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DEFINING INNOVATION WITH RESPECT TO NEW MEDICINES: A SYSTEMATIC REVIEW FROM A PAYER PERSPECTIVE

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Objectives: The aim of this study was to investigate how innovation is defined with respect to new medicines.
Methods: MEDLINE, Embase, and EconLit databases were searched for articles published between January 1, 2010 and May 25, 2016 that described a relevant definition of innovation. Identified definitions were analyzed by mapping the concepts described onto a set of ten dimensions of innovation.
Results: In total, thirty-six articles were included, and described a total of twenty-five different definitions of innovation. The most commonly occurring dimension was therapeutic benefit, with novelty and the availability of existing treatments the second and third most common dimensions. Overall, there was little agreement in the published literature on what characteristics of new medicines constitute rewardable innovation.
Conclusions: Alignment across countries and among regulators, health technology assessment bodies and payers would help manufacturers define research policies that can drive innovation, but may be challenging, as judgements about what aspects of innovation should be rewarded vary among stakeholders, and depend on political and societal factors.

Keywords: Diffusion of innovation, Technology assessment, Biomedical, Economics, Pharmaceutical

One way in which governments, health technology assessment (HTA) bodies, and healthcare decision makers can seek to encourage the development of truly new medicines (and new drug classes) is to recognize and reward innovation. In addition to the market advantages granted by providing better outcomes than existing therapies, innovation is commonly rewarded by the acceptance of a premium price for a new product during reimbursement and price-negotiation processes; ideally these processes should stimulate ongoing innovation while obtaining good value for money. A recent report in the United Kingdom has suggested that a focus solely on price minimization, rather than on product quality and entire life-cycle cost optimization, could reduce the incentives for innovation and potentially the attractiveness of the country as a setting for researching and developing pharmaceutical treatments (1). In addition, focusing only on price control may shift manufacturers' incentives toward the development of high-cost drugs with large additional benefits, at the expense of incremental innovation in highly competitive areas, including common diseases.

To recognize important innovation in medicines, decision-making bodies must use explicit or implicit definitions of what characteristics constitute rewardable innovation. Ideally, agreement on such a definition across countries would provide a consistent incentive to manufacturers to conduct research into new methods of treating diseases, and simplify drug development, reducing costs and prices. Several frameworks for assessing the value of new medicines exist, for example, the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have produced value frameworks based on clinical benefit, toxicity, and impact on health-related quality of life (2–4). However, these frameworks do not specifically address innovativeness, and there appears to be little consensus on which types of medicines are in fact innovative.

Innovation in health care does not fully follow the same pattern as other industries. In many sectors, innovation is typically associated over the long term with a reduction in costs as well as an improvement in the end product. This is not routinely the case in health care: a new product is often substantially different from existing therapies, and the improvements in patient outcomes that result from the use of innovative new medicines tend to be accompanied by increased expenditure by the healthcare system (5;6). It

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is, therefore, important to consider what type or level of innovation justifies an elevated price (7). All healthcare systems have finite resources, and there is a risk that inappropriate rewarding of innovation (for example, paying a premium for a drug that does not improve outcomes simply because it is new) could prevent funds being better spent elsewhere, and, therefore, lead to an overall decrease in patient outcomes at both an individual and a population level (8). In addition, recent developments in the personalization of treatment for many conditions may mean that in the future reimbursement may need to focus on outcomes (at an individual or population level) rather than the acquisition costs of drugs; this may require a new approach to the HTA process.

The recent growth in development of new pharmaceutical products that are deemed innovative and efficacious, but are expensive, is accompanied by (and partly the cause of) an increasing focus in Europe, and increasingly in the United States, on the cost and affordability of health care (9). However, discussions about new medicines do not typically involve consideration of cost as a key component of innovation, and there is a risk that, in many countries, innovation in pharmaceuticals may not meet the needs of the wider healthcare system (and by extension, of society as a whole) (10). The aim of this systematic review is to investigate how innovation is defined with respect to new medicines, and to assess the extent to which published definitions of innovation incorporate the impact of new medicines on healthcare costs.

METHODS

Search Strategy

A series of systematic literature searches was conducted on May 25, 2016. Full terms used in all searches are listed in Supplementary Tables 1–5.

MEDLINE, Embase, and Embase Alert databases were searched using ProQuest Dialog (Ann Arbor, MI). The search strategy included multiple free-text terms covering the definition of innovation, combined with terms referring to health care, drugs, medicines, or pharmaceuticals. Additional searches combined healthcare terms with Medical Subject Heading (MeSH) and Emtree thesaurus index terms. Search results were limited to studies published from January 1, 2010, and filtered to exclude studies published only as conference abstracts. No language restriction was applied. The EconLit database was searched using the American Economics Association interface (https://www.aeaweb.org/econlit/). EconLit search terms combined "innovation"/"innovative" with terms including definition, health, drug, and medicine. EconLit search results were restricted to journal articles published in English from January 1, 2010.

Study Selection

Search hits from the three databases were combined, and duplicates were removed using EndNote software (Thomson Reuters, New York, NY). Remaining duplicate articles and conference abstracts were manually removed and titles and abstracts screened for eligibility. Articles were included if they described a definition of innovation with respect to new medicines, or referred to a relevant definition published elsewhere. Articles presenting definitions of innovation in medical devices, surgical techniques, or service delivery were considered to be outside the scope of this review, and were excluded. Full-text versions of articles that passed title/abstract screening were retrieved for further review, and studies not meeting the inclusion criteria were excluded (Supplementary Table 6).

Where studies referred to a relevant definition of innovation published elsewhere, the cited references were screened for inclusion in the review; no date restriction was applied to references identified through citation searching.

Data Extraction and Analysis

Definitions of innovation were extracted from all included references. In addition, terms used to describe components of innovation in each of the included definitions were identified. Because a large number of terms were identified, many of which described similar concepts (for example, "therapeutic benefit" and "therapeutic value"), similar definition terms were clustered together into ten groups; therefore, the resultant "dimensions of innovation" are derived from the identified terms, rather than being defined *a priori.* The mapping of definition terms onto the ten dimensions is shown in Supplementary Table 7. Definitions described in multiple publications were counted more than once in this analysis, but to avoid double-counting the same reference, the results of a previous systematic review of innovation (11) were excluded.

Supplementary Searches

Manual searches of relevant Web sites, including European HTA bodies, the European Medicines Agency, and key professional societies (for example, ASCO and ESMO), were conducted to identify stated policies or methods for assessing innovation. For HTA body Web sites, individual product assessments were not searched. Similarly, for professional societies, conference proceedings were excluded. A full list of Web sites searched and the search terms used is presented in the Supplementary Table 8. Because the Web site searches were not fully systematic, definitions identified from these sources were not included in the analysis of the dimensions of innovation.

RESULTS

Search Results

In total, 2,844 articles were retrieved in the database searches. After removing duplicates from the records, the titles and

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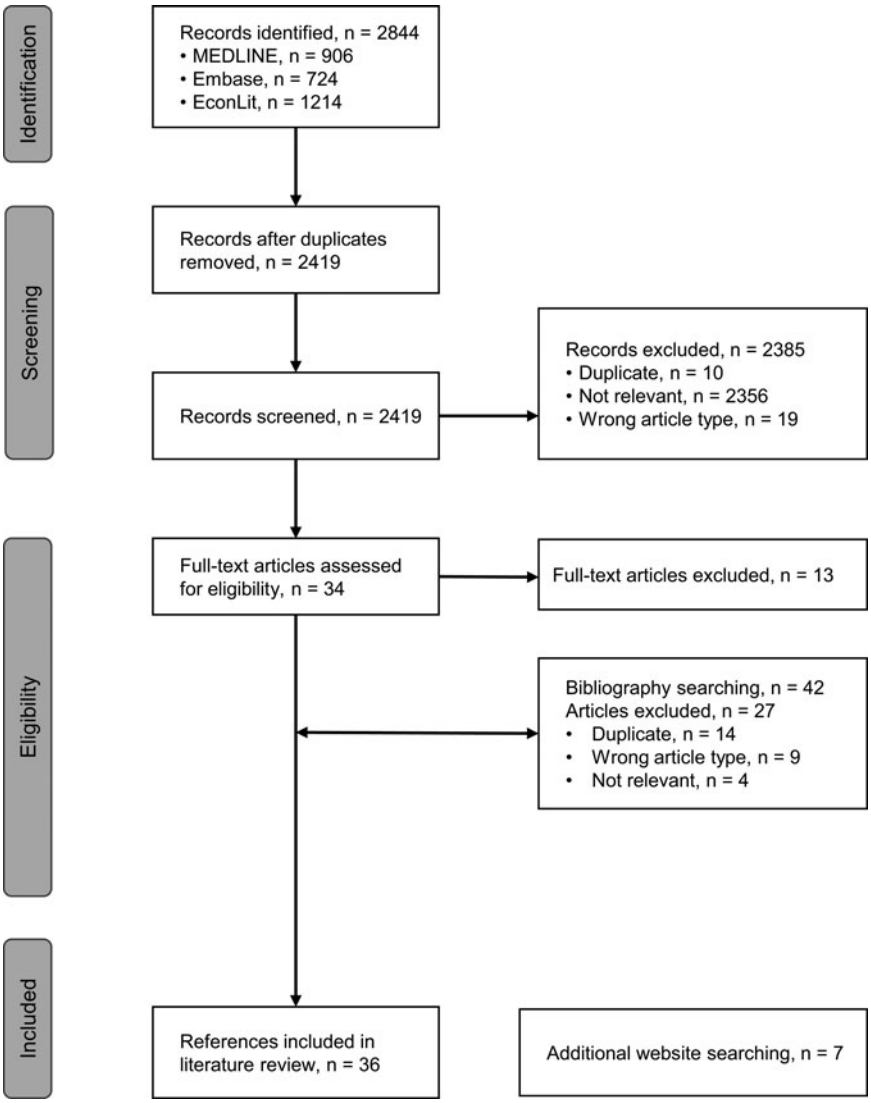

Figure 1. Study selection flow diagram.

abstracts of 2,419 unique articles were screened. In total, twenty-eight articles were identified as being potentially relevant to the review objectives, and full-text versions were obtained. Of these, thirteen articles were excluded (Supplementary Table 6). Citation searching identified a further forty-two potentially relevant articles, of which twenty-four were excluded at the title/abstract screening stage, and three were excluded following full-text review. The flow of studies through the screening process is shown in Figure 1.

Published Definitions of Innovation

In total, thirty-six published articles describing definitions of innovation were included in the review (7;11–45) (Table 1). Of these, one study was a previous systematic review of how innovation is defined in drug development; the majority of articles identified defined drug innovation in terms of the number of yearly approvals of new drugs or patents (11). Because all of the studies in this previous review are included in the present analysis, this study was excluded from the analysis of the dimensions of innovation in published definitions to avoid double-counting. The remaining thirty-five studies described forty-four definitions of innovation, with thirty-five different definitions identified in total.

Several definitions of innovation were presented in more than one reference. In particular, four references described an algorithm based on the availability of existing treatments and therapeutic effect of a new therapy, with technological and pharmacological innovation included in the case of products for diseases responsive to previously available interventions (12–15). This algorithm is used by the Agenzia Italiana del Farmaco (AIFA) in Italy. In brief, drugs for diseases without a recognized standard treatment are classed as important innovations if they have at least a partial benefit on clinical

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Table 1. Definitions of Innovation Identified in the Published Literature

Study	Study description	Definition of innovation	Components of innovation	Dimensions of innovation
Systematic review				
Kesselheim et al., 2013 (11)	Systematic review of innovation in drug development (42 studies reviewed)	Level of innovation defined as: Twenty-one studies, all new drugs (NCEs); of these, five divided drugs according to FDA priority review status, one assessed first-in-class vs follow-on drugs Fourteen studies, therapeutic value; of these, three assessed quality of pre-market trials, one used EVITA algorithm, one included post-marketing data in algorithm; seven compared with alternatives, including orphan areas (one), pharmacological/technical innovations (one), usefulness (one), Canadian Drug Advisory Panel classification (one), or general public health measures (three) Three studies, economic markers Four studies, patent rates	New molecular entity; molecular novelty; therapeutic value; market share; cost-saving	n/a
Motola et al. algorithm				
Andria et al., 2013 (12)	Italian analysis of the innovativeness of new products, using EMA EPAR reports	Algorithm based on disease severity, availability of treatments, and therapeutic effect	Disease severity; availability of existing treatment; clinical benefit; safety; pharmacological/technological differences	Unmet need; availability of existing treatment; therapeutic benefits; safety; novelty
Mol et al., 2013 (13)	Database study of innovative drugs with serious safety issues; Europe, 1999–2012	Algorithm based on availability of treatments and therapeutic effect	Availability of existing treatment; clinical benefit; safety; pharmacological/technological differences	Availability of existing treatment; therapeutic benefits; safety; novelty
Motola et al., 2005 (14)	Review of the innovativeness of new products, using EMA EPAR reports	Algorithm based on availability of treatments and therapeutic effect	Availability of existing treatment; clinical benefit; safety; pharmacological/technological differences	Availability of existing treatment; therapeutic benefits; safety; novelty
Motola et al., 2006 (15)	Review of the innovativeness of new products, using EMA EPAR reports	Algorithm based on disease severity, availability of treatments and therapeutic effect	Disease severity; availability of existing treatment; clinical benefit; safety; pharmacological/technological differences	Unmet need; availability of existing treatment; therapeutic benefits; safety; novelty

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Table 1. Continued

Study	Study description	Definition of innovation	Components of innovation	Dimensions of innovation
NICE approach to innovation				
Bryan et al., 2013 (16)	Review of innovation in healthcare decisions	1) Innovatory products must both meet unmet need and improve health outcomes 2) Innovations must be new, must provide an improvement on existing products, and must offer a step-change in terms of patient outcomes 3) An innovation offers treatment of a condition with no existing effective, or at least no completely satisfactory, intervention 4) An innovation represents effective treatment, prevention or diagnosis of a disease or condition for which no drug (or medical device) is currently licensed	1) Unmet need; health outcomes 2) Newness; health outcomes; step-change 3) Availability of existing treatments 4) Efficacy; availability of existing treatments	1) Unmet need; therapeutic benefits 2) Newness; therapeutic benefits 3) Availability of existing treatment 4) Therapeutic benefits; availability of existing treatment
Green, 2010 (17)	Editorial describing the assessment of innovation by NICE; UK	Innovation is important where an intervention meets three initial criteria: a) that it is " new," b) that it improves on existing interventions and c) that it offers something more – in the way of a " step-change" in terms of outcomes for patients A step-change reflects that: a) the product significantly and substantially improves the way that a current need (including supportive care) is met; b) the need met is one that the NHS has identified as being important; c) where appropriate, research on stratification has identified the population(s) in which the product is effective – this may be all of the population with the condition or just a subset; d) the product has been shown to have an appropriate level of effectiveness (e.g. benefiting 70% of the intended target group); and e) the product has marketing authorisation for the particular indication	Newness; improvement on existing interventions; step-change; unmet need	Newness; therapeutic benefits; unmet need

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Table 1. Continued

Study	Study description	Definition of innovation	Components of innovation	Dimensions of innovation
Ferner et al., 2010 (18)	Analysis of the NICE definition of innovation; UK	1) An innovative medicine is one that is new, constitutes an improvement on existing products, and offers "a step-change in terms of outcomes for patients" (A "step-change" involves clinical usefulness, particularly in the treatment of a condition with no existing effective treatment, or for which there is no consistently satisfactory treatment; making treatment safer or more convenient is associated with a lower level of usefulness) 2) High innovation: new target or molecular mechanism, novel application or improved identification of those who are likely to benefit or be harmed (e.g., through pharmacogenetics). Moderate innovation: new type of compound (e.g. mAb), fewer adverse effects or interactions, or novel structure (substantial change)	1) Newness; improvement on existing interventions; step-change; unmet need 2) Novelty; targeting of population; safety	1) Newness; therapeutic benefits; unmet need 2) Novelty; therapeutic benefits; safety
Linley and Hughes, 2013 (19)	Cross-sectional survey of societal views on prioritization; UK	For a medicine that works in a new way: 1) NICE: product produces a demonstrable and distinct benefit of a substantial nature [that may not be adequately captured in the quality of life measure used] 2) VBP: a treatment representing a significant breakthrough and an important advance over existing therapies would provide a large QALY benefit. It could also be represented by a qualitative assessment of the innovation reported by a new medicine reflecting, for example, new modes of action	1) Novelty; substantial benefit 2) Significant breakthrough; important advance over existing therapies; new modes of action	1) Novelty; therapeutic benefits 2) Novelty; therapeutic benefits
Rawlins et al., 2010 (20)	Review of NICE approach to decision making	[NICE] considers an innovative technology as one where the use of the product produces a demonstrable and distinct benefit, of a substantial nature, that may not have been adequately captured in the quality of life measure used	Substantial therapeutic benefit	Therapeutic benefits
Combination of technology level and comparative effectiveness				
Heible, 2013 (21)	Review of pharmacological progress and economics	Innovation described in a 2 × 2 matrix based on a combination of: a) Technology level: in case of a NME, the technical level of innovation in relation to existing drugs that are aimed to treat the same diseases is to be considered as high b) Comparative effectiveness: the therapeutic value which the drug offers compared to competing products in the same therapeutic class	Novelty; added therapeutic value; level of technology; comparative effectiveness	Novelty; therapeutic benefits

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Table 1. Continued

Study	Study description	Definition of innovation	Components of innovation	Dimensions of innovation
Sorescu et al., 2003 (22)	Review of radical innovation in pharmaceutical industry; USA	Combination of chemical composition and therapeutic potential (assessed by FDA review type): radical innovations: priority review and NME, market breakthroughs: priority review and non-NME, and technology breakthroughs: standard review and NME (Standard review and non-NME products are not considered innovative in this framework)	Novelty; health outcomes	Novelty; therapeutic benefits
Sternitzke, 2010 (23)	Analysis of bibliometric data to investigate different types of innovation, assessed based on FDA status; USA	Combination of chemical composition and therapeutic potential (assessed by FDA review type): update + standard review = incremental innovation, update + priority review = market breakthrough, NME + standard review = technological breakthrough, and NME + priority review = radical innovation	Novelty; therapeutic potential	Novelty; therapeutic benefits
Other studies				
Adami et al., 2012 (24)	Review of clinical relevance of trial endpoints with respect to innovation in pharmacotherapy; Italy	Each of the following criteria is needed: a) The evidence on the new intervention is documented at least by one controlled trial in which the primary endpoint is "clinically relevant"; individual endpoints are recognized to be "clinically relevant" if they are included in predetermined lists by therapeutic area; hard endpoints are included in these lists, but also surrogated endpoints can be included if they are thought to be highly predictive of the occurrence of hard endpoints. b) The controlled trial evaluating the new intervention is a superiority trial in which the difference in favor of the new intervention has reached the conventional level of statistical significance ($p < .05$) c) The controlled trial evaluating the new intervention includes a control group treated according to current best practice; this criterion must be specifically documented by an authoritative therapeutic guideline still recognized to be valid	Clinical relevance of endpoints; evidence of superiority; use of adequate comparator	Therapeutic benefits; clinical evidence
Alexander, 2011 (25)	Review of adoption of new drugs; USA	New drugs have the potential for transformative innovation. Improvements in outcomes and adverse effect profiles, as well as simpler regimens that improve convenience and adherence, all reflect important increases in the clinical utility of new products	Improved outcomes; adverse effect profiles; convenience; adherence	Therapeutic benefits; safety; administration

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Table 1. Continued

Study	Study description	Definition of innovation	Components of innovation	Dimensions of innovation
Aronson et al., 2012 (7)	Literature review and proposal of a definition of innovation with respect to medicinal products	1) A rewardable innovation… can be defined as: "a medicinal product that provides, through a step-change, something novel, with the potential or proven ability to yield, for individuals and/or their society, a treatment not previously available or a clinically significant improvement in treatment, with large health gains and a favourable benefit to harm balance, at an acceptable cost" 2) Multiple components of innovation are described in references cited in article Supplementary Table 1	1) Step-change; novelty; availability of existing treatments; clinical improvements; health gains; benefit–harm ratio; cost 2) Newness; novelty; usefulness; cost-effectiveness; source of innovation (revolution/evolution)	1) Therapeutic benefits; novelty; availability of existing treatment; cost 2) n/a
Autret-Leca, 2010 (45) (French)	Review of innovation with respect to drugs used in pediatric practice	Degree of innovation is determined by the magnitude of effect and performance in comparison with alternative treatments	Therapeutic effect, additional benefit	Therapeutic benefit
Barbui et al., 2007 (26)	Analysis of CNS drugs products in Europe, based on EMA EPAR reports	Innovation considered to be superiority over active comparator in clinical trials supporting the approval of drugs	Therapeutic improvement; use of active comparator	Therapeutic benefits; clinical evidence
Cadranel et al., 2015 (43) (French)	Review of innovation in thoracic oncology	1) … [It] is the amount of life gained that best defines therapeutic innovation 2) … Innovation cannot be decreed or planned, and is defined by the societal (or commercial) success that results. In thoracic oncology, it is clear that innovation is less about the production of new targeted molecules… [than about] the treatment provided to patients in terms of therapeutic efficacy and tolerability	1) Amount of life gained 2) Societal or commercial success, therapeutic efficacy, tolerability	1) Therapeutic benefit 2) Therapeutic benefit; other
Caprino and Russo, 2006 (27)	Development of algorithm for assessing drug innovation	Algorithm based on multiple characteristics: drugs for diseases lacking satisfactory treatment; structural novelty or new therapeutic innovation vs structurally related compounds; products obtained using innovative technologies vs known products with new characteristics; use of active comparator; assessment of efficacy, tolerability, and adherence; size (international vs national) and design of clinical studies, including choice of comparator; patient selection and time span/number of patients; type of clinical outcome; and drug benefit	Availability of treatment; novelty; comparator; efficacy; safety; adherence; clinical study design	Availability of existing treatment; novelty; clinical evidence; therapeutic benefits; safety; administration
Gonçalves et al., 2016 (44) (French)	Review of innovation in oncology	A medicinal innovation could be a product which through radical change brings something new and has the potential to be a treatment where nothing previously existed, or to significantly improve current standard treatment. Medical gains must be large with a favorable risk–benefit profile and, ideally, acceptable costs	Radical change, newness, availability of existing treatment, additional benefits, favourable risk–benefit profile, acceptable cost	Novelty; newness; availability of existing treatment; therapeutic benefit; cost

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Table 1. Continued

Study	Study description	Definition of innovation	Components of innovation	Dimensions of innovation
Gonzalez and Hofer, 2015 (28)	Review of FDA breakthrough therapy designation; USA	[A breakthrough therapy is defined as a drug that is] … intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development	Serious or life-threatening disease; improvement over existing therapies	Unmet need; therapeutic benefits
Gridchyna et al., 2012 (29)	Assessment of the characteristics of innovative inpatient medicines; analysis of DRG list; France	1) [Aspects of innovative medicines]: the period of time that the medicine is on the market, the benefit that it renders to patients, its added therapeutic value, and its impact on population health 2) Amélioration du Service Médical Rendu definition	1) Period of time on market; patient benefits; added therapeutic value; impact on population health 2) Added therapeutic value	1) Other; therapeutic benefits 2) Therapeutic benefits
International Workshop on Drug Innovation, 2008 (30)	Workshop; proposal of a definition of innovation in drug development; Europe	An innovation in the field of medicinal products consists of a completely or partially new active substance or biological entity or combinations of such entities acting against a disease, relieving symptoms or preventing a disease through pharmacological or molecular mechanisms, and developed and made available as a medicinal product that can improve the quality of patient management and outcomes. The present definition of drug innovation may also include new indications, technological and manufacturing processes, new formulations (including combinations), and delivery systems of known drugs	Novelty; improvement in quality of patient management and outcomes; new indications	Novelty; therapeutic benefits
Joppi et al., 2005 (31)	Analysis of biotech products in Europe, based on EMEA approvals	Therapeutic innovation: drugs for diseases without effective treatment, more effective than existing treatment, or active in patients resistant to current treatment	Availability of existing therapies; increased effectiveness; active in patients resistant to current therapies	Availability of existing treatment; therapeutic benefits; unmet need
Kwong and Norton, 2007 (32)	Analysis of the effect of advertising on new product novelty; USA	Creative products are products with a new pharmacological mechanism of action that differs from that of other existing marketed or investigational products for the same therapeutic indication	Novelty	Novelty

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Table 1. Continued

Study	Study description	Definition of innovation	Components of innovation	Dimensions of innovation
Lexchin, 2012 (33)	Analysis of pharmaceutical innovation based on published assessments of new drugs; Canada, France	1) Canadian Human Drug Advisory Panel: Breakthrough drug product: the first one to be sold in Canada that treats effectively a particular illness or addresses effectively a particular indication. Substantial improvement is provided by a drug product that, relative to other drug products sold in Canada, provides substantial improvement in therapeutic effects 2) *Prescrire International* evaluations, first three categories: Bravo (major therapeutic innovation in an area where previously no treatment was available) A real advance (important therapeutic innovation but has limitations) Offers an advantage (some value but does not fundamentally change the present therapeutic practice)	1) Availability of existing therapies; effectiveness; therapeutic improvement 2) Availability of existing therapy; therapeutic benefit	1) Availability of existing treatment; therapeutic benefits 2) Availability of existing treatment; therapeutic benefits
Morgan et al., 2008 (34)	Literature review and proposal of a definition of pharmaceutical innovation	Pharmaceutical innovation requires novelty of effectiveness. Pharmaceutical innovations create value to society by making it possible to generate improvements in patient health (net of treatment risks) that were previously unattainable. It is the uniqueness of such health improvements that defines pharmaceutical innovations. A drug can be considered a pharmaceutical innovation only if it meets otherwise unmet or inadequately met health care needs. This will depend on its efficacy, safety and convenience of use relative to the technologies available when it is introduced	Effectiveness; improvement in patient health; unmet need; safety; convenience	Therapeutic benefits; unmet need; safety; administration
Nelson et al., 2009 (42)	Systematic review of decremental cost-effectiveness	Any novel approach to diagnostics, therapeutics, or organization of medical care relative to an accepted and available standard … potentially including new applications of old technologies	Novelty	Novelty
O'Connor et al., 2016 (35)	Review of UK Early Access to Medicines Scheme	Promising innovative medicine designation – must meet all of: a) The condition should be life-threatening or seriously debilitating and with high unmet clinical need b) The medicinal product is likely to offer major advantage over methods currently used in the UK c) The potential adverse effects of the medicinal product are likely to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit–risk balance	Disease severity; unmet need; advantages over existing methods; benefit–risk balance	Unmet need; therapeutic benefits

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Table 1. Continued

Study	Study description	Definition of innovation	Components of innovation	Dimensions of innovation
Petrini, 2013 (36)	Review of innovation	Covers three concepts: a) "commercial concept" ("any newly marketed me-too product, new substances, new indications, new formulations, and new treatment methods") b) "technology concept" ("any industrial innovation, such as use of biotechnology, or the introduction of a new substance delivery system (patch, spray, etc.), selection of an isomer or a metabolite") c) "the concept of therapeutic advance" ("a new treatment that benefits the patient when compared to previously existing options")	Newness; novelty; therapeutic benefit	Newness; novelty; therapeutic benefits
Puntmann et al., 2010 (37)	Development of scoring system and algorithm for evaluating pharmaceutical innovation	Algorithm (EVITA) incorporating efficacy, safety, NNT, type of endpoint (surrogate vs final) and therapeutic aim	Improvement in efficacy; improvement in safety; clinical relevance of endpoints; disease severity	Safety; therapeutic benefits; unmet need
Raymond, 2010 (38)	Review of EMA innovative products strategy	In Europe, the "innovative medicine" status is granted if the active substance satisfies the criteria of innovation from a "scientific," "technical," or "therapeutic" point of view Within "scientific innovation," most are "new type" and "new mechanism of action" and relatively few "personalized medicine targeted therapy." The definition of "technical innovation" includes new manufacturing processes, new delivery systems and nanotechnology	New type/mechanism; technical innovation; therapeutic benefit	Novelty; therapeutic benefits
Salter et al., 2015 (39)	Review of biomedical innovation	Medical innovation: "the main goal of innovative care is to improve an individual patient's condition"	Improvements in patient condition	Therapeutic benefits
Soleimani and Zenios, 2011 (40)	Review of disruptive innovation in health care	A new treatment for a disease should be considered disruptive when no good treatment option previously existed. An innovation in the healthcare sector should also be considered disruptive if it allows a particular procedure or service to be transferred from the inpatient to outpatient setting or from the inpatient/outpatient setting to the patient's home. In some cases, it is possible that an innovation does not shift the treatment venue but still significantly alters the degree of invasiveness of a procedure or service (e.g., changes invasive procedure to pill)	Availability of existing treatment; change of venue; degree of invasiveness	Availability of existing treatment; administration; safety
Wardell and DiRaddo, 1980 (41)	Review of pharmaceutical innovation	A pharmaceutical innovation may be defined as any development that is intended to produce a therapeutic advance	Therapeutic advance	Therapeutic benefits

CNS, central nervous system; DRG, diagnosis-related group; EMA; European Medicines Agency; EPAR; European public assessment report; EVITA, EValuation of pharmaceutical Innovations with regard to Therapeutic Advantage; FDA, Food and Drugs Administration; mAb, monoclonal antibody; n/a, not applicable; NCE, new chemical entity; NICE, National Institute of Health and Care Excellence; NME, new molecular entity; NNT, number needed to treat; QALY, quality-adjusted life-year; UK, United Kingdom; USA, United States of America; VBP, value-based pricing.

endpoints, but not if they provide only a minor or temporary benefit. In the case of diseases where subsets of patients have a limited response to existing treatments, a new therapy would need to provide a major benefit to be classed as an important innovation. For conditions responsive to existing treatment, new products could achieve a moderate innovation rating if they provide a major therapeutic improvement, but those with similar efficacy and safety to existing therapies are likely to be classed only as technological or pharmacological innovations (14;46). The descriptions of this algorithm in two studies also included disease severity as a factor (12;15).

In addition, five references described the approach to innovation taken by the National Institute for Health and Care Excellence (NICE). NICE considers a product to be innovative if it "adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY (quality-adjusted life-year) measure" (16–20), and if the product offers a "step-change in terms of outcomes for patients" (16–18). To be a "step-change," a product must have a clinical benefit, particularly in the treatment of a condition with no existing effective treatment, or for which there is no consistently satisfactory treatment (18).

A further three references described innovation in terms of a combination of the technology level and comparative effectiveness (21–23). For example, one study considered technology level to be the technical level of innovation in relation to existing drugs for the same diseases; for new molecular entities, the technology level would be high. Comparative effectiveness was defined as the therapeutic value which the drug offers compared with competing products in the same therapeutic class (21); other authors have used a product's Food and Drugs Administration (FDA) review type (standard or priority) as a proxy for therapeutic potential (22;23). In this framework, substantial technical advances coupled with high therapeutic potential constitutes radical innovation. High levels of technical advance or therapeutic potential alone are classed as technological and market breakthroughs, respectively (22).

The remaining twenty-seven definitions (Table 1) included a wide range of approaches to innovation. Some approaches are straightforward: one study defined a pharmaceutical innovation as any development that is intended to produce a therapeutic advance (41), and another considered innovation to be superiority over an active comparator in clinical trials (26). Other definitions included multiple aspects. For example, one proposed definition of innovation was "a medicinal product that provides, through a step-change, something novel, with the potential or proven ability to yield, for individuals and/or their society, a treatment not previously available or a clinically significant improvement in treatment, with large health gains and a favorable benefit to harm balance, at an acceptable cost" (7). Similarly, an international workshop on drug innovation defined an innovation as a new active substance or biological entity that can improve the quality of patient management and outcomes, but also suggested that new indications, technological and manufacturing processes, formulations, and delivery systems could constitute innovations when applied to existing drugs (30).

In addition to the approach used by AIFA, two further studies described algorithms for assessing drug innovation (27;37). Both algorithms were more complex than the AIFA method, but included similar elements, being broadly based on efficacy, safety, and unmet need (disease severity or absence of available treatments). One algorithm also incorporated the type of endpoint (surrogate vs clinical) used to demonstrate improvements in efficacy (37), while the other included the design of key clinical studies (e.g., use of an active comparator) and an assessment of adherence to a new product (27).

Overall, twenty-five distinct definitions referred to clinical effectiveness, which was described using a variety of terms (7;15–17;19;21;24–31;33–39;41). Terms relating to the availability of existing treatments (eleven definitions) (7;13;15;16;27;31;33;40;44) and to disease severity or unmet need (seven definitions) (15–17;28;34;35;37) were also commonly used. Novelty was mentioned in eight definitions (7;18;21;27;30;32;36;42), while a further three referred to newness as a characteristic of innovative drugs (17;29;36). Trial endpoints or the use of an active comparator were important factors in four definitions (24;26;27;37). Notably, only two definitions included cost as an element of innovation. The definition proposed by Aronson et al. in 2012 requires innovations to provide therapeutic advances "at an acceptable cost" (7), while that described by Gonçalves et al. in 2016 suggests that "medical gains must be large with a favorable risk–benefit profile and ideally, acceptable costs" (44).

Additional Definitions of Innovation

Manual Web site searches identified definitions of innovation from NICE and AIFA that matched those in the published literature, as well as additional definitions from the Haute Autorité de Santé (HAS; France), the Tandvårds- och läkemedelsförmånsverket (TLV; Sweden), the Scottish Medicines Consortium (SMC), the Zorginstituut Nederland (ZINL), and the National Health Service in England (NHS England) (Table 2) (46–53). In France, HAS defines innovative products as those for which the manufacturers claim a moderate to major improvement of the clinical benefit compared with that provided by existing treatments (i.e., Amélioration du Service Médical Rendu [ASMR] of level I, II, or III) (35). By contrast, in the Netherlands innovative medicines are considered to be those which are promising, but for which insufficient data are currently available to be able to grant positive advice (52). The TLV, the SMC, and NHS England all included newness or novelty in their definitions, but required this to be associated with added value (50), benefits for patients (51), or improvements in the quality of health and care (53), respectively. In Germany, innovation is not part of the legal framework for the

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Table 2. Additional Definitions of Innovation Identified in Web Site Searches

Organisation	Definition of Innovation
National Institute of Health and Care Excellence (NICE), England	1) Judgements will … take account of … The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature that may not have been adequately captured in the reference case QALY measure (47). 2) If you consider the technology to be innovative with potential to make a substantial impact on health-related benefits that are unlikely to be included in the QALY calculation: state whether and how the technology is a "step-change" in the management of the condition (48).
Haute Autorité de Santé (HAS), France	Innovative products are defined as those for which the manufacturers claim a moderate to major improvement of the clinical benefit compared to that provided by existing treatments (i.e., "ASMR" of level I through III) (49).
Agenzia Italiana del Farmaco (AIFA), Italy	Describes algorithm reported in Motola *et al.*, 2005 (14;46).
Tandvårds- och läkemedelsförmånsverket (TLV), Sweden	Innovation is about new and better ways to create value for society, enterprises, and individuals. Innovations are new solutions that meet the needs and demands of everyday life and the outside world. The value arise in the utilization and application of an idea. The value created can take many forms: economic, social, or environmental values. An innovation is therefore a new solution or an idea that is a result of a development process and responds to the needs of the market (50).
Scottish Medicines Consortium (SMC)	"SMC doesn't have a definition of what an innovative medicine is- but we recognise it when we see it. " [There exists a] concept of "rewardable innovation" – medicines that are novel, useful, and represent revolutionary or incremental change But [SMC] wants to avoid innovation for innovation's sake – product needs to show it still meets a need or benefits patients (51).
Zorginstituut Nederland (ZINL)	As [ZINL] sees it, this [conditional reimbursement] applies not only to innovative health care (care that is promising, but for which insufficient data are currently available to be able to arrive at positive advice) … (52).
National Health Service (NHS), England	An idea, service or product, new to the NHS or applied in a way that is new to the NHS, which significantly improves the quality of health and care wherever it is applied (53).

ASMR, Amélioration du Service Médical Rendu; QALY, quality-adjusted life-year.

assessment of new drugs, which focusses on the additional benefit provided.

Dimensions of Innovation in Published Definitions

The results of reducing the terms used to describe innovation from all forty-four definitions identified in the literature (including duplicates) to ten dimensions of innovation are shown in Figure 2. Therapeutic benefit was the most commonly occurring dimension, found in forty definitions. No other dimension was seen in more than half of the definitions, with novelty and the availability of existing treatments the second and third most common dimensions. Unmet need and safety were each factors in ten definitions. Administration (which includes factors such as convenience and adherence) occurred less frequently than newness.

DISCUSSION

In total, the systematic search found forty-four definitions of innovation, with a further seven identified through manual Web site searching. Some definitions occurred more than once; in particular, the algorithm used by AIFA in Italy (12–15) and the approach used by NICE in England (16–20) were both mentioned in several publications.

Analysis of the dimensions of innovation included in the definitions identified suggested that the therapeutic benefit offered by a new product is generally considered to be the most important factor in categorizing a new medicine as innovative. However, quantification of therapeutic benefit is consistently absent from definitions, and is left to subjective interpretation. Under several definitions, drugs for indications where no previous therapies exist and those with novel structures or mechanisms of action would also be considered innovative, although novelty of structure of mechanism alone is not rewarded by HTA bodies, payers, or clinicians. Notably, only two definitions included cost, and these required only that the cost of an innovation be "acceptable" (7;44).

Our findings are similar to those of a 2013 systematic review of innovation in drug development, which found that the majority of articles identified defined innovation in terms of the number of new drugs (21/42; 50 percent) or patents (4/42; 10 percent); the three studies that included economic elements assessed innovation in terms of productivity, cost-effectiveness, and market share (11). The potential for innovations to reduce costs is rarely described in the literature. One study identified in this review was a 2009 systematic review of the cost-effectiveness of innovations (defined according to novelty),

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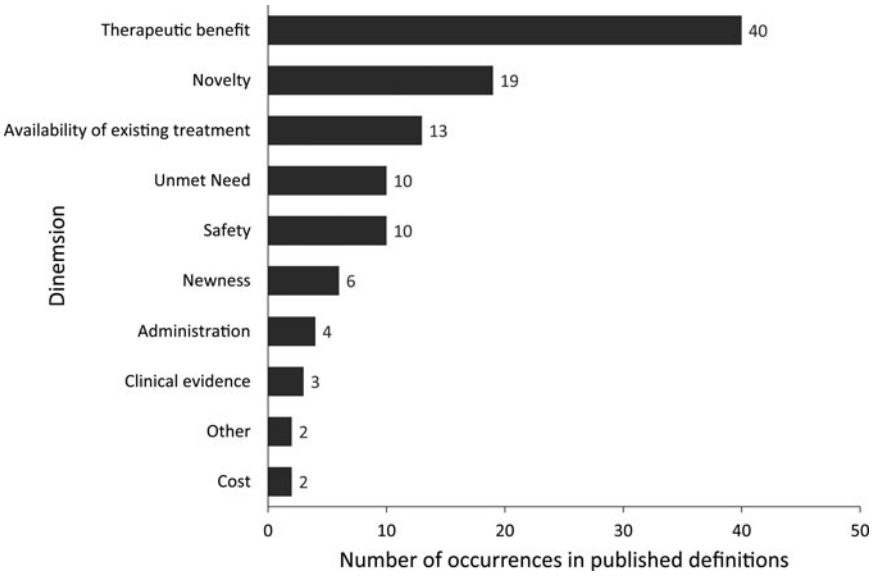

Figure 2. Dimensions of innovation, number of occurrences in identified definitions.

which found that of 2,128 published cost-effectiveness ratios, 1,533 (72 percent) described innovations that increased cost and improved health (42). Only nine comparisons (0.4 percent) described innovations that were decrementally cost-effective, that is, that saved more than $100,000 per QALY lost (42). Of interest, these nine interventions were not new drugs, but comprised changes in devices, procedures, physiotherapy, and behavioral interventions, as well as, in one case, watchful waiting in place of surgical intervention (42).

The definitions described most frequently in the literature were those used by two HTA bodies, AIFA and NICE (12–20;46;47), and in general the definitions used during HTA processes appear to follow a similar trend. The absence of costs from their analysis of innovation is somewhat surprising. We hypothesize that this reflects a two-step process, with price negotiations taking place after an assessment of clinical value (in some countries innovation, together with other factors, is incorporated through acceptance of a higher cost per QALY threshold), but it may contribute to the tendency for new innovations to be associated with increasing costs.

Several studies addressed the type of innovation displayed by a new product, in terms of both technical differences and therapeutic potential (21–23). For example, an entirely new molecular entity with a high degree of additional clinical benefit might constitute a radical innovation, whereas a small chemical change providing only minor additional benefits would be described as an incremental innovation (21–23).

Surprisingly, although the availability of existing treatments was included in eleven definitions of innovation (7;13;15;16;27;31;33;40;44), there was no specific mention of drugs for orphan diseases in any of the definitions identified. It is unclear whether the innovativeness of orphan drugs is fully captured by the definitions currently in use; in particular, these may not take into account the possibility that the funding of orphan drugs may lead to the future development of treatments for broader patient populations.

From an economic perspective, all current definitions of innovative medicines are incomplete. Inclusion of drug costs may allow the construction of a partial economic definition, but the nature of approval and reimbursement processes means that innovation in medicine is inherently different from innovation in other industries, which relies substantially on diffusion (54).

In industries with functioning markets, a product's characteristics and price may lead it to become a drastic innovation (making current products obsolete) or a nondrastic innovation (improving on current products, or reducing costs); the definition of a product as innovative is confirmed after launch, and is typically dependent on uptake. The reward for developing an innovative product is, therefore, its uptake by a large number of consumers. By contrast, of the studies identified in the literature, only a single review article referred to innovation being determined by the success (societal or commercial) of a new drug (43). The innovativeness of a new medicine is typically decided by HTA bodies or regulators alongside assessment of therapeutic benefit, that is, before the medicine is in widespread use, and without necessarily addressing the economic implications. There is often no formal attempt to quantify therapeutic benefit, and despite some use of multi-criteria decision analysis methods, decisions are often dependent on rough comparisons between therapeutic areas and/or patient characteristics.

Utility/QALY-based approaches are used in some countries, but have been shown to fail in certain areas, leading to the implementation of various adjustments (end-of-life criteria,

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the UK Cancer Drugs Fund, specific conditions for ultra-orphan diseases, etc.) (55). When the innovative nature of a product leads to acceptance of a high price, affordability issues may lead to restrictions on use; consequently, some new drugs (e.g., Sovaldi® for hepatitis C) may meet an HTA definition of innovation, and may be a commercial success, but not be considered to be a drastic innovation in an economic sense due to limited uptake. In other words, because there is not a perfect market for pharmaceuticals (market failure), the price is not determined by the equilibrium between the willingness to pay consumers and the profit expectations of manufacturers, leading to underutilization of a drastic innovation.

Another potential consequence of the way the innovativeness of new medicines is assessed is that it is possible for a new product to be classified as not innovative, because the active ingredient has been used in other indications for many years; nevertheless, the demonstration of efficacy in a new indication may be a major advance scientifically, and may provide substantial therapeutic benefits for patients. This situation, and the resulting challenges to drug prices (as, for example, occurred following the authorization of dimethyl fumarate for relapsing–remitting multiple sclerosis) (56) may both delay patients' access to effective therapies and reduce the incentive for manufacturers to investigate potential drug repurposing opportunities. The assumption in some definitions that a product must be novel to be innovative may, therefore, lead to a failure to fully recognize clinical benefits. Notably, the German approach of considering only the additional benefit provided by a new product avoids this situation.

Conversely, there is no consistent relationship between research and development activities, which by their nature involve a form of innovation, and whether the new medicines that result are considered innovative. Although novelty is included in several of the definitions of innovation identified in the systematic search, it is not typically rewarded *per se* by HTA bodies, while payers and clinicians are likely to prioritize improvements in patient outcomes over novelty. Consequently, there is a distinction between the concept of innovation during research and that of a new medicine being innovative from an HTA perspective.

This systematic review has some limitations. First, the EconLit search was restricted to articles published in English, and some relevant economic literature published in other languages may have been missed. No language restriction was applied to the MEDLINE or Embase searches, and several studies published in French or Italian were reviewed; it is, therefore, likely that the relevant health economic literature is captured in the review. However, the economic dimension in pharmaceutical innovation may be under-represented in the literature, which focuses mainly on aspects related to research and development costs, and represents the perspective of manufacturers rather than HTA bodies. Second, some studies published before 2010 which were identified through citation searching were included, but the systematic search was limited to references from 2010 onward. It is likely that the older definitions included represent those which are still considered to be useful (and cited); older definitions not included in the review are, therefore, likely to be of lesser interest. Third, inclusion of references identified through citation searching in the analysis of the dimensions of innovation mean that this analysis should not be considered to be fully quantitative. However, this potential bias toward more popular definitions means that the results may be considered a reasonable indication of the weight currently given to particular aspects of innovation.

This review has focused on healthcare innovation with specific reference to new medicinal products. Future research is needed to investigate the factors that influence uptake of innovative medicines, and particularly whether the usage of some products is lower than expected due to greater consideration by payers of cost and affordability issues than innovativeness and cost effectiveness. The limitations of a focus by decision makers on drug acquisition costs are likely to become increasingly clear as the treatment of many diseases becomes personalized, with outcomes dependent on processes incorporating the use of diagnostic tests and the selection of the most suitable treatment for each patient, rather than on the efficacy of drugs alone; encouragement and rewarding of innovation in these areas is likely to require an approach different from that currently in use.

The innovativeness of devices, surgical interventions, and other procedures may be assessed differently (42), as may innovation in the development of drugs for orphan diseases, which was not described in the literature identified by our systematic search. Additional work will be needed to investigate innovation in other areas of health care, and to compare this with the way innovation is considered in the wider economic literature and in other industries. For example, diffusion of innovations may be more prevalent with regard to the use of particular procedures and devices than appears to be the case for new medicines.

RECOMMENDATIONS

In conclusion, overall, this systematic review of the published literature has found that the most commonly referred to aspect of innovation with respect to new medicines is therapeutic benefit; other key elements are unmet need, safety, and the availability of existing treatments. Novelty (of structure or mechanism of action) was also a common component of the definitions identified. However, we do not believe that novelty alone, in the absence of added therapeutic benefit, should constitute a rewardable innovation, as this may prevent funds being better spent elsewhere. For products that improve patient outcomes, the extent to which novelty should increase the acceptable price is not straightforward: by encouraging research and development, rewarding novelty may lead

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to long-term gains in terms of new medicines, at the expense of short-term increases in expenditure. The weight given to novelty may, therefore, be a political judgement based on societal values, and require a perspective broader than that of the individual product and condition under consideration. It is clear that, other than therapeutic benefit, there is little agreement on what characteristics of new medicines constitute rewardable innovation.

Finally, alignment across countries and among regulators, HTA bodies, and payers would help manufacturers define research policies that can drive innovation and lead to new methods of treating diseases, but may be challenging, as judgements about what aspects of innovation should be rewarded vary among stakeholders, and depend on political and societal factors.

SUPPLEMENTARY MATERIAL

Supplementary Table 1:
https://doi.org/10.1017/S026646231 8000259
Supplementary Table 2:
https://doi.org/10.1017/S026646 2318000259
Supplementary Table 3:
https://doi.org/10.1017/S026646 2318000259
Supplementary Table 4:
https://doi.org/10.1017/S026646 2318000259
Supplementary Table 5:
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Supplementary Table 6:
https://doi.org/10.1017/S026646 2318000259
Supplementary Table 7:
https://doi.org/10.1017/S026646 2318000259
Supplementary Table 8:
https://doi.org/10.1017/S026646 2318000259

CONFLICTS OF INTEREST

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