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Identifying stakeholder opinion regarding access to "high-cost medicines": A systematic review of the literature

Review Article

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Abstract: Objective: To identify the viewpoints and perceptions of different stakeholders regarding high cost medicines (HCMs). Methods: A systematic review of the literature was performed to identify original research articles. Using predefined categories, data related to the viewpoints of different stakeholders was systematically extracted and analyzed. Results: Thirty seven original research articles matched the criteria. The main stakeholders identified include physicians, patients, public and health funding authorities. The influence of media and other economic and ethical issues were also identified in the literature. A large number of stakeholders were concerned about lack of access to HCMs. Physicians have difficulty balancing the the rational use of expensive drugs while at the same time acting as "patients' advocate". Patients would like to know about all treatment options, even if they may not be able to afford them. The process and criteria for reimbursement should be transparent and access has to be equitable across patient groups. Conclusion: Access to HCMs could be improved through transparency and involvement of all stakeholders, especially patients and the public. Moral issues and the "rule of rescue" could influence decision-making process significantly. At system level, objectivity is important to ensure that the system is equitable and transparent.

Keywords: *Access to high cost medicines • Physicinas • Patients funders*

1. Background and rationale

Accesses to HCMs, and the issues surrounding this topic, have both economic and social implications. It would seem that public dialogue relating to access to HCMs is dominated by affected patient groups. The views of patient groups are likely to be more emotive in nature [1]. Pharmaceutical companies develop and market high cost medicines (HCMs) and desire relatively unhindered market access and a price that returns investments [2]. The public health care system is the monopsony for buying these medicines; the physicians are the provider of the drug; and the patient is the consumer in this scenario.

Despite the likelihood of tensions between different stakeholder views, there is little consensus about where the funding threshold should lie with respect to individual HCM and which parameters should be used to determine this. The often cited standard for cost-effectiveness is a threshold of $50,000. The British National Institute for Clinical Excellence (NICE) has set a limit of £30,000 per QALY to recommend individual HCM for reimbursement. Fojo and Grady suggest a threshold of $120,090 which equates to the QALY per year costs of renal dialysis [3], which is supported by others [2].

The objective of this review is to inform this discussion on the basis of the analysis of the available evidence. The issues associated with access to HCMs suggest a complex picture with multiple interested parties and the examination of one or two studies is unlikely to provide a comprehensive understanding of what has been published [4]. Additionally, it is not easy to definitively state what constitutes a HCM and the literature is scarce in this regard. A definition is required in-order to place boundaries around this systematic review and to provide context for the synthesis of issues as the primary output of this paper [5].

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The view is adopted that HCMs are as one would expect high cost, but also new, specialized and utilised to a lesser degree due to their cost differential [6]. From a technical perspective, HCMs include the traditional small molecules but increasingly "biologicals" such as; monoclonal antibodies, recombinant enzymes, and cytokines, which are produced using cellular or molecular processes. In theory, there is significant benefit from targeting certain receptors. In reality, many of these medicines are associated with high costs and have modest benefits in defined target populations [7]. In this perspective, a broad search of the literature was undertaken and it was observed that there is not systematic review of the literature on this issue. Through using the MIP (Methodology, Issues, Participants)-Scheme [8], this paper provides the outputs from a systematic review and synthesis of key issues. This review is expected to provide a better understanding of key stakeholder views through a robust research process and inform theory/literature, outline implications of the findings for policy and practice and provide a platform for a future research agenda. The objectives are to determine the viewpoints of stakeholders and present a descriptive analysis and present the main discourse in this area.

2. Methodology

2.1 Search method

The PRISMA guidelines for conducting systematic reviews were followed [9]. The databases searched (by PW) included: Medline (1999-2013), PubMed (1999-2013), Springer Link (1999-2013), Embase(1999-2013), Science Direct (1999-2013) alongside Lancet (1999-2013), Health affairs (1999-2013), health Policy (1999-2013), Cost-effectiveness and resource allocation (1999-2013) and Pharmacoeconomics(1999-2013). A search strategy was developed and executed under the guidance of ZB and a senior medical librarian from the University of Auckland. Keywords included the following: ("Access*" or reimbursement") and ("high cost" or "costly" or "expensive") and ("drugs" or "medicines" or "pharmaceuticals") as well as keywords about the methodology of research: ("Survey" or "interview*") and ("physician*" or "oncologist*" or "practitioner*") or ("patient*") or ("public") or ("decision-maker*" or "health policy maker*" or "health care authority*" or "health care provider") or (stakeholder*). The keywords were combined and adapted to search databases. To ensure optimal coverage, additional articles were found within the reference section of retrieved articles and through citation snowballing wider searches were undertaken.

2.2 Selection of manuscripts and data extraction

The title and abstract of all retrieved articles were reviewed by the lead author (PW). Articles that met the inclusion criteria (Table 1) were retrieved and examined more closely in conjunction with ZB. The quality of research papers was evaluated according to adequate description of the theoretical framework, background and methodology [10].

• Survey response rate and participant type were examined for comparability with the target population. The use of descriptive versus inferential statistics was con-

Table 1. Selection and sorting criteria for studies.

No	Category	Criteria
1	Year of release	1999-2013
2	Countries covered	Deals about a developed or high-income countries with publicly funded health system and ability to afford funding
3	Kinds of medicines	High cost general, biological , targeted cancer medicines
4	Definition and issues to include	High cost medicines; target, specialized therapies, orphan drugs, biologicals : • Access and usage • Reimbursement, payment • Off label use • Orphan medicines • Willingness to pay
5	Methodology and topic of research	survey (quantitative), interviews (qualitative) about: Patients: willingness to pay, information, attitudes, patient-physician communication about high cost medicines (patient side) Physicians: attitudes to cost, attitudes to health politics, patient-physician communication about high cost medicines (physician side) Public, society: attitudes, information, willingness to pay Health policy decision-makers: criteria, attitudes statistics (always quantitative) different outcomes
6	Source of publicity	Peer review journal
7	Language	English, German

sidered alongside statistical control measures such as p-values.

Interviews were categorised by the type of interviews (structured, semi-structured, etc.), the examined population and the usage of findings from quantitative research were used to "test" qualitative findings.

For those papers that fulfilled the criteria for quality, a modified template based on the work of Willman and Stoltz was used to abstract important information [11]. The form was tested using a sample of studies before full data extraction was initiated. Data collected on individual papers included: author, objective, study site, dates of data collection or publication, research methods, collected data and outcome measures (see Appendix).

2.3 From systematic review to synthesis

The purpose of undertaking a systematic review was to ensure that the narrative synthesis generated was based on a body of literature which was sourced in the most robust way possible. Papers were sorted by stakeholder groups including patients, public, health-policy decision-maker and physicians. Stakeholders were defined in this review through application of the definition of Lu as "individuals or groups of people have the potential to influence the decisions on the access s" [12]. Decision-makers are heterogeneous group consisting of health policy makers, insurance managers, committee members, hospital managers and others. However, they all have similar perspectives when deciding about population-based treatment.

Subgroups were generated through issue identification and labelling. When no new categories were generated for the subgroups, saturation was deemed to be reached [11]. The sorted categories enabled a comparison to be made between the views and expectations of the stakeholder groupings on issues regarding access. After extracting the information, a narrative synthesis was performed [11,13]. Synthesis of the studies was performed to examine the perspective and experiences of different stakeholders.

3. Results

3.1 Search outputs

7402 papers were retrieved (Table 2) and 5975 (80%) were excluded due to being duplicates or not being focussed on access to HCM (Figure 1). Of the remaining 1427 articles, 72 articles were selected for review by two authors (PW, ZB) following the criteria in Table 1.

Table 2. Number of search results in databases (similar expressions were adapted for different databases) 21.05.2013.

DATABASES	("Access*" or reimbursement") and ("high cost" or "costly" or "expensive") and ("drugs" or "medicines" or "pharmaceuticals")	"Access" and "high cost medicines" and "cancer"	("access*" or reimbursement") and ("drug*" or "medicine*" or "pharmaceutical*")	("Survey" or "interview*") and (("physician*" or "oncologist*" or "practitioner*")) or ("patient*") or ("public") or ("decision-maker*" or "health policy maker*" or "health care authorit*" or "health care provider") or (stakeholder*))	("Survey" or interview*") and ("access*" or reimbursement")
Medline	554	64		313 + ("Access*" or reimbursement") and ("high cost" or "costly" or "expensive")	310 + ("high cost" or "costly" or "expensive") and ("drug*" or "medicine*" or "pharmaceutical*")
Pubmed	1178	49		148 + (("Access*" or reimbursement") and ("drug*" or "medicine*" or "pharmaceutical*"))	134 + ("high cost" or "costly" or "expensive") and ("drug*" or "medicine*" or "pharmaceutical*")
Science Direct/Embase	341			96 + (("Access*" or reimbursement") and ("drug*" or "medicine*" or "pharmaceutical*"))	27 + ("high cost" or "costly" or "expensive") and ("drug*" or "medicine*" or "pharmaceutical*")
Google scholar	2860				
SpringerLinks	467				
Journals					
Lancet	8		84		29
Health Affairs	83				197
Pharmaeconomics	36				21
Health Policy					202
Cost-effectiveness and resource allocation	94				107

From this cohort, 37 papers were selected for synthesis [12,14-50]. In five cases, two different publications described the same patient population and were counted as one study [12,14,23,25,30,32,34,40,46,48].

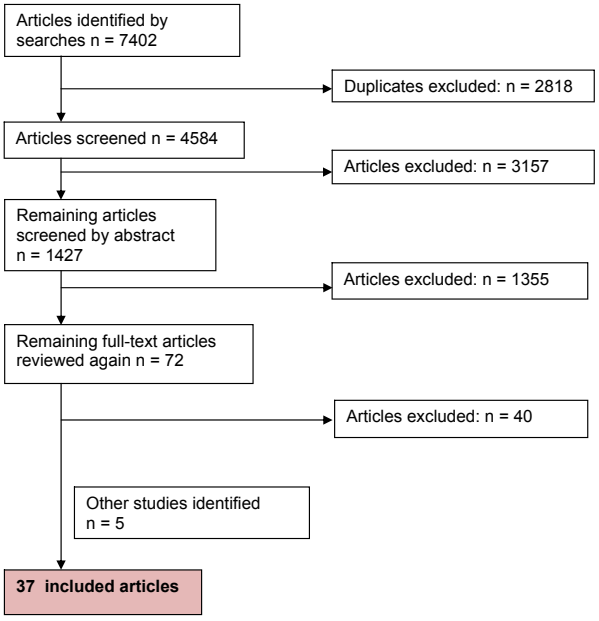

Figure 1. Literature selection flow diagram [1].

3.2 Viewpoints of stakeholders

Table 3 outlines the different categories of papers and the findings with respect to the viewpoints of each stakeholder group, while Table 4, 5 and 6 indicate quantitative survey results for patients, physicians and the public.

3.2.1 Patients- the consumers

Health policy

The review highlights that patients fear restrictions to HCMs, especially if the process is too complicated (e.g. requirement to test multiple laboratory parameters) or if there is a perceived lack of transparency.

Table 4. Patients' opinion on access to high cost drugs.

Item	Agree
The most important criteria to value a drug was efficiency [29]	85%
Preference to do shared decision-making about treatment decisions [29]	59%
Preference to decide independently [29]	28%
Patients would discuss their financial circumstances with their oncologist [29]	89%
Patients feel comfortable talking about the cost of cancer care with the physician [17]	76%
Patients consider their out-of-pocket costs for decisions about cancer treatment [17]	24%
Patients consider the costs for the society for decisions about cancer treatment [17]	17%

Table 3. Number of papers representing viewpoints of different stakeholders.

	Patients	Public	Physicians	Decision-makers
Quantitative Research (Survey)	2 [17,49]	5 [19,37,42,16,22]	10 [47,39,40,14,35,44,20,30,48,18]	1 [36]
Qualitative Research (Interviews)	5 [12,29,31,32,43]	1 [31]	5 [6,12,15,21,28,32]	9 [6,12,23-25,32,36,38,43,45,46]
Others (Media reports)	1 [26]	3 [33,27,41]		
Sum	9	9	15	10

Table 6. Publics' opinions on access to high cost drugs

Item	Agree
Preference of the plan with high out of pocket costs compared to specialty drug coverage by same costs of coverage [42]	22 %
Reimbursement of high cost interventions which are safe and effective regardless the costs [16]	64 %
Limiting access to new high cost interventions [16]	32%
Support of reimbursement decisions by comparative effectiveness consideration [16]	63%
Support of reimbursement decisions by cost-effectivness considerations [16]	32%
Support of a government decision-making body which recommend drugs to reimbursement agency by considering their costs [16]	57%
Willingness to be informed about high cost drugs [37]	91%
Higher willingness-to-pay, if the drug improves quality of life [37]	71%
Higher willingness-to-pay, if there isn't any effective standard treatment [37]	76%
Willingness to be informed about expensive drugs, which improve survival options in cancer even if they don't want to pay or aren't able to pay [37]	91%
Willingness to be informed about a new drug with a gain in quality of life, even if they don't want to pay or aren't able to pay for it [37]	97%
Willingness to be informed about a drug without a standard treatment option, even if they don't want to pay or aren't able to pay for it [37]	96%
The government should pay for expensive treatment options [37]	68%
Patients could obtain the drug by asking health care insurance [37]	21%
Equal access to health care for all patients regardless the costs [22]	Mean 4.5 of 5
Health authorities should provide the greatest possible health benefit with limited resources [22]	Mean 3.9 of 5

Table 5. Physicians' opinions on access to high cost drugs.

Item	Agree
Opinions on funding decisions and policies	
Feeling of inconsistency in funding condition between different Primary Care Trust (PCT) districts in the UK [35]	54%
It is easier to obtain specialised medicines (Bortezomib) for private patients in the UK [35]	88%
The role of medicines costs (for new drugs) will increase in the next 5 years in the US [39]	67%
Greater rationing is needed because of these costs [39]	71%
Decisions about value of drugs by the government aren't trusted [14]	79% US, 64% Canadian
Decisions about value of drugs by insurance companies aren't trusted [14]	94% US, 89% Canadian
Decisions about value of drugs by physicians are trusted [14]	60% US, 64% Canadian
Decisions about value of drugs by non-profit organisations are trusted [14]	57% US, 73% Canadian
Feeling of responsibility in using healthcare resources [44]	60%
Physicians would prescribe a high cost drug, if it is subsidized [47,20]	73-99% (NZ), 72-94% (AUS) (depending on scenario)
Desire for governmental price controls and other interventions [14]	57% US, 68% Canadian
Patients should pay a bigger part of high cost medicines [14]	29% US, 41% Canadian
Opinions on the role of cost-effectiveness	
Patients should have free access to "effective" drugs, (independently of their costs) [39]	78%
The "right" threshold is between 50,000 and 100,000$ per QALY [14,15]	49% US, 56% Canadian
Patients should have free access to "effective" treatment regardless of the costs [14,15]	67% US, 52% Canadian
Physicians would consider cost-effectiveness in their treatment decisions [44]	66%
Physicians would prefer to use more cost-effectiveness data in the decision-making process [14]	80% US, 69% Canadian
Physicians don't feel able to use cost-effectiveness data [14]	42% US, 49% Canadian
Opinions on communication towards patients about high cost drugs	
Uncomfortable to discuss drug costs with patients [44]	31%
Knowledge of physicians about the financial status of their patients at some point in time [44]	87%
Feeling of responsibility for the patients' financial well-being [44]	86%
Patients' finances are important regarding treatment decisions [44]	80%
Physicians would discuss costs, if asked by the patient [44]	86%
Physicians would discuss costs, if they expect them as a factor in the treatment decision [44]	71%
Physicians discuss costs of chemotherapy with their patients [44]	42%
Physicians frequently discuss these issues with their patients [14]	43% US, 48% CAN
US oncologists consider patients' out-of-pocket drug costs in their recommendations [39]	81%
US oncologists and Canadian oncologists stated the same in a survey of Neumann [40]	84% Us, 80% Canadian
Physicians would not discuss expensive drug options [20]	6,4-11,1%
Physicians would not omit a high cost drug option, if it is not funded [47]	28% - 41% (depending on scenario)
Uncomfortable feeling to discuss drug costs with patients [44]	31%
Knowledge of physicians about the financial status of their patients at some point in time [44]	87%
Feeling of responsibility for the patients' financial well-being [44]	86%
Patients' finances are important regarding treatment decisions [44]	80%
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Physicians would not omit a high cost drug option, if it is not funded [47]	28% - 41%
Uncomfortable feeling to discuss drug costs with patients [44]	31%
Knowledge of physicians about the financial status of their patients at some point in time [44]	87%
Patients' awareness of treatment costs is important [44]	72%
Influence in recommendations by the costs of new drugs [39]	30%
No influence in their treatment decisions by costs of drugs [44]	20%

For example, patients who suffer from rheumatoid arthritis (RA) may not tell their physicians about infections caused by the immunosuppressive effects of RA biological. This because they fear their treatment might be discontinued.

Patients desire fair and equal decision-making processes developed in conjunction with patient and public input [43]. If there is no opportunity to participate in decision-making processes, patient groups can initiate media campaigns [43]. However, the literature suggest the gaps in patients' knowledge about the funding and decision-making process [29].

Treatment costs

In a setting of limited resources and restricted funding, costs of treatment and information about treatment options are two significant concerns for patients with regards to access to HCM. There is evidence to suggest that demand for medicines to treat life-threatening illness is very high regardless of cost [26,29].Survival gain, or gain in quality of life seems to justify even higher cost; at least from the patient perspective. Inequalities regarding willingness-to-pay are related to the financial status of the patient. The willingness-to-pay for treatments also increases with perceived clinical benefits and patients do not appear to have an "any treatment at all cost" mentality even in the setting of cancer treatment. An example is that patients who had experienced high treatment costs in previous courses of treatment were less willing to pay for HCM as part of subsequent therapy options [49].

Patient-physician relationship

Patients would like to be informed about all possible treatment options, even if they cannot afford them. There is a level of disagreement with medical paternalism; the notion that the doctor will consider what is best for patients [29]. Out-of-pocket costs for patients may influence the information and recommendations provided about treatment options by doctors [28]. It is generally accepted that physicians want to protect their patients against stressful situations, particularly expensive treatment options which may be deemed unaffordable. As a result, medical paternalism can lead to lower levels of usage of high-cost cancer medicines; resulting in potential ethical issues [20]. These situations cause patient considerable distress, because the best decision may not have been made for them and they may feel neither respected nor represented [29].

3.2.2 Physicians- the providers

Health policy

The literature suggests that physicians see limiting access to HCM as a vital way to contain costs. However, some report the need for autonomy in their treatment decisions and are unwilling to accept restrictions imposed by governments and health authorities and will resist or find ways to overcome these restrictions [15]. Physicians - in their role as patient advocates - would like politicians to take responsibility for funding decisions [28,43]. Physicians saw the need to have "direct consumer representation in an open and transparent process" [12].

Patient-physician relationship

Physicians have been reported to discuss drug costs with patients [14,15,21,44]. The willingness to do so is dependent on the level of reimbursement of medicines within the health care system. Patients and physicians from health systems with predominantly unfunded medicines are more likely to discuss costs. Physicians who work in environments with high patient co-payments are also more likely to discuss these payments. Further, the higher the level of funding within a health system, the greater the expectation that HCM will be subsidised. This suggests that communication between doctor and patient is likely to be dependent on health care funding mechanisms. It becomes more difficult therefore to discuss these issues with patients in light of the fact that specific HCM medications may not be funded. In one US study, 84% of oncologists would mention treatment options to patients, even if they thought that the patient could not afford them [44]. In the context of that study, oncologists felt prepared to discuss all possible treatment options due to the fact that "out of pocket" co-payments made by patients were commonplace. The fact that physicians may not be easily able to manage conversations relating to the funding of HCM may also influence whether the subject is being mentioned. Alternative options for the patients are shift to cheaper, older drugs or drugs with different reimbursement characteristics [28].

3.2.3 Cost-effectiveness and social responsibility

There is a school of thought that believe drug costs should not play a major role in influencing decision making for individual patient care [28]. Physicians who agree a reasonable cost-effectiveness threshold often ignore this threshold when deciding about therapy for an individual patient [48]. Their view is that the relationship with the patient potentially biases an objective approach [21]. Further, the feeling of social responsibility to advocate for the benefit of society increases when there is the opportunity to discuss drug costs with patients [44]. This shows the potential for conflict and tension between societal responsibility and the well-being of individual patients. In some countries, the

costs to the health care system are more relevant to physicians than the costs for patients [28]. Physicians' preferences for certain treatment benefits can be different from health economic considerations. Conditions that are chronic and not life threatening can lead to different conclusions about cost issues [28,30] and life-prolonging treatments to higher cost-effectiveness thresholds [30]. The body of literature supports physicians' opinions that it is appropriate to use cost-effectiveness data to make treatment decisions involving HCM [14,44]. Still, physicians are not consistent in using treatment options which exceed a certain cost-effectiveness threshold which they defined as reasonable [30,48]. Overall, the viewpoint of physicians is not clear and is influenced by individual patients and rational as well as emotional considerations.

3.2.4 Public – the taxpayers view

The public's view of the about HCM access suggests a high level of emotional involvement [27,33]. On the one hand, people may agree to the need for containing high costs of public health care spending and realise and accept the need to limit health care service utilisation. Societal preferences do not value rarity of a certain illness with high treatment costs per se [22].On the other hand, identifying which specific patient groups can lead to an emotional demand of the public for funding of certain pharmaceuticals is also a challenge [33]. In the Australia, 68% of public respondents believe that the Government should pay for HCM [37].

An international four country survey confirms these findings and highlights the favour of the public for comparative effectiveness instead of cost-benefit in decisions about HCMs [16]. The Australian public also wants to remain informed about expensive and unfunded therapies. There is strong support for government funding of HCM [16] with the publics' willingness-to-pay often being limited dependent on socio-economic status of the individual pateints [37]. However, the WTP for generous coverage is higher in lower-income respondents. However, it is interesting to note that the WTP for drug coverage decreases with improvements in self-reported health [42].

3.2.5 Health-policy decision-makers - the insurers and the government

In literature it was observed that the policy-makers are involved from wide stakeholder groupings. This included both macro and micro level. Macro level includes national, while micro include physicians, formulary pharmacists, representatives of government, hospital executives, ethicists, administrators and pharmacy managers [24,43]. Table 7 highlights the composition of different decision-making bodies. A step toward equitable access could be achieved by involving multiple stakeholders, especially the public in the decision-making process [43]. A key element is a selected group of community and patient representatives [43].This leads to increased legitimacy and transparency of the funding process [12,24].

There is the belief that ideal decision-making processes have to be transparent, consistent and utilitarian [24,38,46]. Some decision-making committees explicitly state their decision-criteria, as an example can be seen in Table 8. Efficiency and clinical benefit are also considered to be important aspects of the decision making process. Simple cost arguments are often more convincing than complex questions of cost-effectiveness. The "rule of rescue" which implies help through whatever means no matter the cost, plays a role in these decisions, especially at the individual patient level. Survival gain can be an important criterion

Table 7. Stakeholder in different decsion-making bodies.

Decision-making body	Country	Professions
Hospital executive management [25]	Australia	Executive directors, area health service managers, directors of hospital pharmacy departments and professors of medicines
Pharmaceutical benefits advisory committee (PBAC) [6,12]	Australia	Clinical experts, health economists, academics, a consumer representative
Different pharmaceutical and therapeutics (P&T) committees [36]	Canada	31-60% physicians, 17-25% pharmacists and 6-30% administrators
Expert Drug Advisory Committee [43]	Canada	Health professionals, public representatives
The Alberta Cancer Board's P&T committee [45]	Canada	Senior oncologists and non-physician like representatives from the provincial ministry of health
Israeli Basket Committee [43]	Israel	Representatives from ministry of health and ministry of finance, health economics, hospital manager, public representatives, ethicist, lawyers, health professionals
National Institute for Health and Clinical Excellence, Technology Appraisal committee [43]	UK	Health care administrators, patient representatives, academics, industry representatives
US State Medicaid Pharmacy Policy Committee [43]	US	Health care administrators, members of the Drug Utilization Review, e.g. pharmacists, physicians

Table 8. Criteria of different authorities.

Authority	Criteria
The Cancer Care Ontario Policy Advisory Committee [34]	1. Clinical benefit like survival and higher quality of life are expanded to 2. Evidence criteria like tumour shrinkage or reduction in toxicity. 3. Rarely used cost effectiveness analysis in
First high cost drug committee in an Australian Hospital [24]	1. Effectiveness, costs and budgetary impact 2. Lack of alternative treatment and the kind of benefit
Diverse decision-makers (executive directors, area health service managers, directors of hospital pharmacy departments and professors of medicines) [25]	1. Efficiency, safety, effectiveness and costs. 2. Quality of life, clinical need, and the lack of alternative treatments. 3. Cost-effectiveness
P&T committees in Canada [36]	1. Pharmacological data (4.5 of 5) 2. Comparisons to existing therapies regarding their availability and effect (4.3 of 5) 3. Information about impact in the budget (4.0 of 5) and patient preferences (3.2 of 5)

for policy-makers; even for short periods of time e.g. two months [45]. Internal frameworks and personal values of decision-makers have been reported to be in contrast with decision criteria. This may influence the approach by decision-makers (or policy-makers) to equality; for example between the needs of a young mother versus an older man [45].

Decision-makers have stated concerns about the equality and transparency of the funding process, especially for patients having public and private insurance. Evidence suggests that equity of access to HCM amongst different patient groups, particularly of biologicals is difficult. These issues relating to why one patient group is seen as more important than another and how decisions with respect to which medicines should be available to each patient, is being raised in this dialogue [24].

It has been reported that physicians want to be more flexible in their decisions, but this is very difficult because small changes can have significant implications for budgets [12]. The pharmaceutical industry has been described as highly strategic in using marketing to achieve their aims [25]. In some contexts, the pharmaceutical industry and representative governments have implemented innovative risk-sharing agreements to help to resolve the fiscal issues associated with sourcing HCMs. Some researchers see benefits in these agreements as they are regarded effective as a cost-containment measure [13,38].

4. Discussion

Of the 37 papers analysed, most of the evidence originates from countries where cost-effectiveness approaches are already in use. These countries include the UK, Canada and Australia. Five themes were generated from the review. These themes are transparency, equality, information, media influence and ethical frameworks.

4.1 Transparency of process and criteria for funding of HCM

The review suggests that for benefit of physicians, patients and other key stakeholders, there is a need to ensure that processes related to decision-making are transparent. Transparency can be maximised through involvement of multiple stakeholders in the different phases of decision making [43]. Industry stakeholders may not necessarily be part of this. Levels of mistrust with the process will decrease through improved transparency and legitimacy. Physicians are more likely to accept restricted access and rationing if the decisions are legitimate and fair [12]. Daniels suggests "transparency regarding decisions which meet health needs fairly [51]."

4.2 Equity regarding access to HCM

The evidence suggests that collaboration between stakeholders in the decision-making process leads to greater levels of equity [12,24]. Inequity could be a result of restricted access to HCM in a number of ways and at different levels [25]. At physician level, the limitation of prescribing rights could lead to inequity, while in hospitals, budget pressures may lead to similar situation. The scenarios, where the majority of HCMs are not subsidized leads to inequalities between more and less wealthy patients. The issue seems vital across all stakeholder groups in the studies reviewed [12,14,24,25,29,37,39]. Children and older adults need special care and equality is important in the context of saving lives or improving the quality of life of vulnerable or disadvantaged groups.

4.2.1. The importance of education for managing processes and expectations

Education of physicians and patients is crucial for better understanding and acceptance of decision making processes. Lack of knowledge about the funding process

and the political decisions are reasons for uncertainty among patients and public. This results in feelings of unfairness and the perception that the decision-making process is not fair. Such issues can be addressed by educating public and patients and consumer organisations and health professionals such as pharmacists can support patients' education [12]. In this context, decision-makers should provide clearer information about the funding process. When the state rather than the patients are paying for HCMs, patients behave differently [52]. Another option is to educate physicians on how to communicate access restrictions with patients. The physicians are uncertain that how they should talk to patients about HCMs, especially if they are unsubsidized. Another part of physicians' education is the need to support them in better interpretation of cost-effectiveness data, as many physicians lack knowledge regarding economics issues.

4.2.2. Lobbying and the importance of voice

The media is an important platform used to debate HCM funding by patient advocacy groups, physicians, funding and regulatory authorities and the pharmaceutical industry. It is important to note that most of the recent media commentary and ethical debate regarding funding of HCM and the analysis thereof, appears to be related to cancer therapies, and more specifically regarding Herceptin®(Trastuzumab) [21,27,33,47,53].

The ability of some patient groups to attract attention may potentially influence the objectivity of the decision-making process and may lead to uneven distribution of funding. There is evidence that pharmaceutical companies may lend support to these patient groups [54,55]. In addition, some patient groups may not be as vocal as others. However, this should not imply that their cause is less important than others. Open access to HCMs to "rescue" people is reported as a popular way of decision-making by politicians. However it could be argued that investments in prevention need the same attention as financial resources could be used in a more efficient manner.

4.2.3. Ethical frames: the influence of values in decision making

Medical paternalism and willingness-to-pay are two main issues which contributes towards the issue of high cost medicines [20,31,37,40,44,47,49]. The willingness-to -pay for medicines for life-threatening illnesses such as cancer is very high among all patient groups [29]. Physicians are in a difficult position as they have to decide resource allocation between two different groups of patients. There are identifiable patients, who sit in front of physicians where a personal patient-doctor relationship may have developed and then on the other hand, there are anonymous faceless patients, who could probably benefit through better allocation of resources [56]. In general, it is accepted that physicians empathize with their patients and want the best for them, even if they know that these resources could be better used elsewhere. This is Jonsen's "rule of rescue": an imperative to help individuals "facing avoidable death", even if the helper knows about the associated high costs in the context of limited resources [57]. The "rule of rescue", is underpinned by the mantra "to help at all cost". This rule influences decisions even in non-life-threatening situations [58]. The results of this review suggest that the physicians may not be able to combine social responsibility for high cost treatments with their role as patients' advocate.

Hence the best possible scenario may be to have a societal agreement; a collective solution for society (patients and citizens) to address rationing issues and the decision-making process associated with this. In short, it is vital to have all stakeholders engaged before allocating medical resources [43,59].

The "rule of rescue" also influences public discourse and policy makers' decisions about fair and reasonable access to HCMs [33]. It has been shown that the individual case studies on media could have greater impact on decision-making rather than the presentation of facts and statistical data [60]. People place the treatment of illness at a higher value. Decision-making process is also influenced by identifiable and non-identifiable patients. Identifiable patients, who can be helped, are more visible and gain attention.

Hope [56] provides following reasons for paying more resources to save life (per life year saved) for "rescue interventions" rather than for preventive strategies. Scepticism about the effectiveness of preventive treatment

- A life in the hand is worth two in the bush
- Rescue is rare, so we can always afford it
- Rescue has more effect on quality of life than prevention
- It is good to care about identifiable individuals

Nevertheless, Hope rejects all of the above mentioned notions and argues for the same threshold for rescue treatments as for preventive interventions [56]. However, other evidence suggests that taking the "rule of rescue" into account increases people's well-being [57], though, this opinion misses the issue of fairness.

The use of equal thresholds (based on utilitarian rationality) and the rule of rescue build a strong contrast at several levels. This is evident from Figure 2. A solution could be adoption of decision tools like multi-criteria decision analysis (MCDA). MCDA take different stakehold-

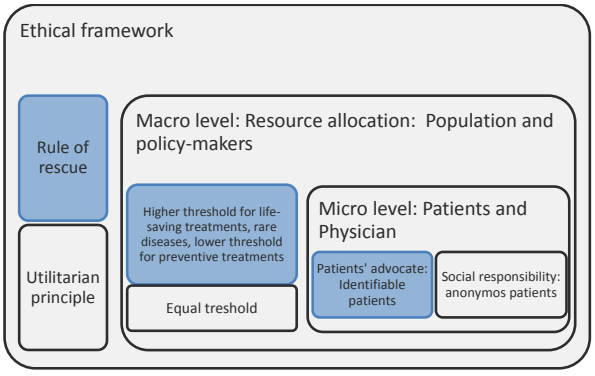

Figure 2. Viewpoints on access to high cost drugs (grey = rule of rescue, white = ulitarian prinziple).

ers' preferences into account by separating the evaluation of decision criteria and the evidence about health technologies [61]. Different stakeholder groups can participate in the MCDA decision process and thus improve the communication in a systematic manner. This is also suggested by Daniel's concept of "accountability for reasonable" [51]. Daniel argues that the ddecisions and criteria regarding funding allocations should be accessible to public. Daniels and Sabin believe that requiring the involvement of the public will develop public confidence and would further enhance the view that the decisions are made for ethical and not for self-interested reasons [62].

4.3. Limitations of the paper

Despite the contribution that this paper makes in terms of understanding a body of literature, there are limitations and the findings need to be considered in light of these. When identifying the funders of research papers, it is possible that certain results may have led to bias with or without awareness. Publication and outcome reporting bias may have led to underrepresentation of negative, uninteresting or unwanted results. The results, which are reported in journal articles, could be systematically different from those presented in the grey literature, which has not been included in the review [63]. Despite these limitations, this work covered a broad literature base regarding access to HCMs, and contributes significantly to the literature in this field. The included studies did not examine the perspective of the industry. Generally, they are not seen as necessary participants in resource allocation decisions as they are the main providers of information to the committees [43]. Thus, they already contribute to decisions by providing the underlying evidence.

4.4. Implications for future research

Further work is required to explore influences on objectivity. It would be of benefit, if the viewpoints of physicians and barriers to access at several levels could be explored at different level. It is important to consider new decision-making tools to decide about funding modalities of HCMs. Also, this review raises the question whether cost-sharing is the right way to address budget limitations, because patients still want these medicines, even if they have to share the cost of medicines.

5. Conclusion

There is some consensus amongst stakeholders that access to HCMs could be improved through better transparency and involvement of all stakeholders in the decision making process, especially patients and the public. Hence public involvement in general is encouraged. Moral issues and the "rule of rescue" could influence decision-making process significantly. At micro level, the patient-physician communication is negatively affected by high cost of some medicines. It's challenging for physicians to make decisions about new expensive medicines while on the other hand they have to act as communicators and patient advocates. Education of physicians about usage of cost-effectiveness data, as well as education of patients about the decision-making process could be the part of the solution.

At system level, objectivity of the funding process is important to ensure that the system is equitable. Decision-makers and politicians' view may be influenced because of the emotive nature of the issue and by pressure of lobbying groups. Health care authorities should take responsibility for funding allocation and this should not be left alone for physicians to decide regarding rationing of HCMs.

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Conflict of interest statement

Authors state no conflict of interest.

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Appendix

General characteristics of included studies.

Study (first authors' name)	Study Site(s), Year	Research methods, collected data	Objective of paper	Outcome measure
Berry [15]	Canada, 2007	Semi structured, on depth interviews with 46 oncologists in Ontario. Each interview was continued until themes were "saturated", issues were sorted in different categories	Description of the medical oncologists' perceptions of how priority setting decisions for new cancer drugs affected their practice	Answers of specific questions were sorted into different categories
Berry [14], Ubel [48]	US, Canada, 2010	Survey was sent to 1355 members of American Society of Clinical Oncology (788 respondends, 57%) and to 238 oncologists in Canada (158 respondents, 65%) about attitude of oncologists about cancer costs and cost-effectiveness of treatments	Compare attitude of oncologists about costs, value and treatment decisions about new expensive drugs and cost-efectivness thresholds	Survey results of oncologists' views, cost-effectivness tresholds based on survey results
Blendon [16]	Germany, Italy, UK, USA 2013	Telephone survey with 2517 adults in the four countries	To compare and assess public opinions about limiting high cost drug/surgical interventions	Support for different scenarios about comparative effectivness decision-making, coverage decisions and government decision-making
Bullock [17]	US, 2010	Survey of oncology patients(771 patients, 256 responded, response rate: 33%)	To measure oncology patients' communication preferences regarding the cost of cancer care, focusing on out-of-pocket costs	Qualitative and quantitative answers about out-of-pocket costs, medicne use and communication with the physician
Chan [18]	Canada, 2012	Survey of onclogists (68 of 164 respondents, 41.4% response rate)	To examine the perspective of onologists about barriers to new expensive drugs, the drug approval and funding processes	Oncologists' view on drug access, approval, funding and co-payments
Chao [19]	USA, 2007	Survey data from two studies (Asset and Health Dynamics Among the Oldest Old study and the Health and Retirement study), this data was statistically analyzed about treatment recommendation about expensive cancer drugs	To analyze how elderly and near elderly adults assess hypothetical EOL treatment choices under different survival chances and out-of-pocket treatment costs	Percent measure about treatment recommendation in different survival and payment settings
Cohen [50]	USA, 2009	Survey of third-party payers about off-label use reimbursement, 34 of 179 survey respondents	Examination of off-label use reimbursement policies	Results of questionnaire about the reimbursement of off-label indications and about the important criteria/ data source for decision

Study (first authors' name)	Study Site(s), Year	Research methods, collected data	Objective of paper	Outcome measure
Dare [20]	New Zealand, 2010	Survey to the 117 New Zealand practicing medical oncologists about 3 cases of expensive treatment decisions	To examine medical paternalism in informing patients about expensive unsubsidised drugs	Survey questions about 3 different cases. The drugs are different with different benefit and costs
De Kort [21]	Netherlands, 2007	Interview of 36 physicians (oncologists, general physicians and physicians involved in guideline development of Dutch Institute for Healthcare Improvement (CBO) and a national medical oncology committee (BMO)) with open questions	How do physician in the Netherlands view their role regarding the cost of potentially beneficial disease-modifying treatments in advanced cancer	Interview results were sorted by two categories about the cost considerations of expensive chemotherapies and about the level of decision-making in cost consideration
Desser [22]	Norway, 2010	Online survey of a random sample (1547 members of the public)	To assess the societal preferences on the treatment of rare versus common diseases	Participitans had to decision about treatment coverage in different scenarios (1. Equal costs for rare and common disease, 2. More costly for rare disease)
Gallego [24]	Australia, 2007	In-dept interview of all 5 members of a High Cost Drug Sub – Committee (HCD-SC) in an Australian hospital. Questions about their role, the process and problems about high cost drugs	Description of the first reported High Cost Drug Sub-Committee in a public hospital in Australia and evaluation of the decision-making process	Interview results were sorted into categories about the roles of stakeholders and the ethical framework "accountability for reasonableness", adapted from Daniel and Sabin
Gallego [23,25]	Australia, 2009	In-dept interview of 24 different kinds of decision makers (directors, manager, senior medical doctors), data was analysed using the grounded theory approach	To investigate the perceptions and concerns of decision-makers regarding access to high cost medicines (HCMs) in public hospitals	Answers of specific questions were sorted into different categories, based on the grounded theory
Goldman [26]	USA, 2010	Economic analysis of the demand among patients regarding their out-of-pocket costs, 71 private health plans covered approximated 10.8 million beneficiary years from 1997 to 2005, focused on 5 drugs: Bevacizumab, Trastuzumab, Rituximab, Erlotinib, Imatinib mesylate)	To examine willingness-to-pay for costly cancer drugs and consumer surplus	Statistics about private health plans converted into a formula to estimate demand elasticity and willingness-to-pay in Dollar
Hind [27]	UK, 2010	Statistical Content analysis of newspaper articles between 2005 and 2006 about expectations and access to Trastuzumab, data were sorted in different categories	Evaluation UK press coverage of pre-licensing access to Trastuzumab (Herceptin)	Statistical data about how newspapers report about Trastuzumab and the access to it
Huttin [28]	France, 2000	4 focus groups discussions with 29 general practicioners in total about four different case studies about different indications (Mild hypertension, dyspepsia, Hayfever, hormone replacement therapy)	To explore how the economic/ insurance status of a patients influence the physician's treatment decison	Physicians' treatment strategies regarding patient's out-of-pocket costs
Kaser [29]	Australia, 2010	E-mal invitation to members of Breast Cancer Network Australia, 47 participants in telephone interviews based of a questionnaire about HCD options	Determine cancer patients' experience and attitudes regarding HCDs	Interview answers
Leighl [31]	Canada, 2005	Structured interview of Cancer patients and healthy participants, demographic data and willingness-to-pay was obtained	To assess the utility of a targeted cancer treatment in cancer patients and healthy participants	Willingness-to-pay and demographic factors
Lu [12,32]	Australia, 2007	Semi-structured interviews of relevant stakeholders which took part in the access process of biological, answers were collected data	Examination of the perceptions and experiences of stakeholders with respect to access to high-cost medicines (anti-rheumatic biologicals) under Australia's PBS	Interview answers, sorted in different topics : resource rationing, excessive bureaucracy, partnerships and inclusive decision-making, education and review
MacKenzie [33]	Australia, 2006	Analyzing news frames in television, mentioning Herceptin between May 2005 and October 2006, these were sorted in different topics	Examine how Australian television media influence drug funding decision	Amount of topics and statements in television about access to Herceptin

Study (first authors' name)	Study Site(s), Year	Research methods, collected data	Objective of paper	Outcome measure
Mehta [35]	UK, 2007	Case study and questionnaire survey of 51 haematologists form Myeloma UK database	Examine different treatment options for private and NHS patients regarding expensive cancer drugs	Survey results about denied and accepted funding
Mileshkin [37]	Australia, 2009	Telephone survey of random selected people about 3 different drugs, their, statistical analysis of this data	Determination of the views of the general public about being informed of EACDs in order to help inform clinical practice and improve discussions about EACDs	Willingness-to-be-informed and willingness-to-pay
Morgan [38]	Canada, 2010	Telephone interviews (24 participants), online survey (82 respondents), deliberative workshop (30 participants)	To identify priorities for pharmaceutical policy issues in the Canadian setting	Identification and description of certain pharmaceutical policy issues
Nadler [39]	USA, 2006	E-mail distributed survey to 139 clinical oncologists about costs, value and treatment decisions of new drugs	Attitude of practicing oncologists about costs, value and treatment decisions about new expensive drugs	Answers of survey questions about value and treatment decisions, calculation of C/E ratios out of 70000 Dollar costs for a new treatment and question about the more of benefit for it. This ratio was linked to the results of all other questions
Neumann [40], Kozminski [30]	USA, 2010	Questionnaire to American Society of Clinical Oncology (ASCO) members (786 of 1387 responses, 58%) about attitude of oncologists about cancer costs and cost-effectiveness of treatments	Attitude of oncologists about costs, value and treatment decisions about new expensive drugs, preferences for qualtity of live and survival	Survey results of oncologists' views, implicit cost-effectivness tresholds based on survey results
Robertson [41]	Australia, 2013	Analyzing news paper articles between 2006 and 2007 about medicines recommended for reimbursement	To examine timing and content of newspaper reports regarding the PBAC decisons	Quantity, timing and content of articles for certain medicines
Romley [42]	US, 2012	Survey of 270 US adults (270/352 = 77 % respondend rate)	To quantify willigness to pay for generous specialty drug coverage versus standard health plan	Willigness-to-pay and demographic factors
Rosenberg-Yunger [43]	Australia, Canada, Israel, Uk, US	Semi-structured interview (30-60 min length) with 48 committee members	To explore stakeholder involvement of drug reimbursement commitees	
Schrag [44]	US, 2006	Survey of oncologists with hypothetical patient scenarios, open-ended questions was sent to random sample of ASCO members, data was analyzed descriptively	To understand oncologists' attitude toward communication with patients about costs of high cost drugs and the circumstances around it	Survey answers of oncologists, which were analyzed descriptively
Sinclair [45]	Canada, 2007	Qualitative study, role-playing exercise of participants (clinical Oncologists and non-physicians' of the Alberta Cancer Board's P&T Committee) during a 2 –day-meeting in June 2006. Roles were created to play different stakeholders to show the influence on the decision-making process	Investigate the internal frameworks that influenced stakeholders as they applied a new objective and transparent decision tool	Qualitative data was sorted in four over-aching categories containing nine specific themes about participants' experiences with the decision- making process
Singer [34,46]	Canada, 2000	Interviews of members of the Cancer Care Ontario policy advisory committee and the Cardiac Care Network of Ontario expert panel, besides review of information about the two organisations, analysis was performed by using the grounded theory	Describe priority settings of new technologies in medicine	Themes or ideas, which were grouped into certain categories (people, factors, reasons, process, appeals)
Thomson [47]	Australia. 2005	Survey of oncologists, envelop were send to all 274 members of MOGA Medical Oncology Group of Australia	Examine opinions and practise of oncologists regarding discussions HCD treatment options	Answers of survey questions about treatment with HCM, shown in a percent table, chi-squared tests to determine link between doctor characteristics and attitude about HCM
Wong [49]	USA, 2010	Survey of cancer patients about three scenarios to elicit the maximum co-payment	Examine the influence of cost on the treatment choices of patients with life-threatening illness	Survey answers whether they are ready to pay or not