRef PubMed
10. Alami S, Boutron I, Desjeux D, et al. Patients' and practitioners' views of knee osteoarthritis and its management: a qualitative interview study. PLoS One. 2011;6(5):e19634. CrossRef PubMed
11. Kaplan RM, Babad YM. Balancing influence between actors in healthcare decision making. BMC Health Serv Res. 2011; 11(1):85. CrossRef PubMed
12. Radinmanesh M, Ebadifard Azar F, Aghaei Hashjin A, Najafi B, Majdzadeh R. A review of appropriate indicators for need-based financial resource allocation in health systems. BMC Health Serv Res. 2021;21(1):674. CrossRef PubMed
13. Li N, Cornelissen D, Silverman S, et al. An updated systematic review of cost-effectiveness analyses of drugs for osteoporosis. PharmacoEconomics. 2021;39(2):181-209. CrossRef PubMed
14. Hiligsmann M, Kanis JA, Compston J, et al. Health technology assessment in osteoporosis. Calcif Tissue Int. 2013;93(1):1-14. CrossRef PubMed
15. Bruyère O, Reginster JY, Honvo G. Health economic evaluation of a high and low molecular weight hyaluronic acid formulation for the treatment of knee osteoarthritis. Post hoc analyses from a randomized clinical trial. Rheumatol Ther. 2022;9(4):1119-1128. CrossRef PubMed
16. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-1589. CrossRef PubMed
17. Bruyère O, Honvo G, Veronese N, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum. 2019;49(3):337-350. CrossRef PubMed
18. Bruyère O, Cooper C, Pelletier JP, et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis–from evidence-based medicine to the real-life setting. Semin Arthritis Rheum. 2016; 45(4)(suppl):S3-S11. CrossRef PubMed
19. Wang CP, Lee WC, Hsieh RL. Effects of repeated co-injections of corticosteroids and hyaluronic acid on knee osteoarthritis: a prospective, double-blind randomized controlled trial. Am J Med. 2022;135(5):641-649. CrossRef PubMed
20. He WW, Kuang MJ, Zhao J, et al. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: a meta-analysis. Int J Surg. 2017;39:95-103. CrossRef PubMed
21. Migliore A, Procopio S. Effectiveness and utility of hyaluronic acid in osteoarthritis. Clin Cases Miner Bone Metab. 2015; 12(1):31-33. CrossRef PubMed
22. Drummond MF, Schwartz JS, Jönsson B, et al. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care. 2008;24(3):244-258. CrossRef PubMed
23. Goodman CS. Introduction to health technology assessment. The Lewin Group; 2004.
24. Dieleman JL, Sadat N, Chang AY, et al; Global Burden of Disease Health Financing Collaborator Network. Trends in future health financing and coverage: future health spending and universal health coverage in 188 countries, 2016-40. Lancet. 2018;391(10132):1783-1798. CrossRef PubMed
25. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-1736. CrossRef PubMed
26. Finch AP, Meregaglia M, Ciani O, Roudijk B, Jommi C. An EQ-5D-5L value set for Italy using videoconferencing interviews and feasibility of a new mode of administration. Soc Sci Med. 2022;292:114519. CrossRef PubMed
27. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. Health Econ. 2018;27(1):7-22. CrossRef PubMed
28. Bouckaert N, Cleemput I, Devriese S, Gerkens S. An EQ-5D-5L value set for Belgium. PharmacoEconom Open. 2022;6(6): 823-836. CrossRef PubMed

29. Ludwig K, Graf von der Schulenburg JM, Greiner W. German value set for the EQ-5D-5L. PharmacoEconomics. 2018;36(6):663-674. CrossRef PubMed
30. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-1840. PubMed
31. Grootendorst P, Marshall D, Pericak D, Bellamy N, Feeny D, Torrance GW. A model to estimate health utilities index mark 3 utility scores from WOMAC index scores in patients with osteoarthritis of the knee. J Rheumatol. 2007;34(3):534-542. PubMed
32. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 4th ed. Oxford University Press; 2015:464.
33. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. Oxford University Press; 2006. CrossRef
34. Sculpher MJ, Pang FS, Manca A, et al. Generalisability in economic evaluation studies in healthcare: a review and case studies. Health Technol Assess. 2004;8(49):iii-iv, 1-192. CrossRef PubMed
35. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ. 2006;15(7):677-687. CrossRef PubMed
36. Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? PharmacoEconomics. 2000;17(5):445-459. CrossRef PubMed
37. Migliore A, Blicharski T, Plebanski R, et al. Knee osteoarthritis pain management with an innovative high and low molecular weight hyaluronic acid formulation (HA-HL): a randomized clinical trial. Rheumatol Ther. 2021;8(4):1617-1636. CrossRef PubMed
38. Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. Glob Health Action. 2018;11(1):1447828. CrossRef PubMed
39. O'Rourke B, Werkö SS, Merlin T, Huang LY, Schuller T. The 'Top 10' challenges for health technology assessment: INAHTA viewpoint. Int J Technol Assess Health Care. 2020;36(1):1-4. CrossRef PubMed