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## Introduction

Health systems in Europe and beyond are facing a combination of upward cost pressures and declining economically productive populations, with population ageing contributing to a growing burden of non-communicable disease and technological progress increasing the opportunities to intervene.<sup>1,2</sup> Public and private expenditure on health systems in EU countries has risen from on average 7.3% of GDP in 2000 to 9.0% in 2012, with further increases expected, increasing demands that these health systems demonstrate their effectiveness and cost-effectiveness.<sup>3,4</sup>

Historically, rising expenditures associated with an ever widening range of pharmaceuticals and medical devices extending the range of conditions that can be treated have led to increasing use of Health Technology Assessment (HTA), a systematic analysis of clinical, economic, societal and other impacts of new technologies compared with existing alternatives.<sup>5</sup> However, HTA has so far mainly been applied to technologies which are being considered for potential inclusion in a benefit package rather than looking at the value of continued investment in existing services. For the many existing procedures and technologies that make up health systems, any systematic assessment of disinvestment options can be associated with technical and political challenges.<sup>6,7</sup>

The availability of health economic evidence has increased dramatically in recent years, as evidenced by the large number of citations in specialist health economic databases. As early as 2005, the NHS Economic Evaluation Database (NHS EED) and Office of Health Economics' Health Economic Evaluations Database (HEED) included over 16,000 and 31,750 citations, respectively.<sup>8</sup> However there are difficulties in applying evidence from these databases in practice for a range of reasons, including budgetary silos between departments and organizations, and differences in the design of economic analyses according to the stakeholders concerned, ranging from wide societal and long-term perspectives to more concrete budgetary and short-term analyses.<sup>9</sup>

One of the objectives of the Research Agenda for Health Economic Evaluation, implemented by the World Health Organization in partnership with the European Commission Consumer, Health, Agriculture and Food Executive Agency (CHAFAEA), is to identify knowledge gaps where further research could facilitate the uptake and impact of economic evidence in practice. An expert panel of health economists and public health practitioners with expertise in the 10 highest burden conditions in the EU was assembled to discuss the available evidence, identify knowledge gaps and make recommendations for future methodological research in the field of health economics.

## Methods

### Identification of the highest burden conditions in the EU

The 10 conditions representing the highest burden of disease in the European Union (EU) were selected based on Disability Adjusted Life Years (DALYs) from the Global Burden of Disease (GBD) study.<sup>10</sup> One disease category identified with this approach, "Other Musculoskeletal Disorders", was an aggregate of 62 discrete conditions with separate International Classification of Disease (ICD) 10 codes. For the present analysis, the most significant single condition from the list of 62 was identified by expert

opinion, and in addition the highest ranking single musculoskeletal disorder (MSD) from the main GBD list was also selected for inclusion.

## Expert panel

Health economic experts on the study conditions were identified by an assessment of the volume of peer-reviewed literature by author. The analysis was carried out with PubReMiner<sup>11</sup> using the search term “(cost-benefit OR cost-utility OR cost-effectiveness)” in combination with the study conditions. The highest ranking European authors were shortlisted and candidates of approximately equal technical strength were considered based on nationality and gender to improve representation. In addition, high level public health experts were invited to join the panel to provide links with the policy cycle and with preventive interventions and policies.

## Literature analysis

As a framework for considering the economic evidence and identifying methodological research priorities, for each of the 10 conditions clinical management was stratified according to disease characteristics and type of treatment based on the Up-to-Date database.<sup>12</sup> Full health economic evaluations and reviews of evaluations indexed by PubMed/MEDLINE (<http://www.ncbi.nlm.nih.gov/pubmed>) were identified using the Medical Subject Headings (MeSH) controlled vocabulary: “Cost-Benefit Analysis [N03.219.151.125]”, “Economics, Pharmaceutical [N03.219.390]” and “Technology Assessment, Biomedical [N03.880]” (including “Technology, High-Cost [N03.880.502]”), combined with MeSH terms for each of the 10 conditions. Although a more exhaustive approach using additional databases and free-text terms could have been adopted, the added sensitivity was not considered to be of primary importance to the objectives of the project.

Inclusion criteria for primary studies were: full economic evaluations (cost-benefit, cost-effectiveness incl. cost-utility), English abstract. Reviews were included if their search strategies included full economic evaluations. Studies without an integrated effectiveness component (i.e. cost or economic burden of illness, cost of treatment, cost-consequence etc.) were excluded. A cut-off year was not enforced for primary studies, but only reviews from 2009 or later were included. No geographical limitations were imposed. All searches were conducted in July-August 2014, except for the category “Other Musculoskeletal Disorders” which were conducted in November 2014. A literature database was constructed in which all included primary studies and reviews were mapped to the relevant clinical management category. Narrative reviews were produced for each study condition based on the identified literature, using recently published reviews (2009 onwards) when available, and by consulting primary studies otherwise.

## Consultation and expert panel meeting

The results of the narrative reviews were appraised by the expert panel and their feedback was incorporated. In addition, a public consultation was held from November to December 2014, during which 51 comments were received and incorporated. The expert panel was assembled for a 2.5 day meeting in Brussels, February 2015, where the results of the literature analysis were discussed to identify limitations of the existing evidence and methodological evidence gaps.

## Results

### High burden conditions in the EU

According to the Global Burden of Disease study,<sup>10</sup> the causes of the highest disease burden in the EU have changed little over the past two decades. Non-communicable diseases and accidental falls account for the top 10 causes of morbidity and mortality in 2010 (Table 1), with only neck pain entering and self-harm leaving the top 10 since 1990. Due to the diverse nature of the “Other Musculoskeletal” category, in the present work we consider osteoporosis as a prominent representative, and augment the category with osteoarthritis, the highest burden single musculoskeletal disorder outside the top-10, resulting in 11 study conditions.

A notable feature of the study conditions is the potential to co-exist in a single individual, by chance, because one predisposes to the other, or because they share common risk factors, such as diabetes and depression,<sup>13</sup> lung cancer and cardiovascular disease or COPD,<sup>14</sup> back pain and depression,<sup>15</sup> stroke survival and falls<sup>16</sup> and so forth. A number of common risk factors can be identified, including smoking (stroke,<sup>17</sup> lung cancer,<sup>18</sup> COPD,<sup>19</sup> ischemic heart disease,<sup>20</sup> low back pain<sup>21</sup>), high blood pressure (ischemic heart disease,<sup>20</sup> stroke<sup>22</sup>), and sedentary lifestyle (ischemic heart disease,<sup>20</sup> stroke,<sup>23</sup> diabetes<sup>24</sup>). Some of these disorders may appear early in the life course during economically productive ages, and there is an increase in multi-morbidity with increasing age.<sup>25</sup>

### Literature analysis

The volume of published economic evaluation studies available for analysis varied significantly by condition, with ischemic heart disease (IHD), diabetes and stroke accounting for the largest volume of economic evidence with 283, 242 and 116 papers respectively included in the present mapping (Table 2). There was no apparent correlation between burden of disease and volume of evidence, with some high burden conditions attracting little economic evidence compared with others (e.g. low back pain and depression with 65 and 61 papers, diabetes with 242 papers).

Notably, in eight out of the 11 conditions examined, less than 100 studies were available per condition, while the number of clinical management strategies in these cases varied from 12 (osteoporosis) to 63 (low back pain). Generally, economic evidence clustered around particular interventions accounting for a significant proportion of studies, such as pharmacology in depression (57% of all studies), bisphosphonates in osteoporosis (48%) and spinal manipulation in neck pain (60%). Consequently many clinical interventions were completely unstudied in the economic literature, or addressed in only a small number of studies (not shown). A detailed account of evidence gaps in the disease specific literature is provided elsewhere.<sup>26</sup>

The narrative reviews were used as a basis for identifying cross-cutting methodological and technical issues common to two or more disease areas, which were considered by the expert panel to derive methodological research priorities.

## **Expert panel recommendations for research**

The Expert Panel consisted of health economic specialists in the 11 study areas, as well as generalists in the field of health economics and public health (Table 3). The panel discussed the results of the literature analysis over a 2.5 day meeting in Brussels, February 2015. The deliberations of the panel regarding methodological and cross-cutting issues are given in the following sections, with recommendations for research summarized in Table 4.

### ***Determination of cost-effectiveness thresholds***

The applicability of the most widespread form of cost-effectiveness evaluation in Europe, yielding incremental cost-effectiveness ratios of study technologies against selected comparators, hinges on the estimation of a cost-effectiveness threshold above which a given technology is not considered cost-effective. Within the panel views varied as to whether there should be explicit cost-effectiveness thresholds expressed, for example, as cost per QALY. When explicit thresholds exist they are currently set arbitrarily, and little or no concern is given to which groups of patients are likely to lose out due to service displacement. Despite several recent attempts, there is still an urgent need to determine appropriate methods of estimating what cost-effectiveness thresholds should be.

### ***Personalized medicine***

Discussions on most disease areas highlighted how care needs to be targeted to patients that benefit the most, using appropriate risk scores, patient characteristics or other methods of stratification. Concerns were raised about personalized medicine, emphasizing the need to go beyond the ‘omics’ approach to include all characteristics that are relevant for stratification. This improves both clinical outcomes and cost-effectiveness of treatment. Discussions also highlighted the need to determine cost-effectiveness of current guideline recommended treatments, focusing on determining for which patients existing treatments are ineffective, and how patients can be guided away from such treatments on the pathway of care in order to free up resources for higher value care.

### ***Disinvestment from low value care***

Apart from leveraging insights from personalized medicine to identify and disinvest from care which is not (cost-)effective, it was noted that evaluations should include all relevant comparators, which is not always the case. Including a hypothetical “doing nothing” scenario in standard economic evaluations, although not usually a realistic clinical option, would allow the cost-effectiveness of existing treatments to be determined. Further research is needed on approaches for identifying candidate treatments for disinvestment.

### ***Real-world evidence***

The limitations of clinical trial evidence for predicting real world effectiveness are well known and described, due for instance to differences between strictly controlled trial populations and the wider patient population.<sup>27,28</sup> Methods of generating, synthesizing and applying real-world evidence from pragmatic trials, registry data and similar sources should be further explored and experiences

exchanged. This would allow evaluation of the cost-effectiveness of treatments in practice, as well as generation of parameter input for real-world model-based cost-effectiveness studies as opposed to trial-based studies. The acceptability of such evidence to key stakeholders, including reimbursement agencies as part of existing HTA processes and for the monitoring of post-launch real-world cost-effectiveness, should be explored.

### ***Early Health Technology Assessment***

Cost-effectiveness research is mostly undertaken in the late stages of treatment development where considerable investments have already been made. Early cost-effectiveness analysis could help manufacturers to decide about further development of a treatment, set realistic performance-price goals, and design and manage a regulatory and reimbursement strategy.

### ***Measures of costs and benefits***

Variations in reporting practices for measurements of input resource use and costs currently constrain evidence transfer between settings and jurisdictions and the applicability of evidence over time. Including a range of expected generic prices following patent expiry as part of an economic evaluation of a new pharmaceutical would be a welcome addition to understanding lifecycle costs of a technology. In addition, economic evaluation studies should report resource use and unit costs separately to improve transferability and reuse of evidence.

Estimating indirect costs due to illness in older people has largely been neglected, and best practices should be developed to realistically assess losses and gains associated with the roles played by those in this age group with respect to informal care, child care and other activities. Similarly, little attention has been paid to return to education in young people with health problems, which can significantly affect their life chances, and thus return on investment.

Finally, applying patient reported outcome measures may be a particular challenge in certain patient groups, such as those receiving palliative care, recovering from stroke or other severe illnesses, where small functional improvements can be perceived to be very important, or where language or cognitive abilities are limiting factors.<sup>29</sup> Further research is needed to understand how benefit can most appropriately be measured in these groups. There is a need for a broader set of health outcome measures that go beyond the outcomes captured by a generically defined QALY, e.g. indicators such as the ability to live an independent life, avoid loneliness, maintain societal status and the ability to cope. Such measures can be used to study the impact of interventions in the care sector as well as the cure sector.

### **Standardized open-access economic models of appropriate complexity**

A significant body of economic evidence is focused on commercial high value products and funded by their manufacturers. Structural and parameter variations are known to significantly affect cost-effectiveness results, and can be chosen selectively to favor particular outcomes resulting in biased analyses. Publicly funded, validated, open-access and open-source economic models would reduce the

risk of bias, provide a common platform for economic evaluations across countries, provide a reliable source of information for reimbursement submissions and reduce duplication of effort across countries. However, as recent experience with treatment for macular degeneration has shown, vested interests may create barriers to such studies.<sup>30</sup>

Research in this area could also usefully establish the tradeoffs inherent in model complexity; more sophisticated models require more data, often to the point where requirements exceed availability, which introduces more uncertainty in results. It is not known whether simplified models with more limited evidence requirements could be reasonable approximations to their more complex counterparts.

### **Complex care, combinations and pathways**

There is little evidence on the cost-effectiveness of complex health interventions such as palliative or integrated care, either generally or for specific conditions (for ethical reasons the role of economic evaluation in palliative care is mostly relevant to the choice between different models,<sup>31</sup> rather than palliative care vs other interventions). Similarly, treatments which are well studied individually are often not studied as part of complex regimens, both in the case of multiple treatments for the same condition, or as simultaneous treatments for multiple, comorbid conditions. The sequence in which individual treatments are given along a pathway of care and cut-off points for changing therapies are often not well understood.

Treatment programmes may also contain mixtures of pharmacological and non-pharmacological interventions, or interventions directed both at patients, healthcare providers and the organization of care, such as integrated care programs or disease management programs. There is a need for methods to address the cost-effectiveness of treatments given under these complex conditions.

### **Evidence within and outside the health sector**

Health in all policies is promoted as a policy principle, but in many cases health benefits are not modelled as part of interventions with an impact on health either directly or through determinants of health, such as social housing and education. The economic methods used in other sectors, often cost-benefit or return-on-investment, are generally different from methods used within the health sector, mostly cost-effectiveness including cost-utility. Increased awareness of the health impacts of actions in other sectors, along with developments to bridge the gaps between the technical approaches of health and other sectors, could encourage the incorporation of health effects in wider policy evaluations. Effects of health interventions external to the health system are included in health economic evaluations in the form of productivity losses/gains, although many evaluations take a more restricted health system perspective in which such values are not included.

## **Discussion**

The present work represents an attempt to outline broad research priorities for the field of health economics in the European Union, as viewed by health economics and public health experts from the region, representing producers and users of such evidence, respectively. This is in contrast to earlier

priority setting exercises which have focused, for example, on the needs of specific HTA agencies,<sup>32</sup> have consulted more widely with governments, industry, academia and other stakeholders on priorities relevant for a particular country,<sup>33</sup> or for a particular health condition.<sup>34</sup> The present approach is intended to be relevant to the European Union broadly, and to address underlying methodological issues, which can be considered universal, without the additional complexity of national variations for example in the approach to HTA or in the organisation of health systems. It is especially relevant as the European Union explores ways of fostering stronger co-operation among HTA agencies.<sup>35</sup>

At the core of health economic evaluation, the question of determining an appropriate cost-effectiveness threshold tends to receive little systematic attention, with acceptable thresholds or ranges largely determined by precedents and without solid justification.<sup>36-38</sup> The underlying premise of a cost-effectiveness threshold, assuming some reallocation of resources is needed to fund the new intervention, is that a newly introduced service should provide more “health benefit” than the services that are foregone to release the required finance. In other words, this interpretation of a threshold implies that as long as total health gain is maximized, it does not matter who gains or loses. This has obvious implications for other health system objectives such as equity,<sup>39</sup> and indeed there is a lack of attention in the literature to which services and/or patient groups tend to lose out when new services are adopted for reimbursement.<sup>40,41</sup> This approach also implicitly assumes that the cost-effectiveness of all existing interventions is known, which is far from the case.<sup>39</sup>

Furthermore, if additional funding is made available in the health budget to finance new interventions, an estimate of the consumption value of health is required, i.e. how much of other forms of consumption we are willing to forgo to increase health outcomes. One (but not the only) way of addressing this is by estimating a societal “willingness to pay” (WTP) for health gains, although it is not straightforward to determine what such a WTP should be. Past decisions are unlikely to provide a good metric as economics are rarely the only consideration behind a decision,<sup>39</sup> and recent work has demonstrated that individual WTP differs substantially between income brackets<sup>42</sup> complicating efforts to obtain a societal value. Interpretation and definition of the cost-effectiveness threshold is a political issue, but research is lacking to support a transparent and evidence based decision. Further to this, it is not clear how non-economic considerations such as ethical (e.g. end of life care) or distributional concerns (e.g. areas with high unmet clinical need) should be integrated. In practice this has resulted in cost-effectiveness thresholds being ignored or extended e.g. for orphan drugs.<sup>43</sup> Multiple Criteria Decision Analysis (MCDA) has been suggested as one way to integrate disparate factors<sup>44</sup> although experience in practice is currently limited to experimental assessment.<sup>45</sup>

The threshold debate is directly related to the issue of disinvestment particularly when healthcare budgets are fixed. Since the systematic process of Health Technology Assessment is largely concerned with assessing technologies for investment at a central level, the freeing of resources (disinvestment) to finance implementation often happens at the local level where economic considerations, i.e. the identification of low-value care, are often not considered. In addition the value of services may differ according to priorities and specific conditions between localities, and consequently central disinvestment (or indeed investment) advice may not be appropriate.<sup>46-48</sup>



The present research recommendations therefore support the identification of substantiated cost-effectiveness thresholds together with efforts to estimate the cost-effectiveness of existing treatments according to patient characteristics, in order to improve information available for the identification of and potential disinvestment from low value care. Treatment effects are well known to vary by subgroups of patients; however in a sample of 97 clinical trials published in the *New England Journal of Medicine* between 2005 and 2006, subgroup analysis was undertaken only for 59 (61%) and results of these were not consistently reported.<sup>49</sup> Though clinical trials can give important clues about subgroups experiencing better clinical outcomes, they are generally designed to optimize internal validity at the expense of generalizability.<sup>50</sup> Examples of prospective real-world trials exist, in which investigators seek to determine in which patient groups an intervention is more cost-effective under everyday practice conditions.<sup>51</sup> Use of pragmatic clinical trials, as well as registry-based studies, is considered a valuable addition to, but not a substitute for traditional explanatory trials, and will give decision-makers more realistic insight into the cost-effectiveness of treatments across patient subgroups in actual clinical practice. Real-world evidence however cannot provide evidence on pure treatment effects, and there are obvious risks of bias if non-randomized study designs are adopted, even though in some circumstances they are the only feasible option, e.g. for public health interventions implemented nationwide. Consequently there is a need to determine the acceptability of real-world evidence to decision-makers, in particular reimbursement authorities,<sup>52</sup> in the context of growing concern about initiatives such as adaptive pathways that call for their greater use as a means of expediting market entry.<sup>53</sup> Notwithstanding this, with caution, real-world evidence can be an important source of data particularly for estimating parameters that are not subject to selection bias, and may contribute to understanding the cost-effectiveness of routine, every-day care and identifying groups of patients which are (un-)likely to benefit from existing interventions.

More recently the real-world evidence principle has been extended to pre-launch clinical testing with the phase III Salford Lung Study.<sup>54</sup> The move towards earlier real-world evidence generation requires early engagement with Health Technology Assessment authorities to understand the potential cost-effectiveness of the intervention, allowing industry to invest in appropriate evidence generation accordingly.

Particular challenges surround the assessment of complex interventions, such as integrated care, and patients with complex needs, such as triple therapy in chronic obstructive pulmonary disease,<sup>55</sup> different sequences of disease-modifying anti-rheumatic drugs in rheumatoid arthritis patients<sup>56</sup> and patients with multiple and potentially interacting co-morbidities. In the latter case, there is evidence to suggest some combinations of conditions increase overall costs, while others decrease overall costs due, for instance, to overlapping treatments.<sup>57</sup> Consequently cost-effectiveness evaluations for individual interventions cannot be considered “additively” but need to be assessed in context. A methodological framework for “Whole Disease Modeling” has been developed by Tappenden et al., which considers all treatments and diagnostics along the pathway of care for a simulated cohort,<sup>58</sup> but the only examples that we could find of this method being used were with colorectal cancer and depression.<sup>59,60</sup>

Multi-morbidity also has implications for quality of life outcome measures which, like costs, do not behave additively over conditions.<sup>61</sup> Outcome measures are also problematic in particular patient groups, such as those with impaired cognitive abilities who may not be able to complete patient reported outcome measures;<sup>62</sup> and in particular interventions, such as palliative care, where the choice of outcome is not straightforward or uniform.<sup>63</sup> The latter point extends to the “care sector” generally, where fewer appropriate outcome tools are available than in the “cure sector”, although recent research such as the Adult Social Care Outcomes Toolkit (ASCOT) has started to address this.<sup>64</sup> Consequently there is an issue of benefit measurement in complex treatment situations and patient profiles. Similarly, indirect costs derived from lost productivity are likely to underestimate the economic burden of conditions affecting older people, where indirect costs are associated with informal care<sup>65</sup> and with loss of economically meaningful activities such as volunteering and child care.

Earlier recommendations have called for resource use and unit costs to be reported separately,<sup>66,67</sup> and the present panel re-iterates this recommendation to facilitate transferability of economic evidence across settings. Transferability and validity may be further enhanced through development of standardized, open-source and open-access economic models that are intended to appropriately reflect disease progression and provide unbiased estimates of cost-effectiveness, subject to contextualized input parameters. The re-use and customization of economic models is commonplace for commercial models, such as the CORE Diabetes model<sup>68</sup> which is cited in numerous analyses, but transparent and validated models in the public domain would be a valuable resource for researchers and reimbursement agencies alike, reducing duplication of effort in economic components of reimbursement submissions across countries along the same principle as the EUNetHTA approach for HTA.<sup>69</sup> Here, there is scope for greater use and further development of standardized approaches such as the Gates Reference Case<sup>70</sup> and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).<sup>71</sup>

Finally the panel recognized the limited cross-talk between health economic evaluation, largely cost-effectiveness, and economic evaluations in other sectors, often cost-benefit. A recent review found health effects were more likely to be considered in economic evaluations if there was a direct link to health and lives saved, such as road traffic safety, but less likely if health was indirectly affected e.g. through social determinants.<sup>72</sup> Quantification of health impacts of non-health policies such as education, work force policies, environment and urban planning could help to bridge this gap.

In conclusion, the panel suggests a research agenda for health economics which includes understanding of the strengths and weaknesses of real-world evidence for the assessment of new and existing health care interventions, uses economic insights to identify patient groups that are most likely to benefit from care and to guide investment and disinvestment decisions accordingly. This includes the assessment of complex, sequential and multi-morbid care. Appropriate methods are needed for capturing costs and outcomes accurately, particularly with more challenging interventions and patient groups, and for encouraging the uptake of health outcomes in economic evaluations outside the health sector. The panel also noted the large proportions of economics analyses that come from vested interests such as pharmaceutical manufacturers and the associated risk of bias. Transparency about funding and other conflicts of interest and commitment from authors to publish full details of methods, inputs and results was considered important, as was the need for publication of independent analyses.



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Rank #	1990	2010
1	Ischemic Heart Disease	Ischemic Heart Disease
2	Stroke	Low Back Pain
3	Low Back Pain	Stroke
4	Lung Cancer	Major Depressive Disorder
5	Road Injury	Lung Cancer
6	Major Depressive Disorder	Falls
7	COPD	COPD
8	Falls	Diabetes
9	Diabetes	Other Musculoskeletal <sup>1</sup>
10	Self-harm	Neck pain

<sup>1</sup>“Other Musculoskeletal disorders is a residual category of 62 discrete conditions including arthropathies, systemic connective tissue disorders, dorsopathies, soft tissue disorders, osteopathies, chondropathies and “Other disorders of the musculoskeletal system and connective tissue” (web table 3 of Lozano et al<sup>69</sup>).

GBD Rank 2010	Condition	Literature Mapping				Literature distribution	
		Screened	Included	Total reviews	Recent reviews <sup>I</sup>	Clinical modalities <sup>II</sup>	Intervention with most evidence <sup>VII</sup> : number of studies (% of all studies)
1	Ischemic heart disease	1,818	232	49	7	30	PCI for angina: 46 <sup>V</sup> (20%)
2	Low back pain	190	64	12	5	63	Physical therapy: 20 (31%)
3	Stroke	461	116	20	9	52	Atrial fibrillation: 39 (34%)
4	Major depressive disorder	151	61	3	2	14	Pharmacology: 35 (57%)
5	Lung cancer <sup>III</sup>	686	49	31 <sup>VI</sup>	6	25	Erlotinib, gefitinib or afatinib in EGFR mutation cancer: 14 (29%)
6	Falls	180	42	3	2	14	Exercise: 16 (38%)
7	Chronic obstructive pulmonary disorder	267	68	11	4	58	LAMA, LABA: 20 (29%)
8	Diabetes type 1+2	1,208	242	77	25	28	Insulin: 28 (12%)
9	Osteoporosis <sup>IV</sup>	352	71	11	5	12	Bisphosphonates: 34 (48%)
	Osteoarthritis <sup>IV</sup>	248	34	8	4	21	NSAIDs: 16 (47%)
10	Neck pain	35	15	2	2	24	Spinal manipulation: 9 (60%)

<sup>I</sup> 2009 or later

<sup>II</sup> Number of clinical management strategies identified through clinical guidelines and expert opinion

<sup>III</sup> NSCLC

<sup>IV</sup> Osteoporosis is selected as a condition of particular importance out of the 62 discrete conditions comprising the “Other Musculoskeletal Disorder” category, which ranks 9<sup>th</sup> in the GBD. Osteoarthritis, being the most significant single MSD in terms of burden of disease, was included to complement the “Other Musculoskeletal Disorder” category

<sup>V</sup> Stable (46) plus unstable (19) ischemic heart disease patients

<sup>VI</sup> for Small Cell Lung Cancer and Non-Small Cell Lung Cancer

<sup>VII</sup> Economic studies are categorized according to all comparators included

PCI = Percutaneous Coronary Intervention; LAMA = Long Acting Muscarinic Antagonists; LABA = Long Acting Beta2 Agonists; EGFR = Epidermal Growth Factor Receptor