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SPECIAL REPORT

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The economic case for precision medicine

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ABSTRACT

Introduction: The advancement of precision medicine into routine clinical practice has been highlighted as an agenda for national and international health care policy. A principle barrier to this advancement is in meeting requirements of the payer or reimbursement agency for health care. This special report aims to explain the economic case for precision medicine, by accounting for the explicit objectives defined by decision-makers responsible for the allocation of limited health care resources.

Areas covered: The framework of cost-effectiveness analysis, a method of economic evaluation, is used to describe how precision medicine can, in theory, exploit identifiable patient-level heterogeneity to improve population health outcomes and the relative cost-effectiveness of health care. Four case studies are used to illustrate potential challenges when demonstrating the economic case for a precision medicine in practice.

Expert commentary: The economic case for a precision medicine should be considered at an early stage during its research and development phase. Clinical and economic evidence can be generated iteratively and should be in alignment with the objectives and requirements of decision-makers. Programmes of further research, to demonstrate the economic case of a precision medicine, can be prioritized by the extent that they reduce the uncertainty expressed by decision-makers.

1. Introduction

Precision medicine, and related concepts including *personalized* and *stratified* medicine, is growing in prominence within the scientific literature and clinical practice [1]. Precision medicine is inclusive of, but not limited to, the targeting of health care interventions to patients that share a specific and identifiable set of characteristics [2]. Most applications to date have used a single test, as a companion diagnostic, to target a defined medicine to a known subgroup of patients. Applications of precision medicine may also include algorithm-based prescribing [3], risk-stratification within population screening programmes [4], and the use of genomic-based diagnostics for rare inherited conditions [5].

The advancement of precision medicine into clinical practice has been highlighted as an agenda for national and international health policy [6,7]. A principal barrier to this advancement is in addressing the requirements of the payer or reimbursement agency for health care [8,9]. The economic case for precision medicine within this context rests, ultimately, on demonstrating value to decision-makers responsible for allocating finite resources for health care. The comparison of relevant alternatives in terms of their costs and consequences, within an economic evaluation, is one method to generate evidence that can inform health care resource allocation decisions [10].

An extensive literature of published economic evaluations of health technologies for precision medicine is developing [11–19] and, in 2016, some 45 systematic reviews on this topic were identified [20]. The specific challenges in designing and conducting economic evaluations of precision medicine have also been described [21–27]. This *Special Report* aims to build on this literature and explain the economic case for precision medicine within a framework (cost-effectiveness analysis [CEA]) for the economic evaluation of health technologies used by decision-makers in England [28]. Section 2 describes the theory of the economic case within this framework. Definitions of key economic terms are provided in Table 1. Four case studies illustrative of precision medicine (see Table 2) are presented in Section 3 to highlight if, and how, evidence to support their economic case exists in practice. The report concludes by discussing the generation of evidence to demonstrate the economic case for precision medicine.

2. The economic case: in theory

The maximization of population health is viewed to be a fundamental objective of any health care system; decision-makers responsible for recommending health technologies are assumed to pursue health maximization, subject to a finite budget for the provision of health care [29]. Any resource allocation decision, therefore, has an opportunity cost, expressed in terms of health forgone, such that those same resources could have otherwise been used to provide an alternative health technology [30]. Population health is subsequently maximized by recommending health technologies if their expected health benefit exceeds their opportunity cost [31,32].

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Table 1. Glossary of key terms.

Term	Definition
Cost-effectiveness analysis.	A method of economic evaluation that compares the expected incremental cost and health outcomes derived from relevant alternative health technologies [10].
Cost-effectiveness plane.	A plot to illustrate the incremental outcomes derived from an intervention health technology versus a relevant comparator [43].
Cost-effectiveness threshold.	The additional cost that must be imposed on the budget for health care to displace one QALY [30].
Decision-analytic model.	A series of mathematical relationships that represent the progression of a patient's diagnosis or disease and the impact of a health technology on diagnosis and/or disease progression. Model-based cost-effectiveness analyses can synthesize all available evidence to inform resource allocation decision-making [51].
Decision uncertainty.	The probability of recommending a health technology that is not cost-effective [35].
Heterogeneity.	The variation in expected costs and consequences that can be explained by patient-level characteristics [37].
Methodological uncertainty.	The uncertainty with respect to the appropriate methods of performing an economic evaluation [83].
Microcosting	Estimation of the specific resources and associated unit costs of a health technology [71].
Opportunity cost.	The (health) benefits forgone due to a change in the allocation of health care resources [30].
Parameter uncertainty.	The uncertainty in the true value of each input within a decision-analytic model [87].
Structural uncertainty.	The uncertainty with respect to the structure (care pathways, model type) of an economic evaluation [86].
Quality-adjusted life years.	A generic measure of outcome that has reference points of one (for full health) and zero (for death) [33].
Reference case.	Pre-defined preferred criteria for performing an economic evaluation [84].
Value of information.	A set of methods to quantify the value of further research to reduce decision uncertainty [89].

Table 2. Case studies of precision medicine.

Diagnostic test and source of heterogeneity	Relevant population and decision	Potential source of value	Challenge when establishing the economic case
Companion diagnostic for activating mutations of epidermal growth factor receptor tyrosine kinase.	To inform the prescribing of gefitinib for patients with non-small cell lung cancer.	Improved clinical effectiveness.	• Limited evidence from test result to cost and health outcomes for all diagnostics.
Thiopurine S-methyltransferase mutation genotyping or enzyme phenotyping.	To inform the prescribing of azathioprine for patients with eligible autoimmune diseases.	Reduced adverse drug reactions.	• Clinicians may implement testing strategy imperfectly.
Assays to detect anti-drug antibodies and to measure drug levels.	To inform the prescribing of monoclonal antibody tumor necrosis factor-α inhibitors for patients with eligible autoimmune diseases.	Improved health outcomes and/or reduced health care resource use.	• Different permutations of multiple tests are possible; • Position of tests in care pathway may be uncertain; • The cost of novel testing strategies may be unknown.
Next generation sequencing gene panel test.	To inform the diagnosis of inherited retinal dystrophies.	Improved diagnostic accuracy and potentially reduced health care resource use.	• Capacity constraints may restrict the number of tests performed; • Non-health consequences may be considered by decision-makers.

CEA is a method of economic evaluation that compares the expected incremental (cost and health) outcomes derived from relevant alternative health technologies [10]. Health outcomes may be expressed using a generic measure, such as quality-adjusted life years (QALYs), to facilitate comparability between different diseases [33]. Judgments regarding the relative cost-effectiveness of a health technology can be made with reference to decision rules that comprise incremental costs, QALYs, and a cost-effectiveness threshold [34,35]. A health technology with a positive expected incremental net benefit versus its relevant comparator(s) is indicative of (average) population health maximization and relative cost-effectiveness [36] (see Table 3).

Heterogeneity in expected costs and QALYs is also likely to exist, conditional on patient-level characteristics, such that subgroups of patients within a population may derive incremental net benefits from the health technology that differ systematically from expected population-level outcomes [37–39]. Precision medicine involves using a mechanism to reveal between-patient heterogeneity that was unobserved previously, for example, using a diagnostic test to measure

Table 3. Decision rules for relative cost-effectiveness.

Decision Rule	Formula
Incremental net monetary benefit	$\lambda(Q_1 - Q_0) - (C_1 - C_0) > 0$
Incremental net health benefit	$(Q_1 - Q_0) - \frac{(C_1 - C_0)}{\lambda} > 0$

λ: cost-effectiveness threshold; Q_1: expected consequences derived from new technology, Q_0: expected consequences derived from comparator technology; C_1: expected cost derived from new technology; C_0: expected cost derived from comparator technology. Equivalent decision rules can be expressed as incremental net monetary or health benefits [34,35].

the quantity of a biomarker predictive of differential treatment response and, consequently, incremental cost and health outcomes [40]. The economic case for precision medicine, in theory, is contingent on whether the expected net benefit of treating patients according to their subgroup is greater than that obtained from a relevant alternative strategy [39,41,42]. The cost-effectiveness plane [43] in Figure 1 illustrates three scenarios of incremental outcomes that may characterize a precision medicine and also be consistent with a positive incremental net benefit.
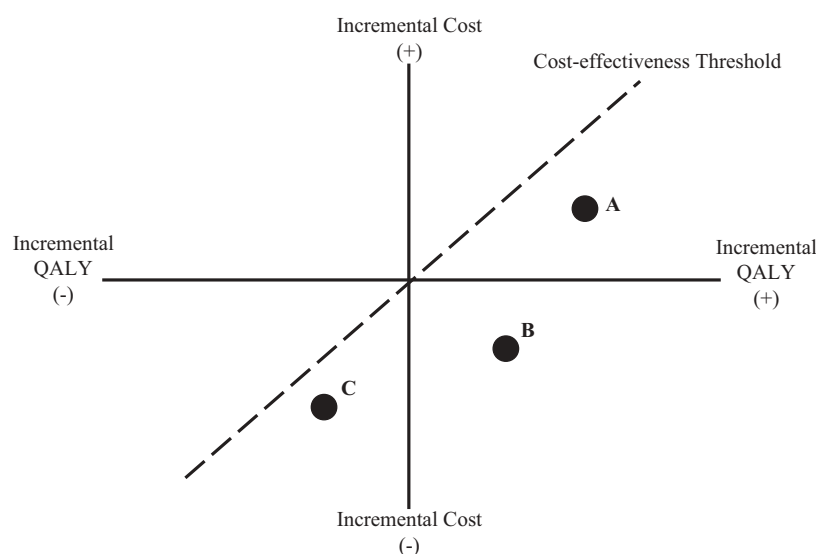
Example	Incremental Cost	Incremental QALY	Decision rule
A	Increase	Increase	Refer to cost-effectiveness threshold
B	Decrease	Increase	Dominant
C	Decrease	Decrease	Refer to cost-effectiveness threshold

Figure 1. Three incremental outcomes consistent with a positive net benefit.

The cost-effectiveness plane [43] illustrates the incremental costs (Y-axis) and incremental consequences (X-axis) between a new health technology (for example, a precision medicine) and a relevant comparator (for example, current practice). The dashed line through the origin of the plane represents the cost-effectiveness threshold. Incremental outcomes that are below the dashed line graphically have a positive incremental net health benefit (see accompanying table). The figure illustrates that different combinations of incremental outcomes are possible for a precision medicine to be a relatively cost-effective use of health care resources.

3. The economic case: in practice

Four case studies illustrative of clinical applications of precision medicine (see Table 2) are now presented. These case studies were selected to highlight specific examples of the process and challenges of demonstrating their economic case in practice.

3.1. Case study 1: testing activating mutations of EGFR-TK and gefitinib

Gefitinib is a first-generation tyrosine kinase inhibitor for non-small cell lung cancer (NSCLC) tumors known to have activating mutations of epidermal growth factor receptor tyrosine kinase (EGFR-TK). In 2005, the Food and Drug Administration (FDA) restricted gefitinib from being used to treat all patients with NSCLC [44]. Subsequent trial evidence revealed heterogeneity in response to gefitinib that was unobserved previously, with respect to EGFR-TK mutation status [45]. The FDA and European Medicines Agency, consequently, granted marketing authorization for gefitinib in patients with NSCLC that had activating mutations of EGFR-TK [46]. The economic case for gefitinib is based on the premise of improved clinical effectiveness by stratifying the population of NSCLC patients by EGFR-TK mutation status.

In 2010, the National Institute for Health and Care Excellence (NICE) in England published a technology appraisal of gefitinib [47]. The technology appraisal recommended gefitinib as first-line treatment for locally advanced or metastatic NSCLC with activating mutations of EGFR-TK, based on the results of an economic evaluation that suggested this was a cost-effective use of health care resources [47]. The diagnostic test to identify mutation status, however, was not specified within the product license of gefitinib [48]. As a consequence, different diagnostic tests were used within the health care system to establish mutation status [49], with unknown implications for the relative cost-effectiveness of gefitinib.

In response, in 2013, NICE evaluated 10 different testing strategies to identify activating mutations of EGFR-TK as part of the Diagnostics Assessment Programme [48]. A subset of testing strategies ($n = 5$) was recommended for routine clinical practice according to evidence of relative cost-effectiveness [49,50]. The economic case for using these tests was a challenge to establish, in practice, because cost and health outcome data were not available for every strategy. A *de novo* decision-analytic model-based CEA [51–53], therefore, addressed deficiencies in the evidence base by (i) assimilating all available evidence and (ii) 'linking' test accuracy and long-term outcome data from different studies or by assuming that the tests had 'equal prognostic value' [48,54]. NICE recommended that future studies could address these evidence limitations by comparing different methods to test activating mutations of EGFR-TK directly and to link these findings to patient outcomes.

3.2. Case study 2: testing TPMT status and azathioprine

Azathioprine is an effective treatment for autoimmune conditions such as Crohn's disease and rheumatoid arthritis; however, a subset of patients may experience dose-limiting adverse drug reactions (ADR) such as severe profound neutropenia [55]. Patients exhibit potentially identifiable heterogeneity in developing ADR to azathioprine according to thiopurine S-methyltransferase (TPMT) enzyme activity. Defined pretreatment genotyping (to identify mutations in the gene that codes for TPMT) or phenotyping (to measure the levels of active TPMT enzyme) can be used to identify patients at high-risk of severe neutropenia [55]. The economic case for testing TPMT is based on the premise that identifying such patients will improve population health outcomes by reducing the quantity of ADRs and the associated cost of managing these harms.

Several published model-based cost-effectiveness analyses concluded that TPMT testing, to inform azathioprine prescribing decisions, was a dominant intervention (see Figure 1) that produced more health benefit at a lower cost compared with not testing [56]. However, a subsequent pragmatic randomized controlled trial found that the relative cost-effectiveness, suggested by these model-based studies, may not be realized in routine clinical settings because clinicians, potentially, failed to adjust their prescribing behavior according to the diagnostic information regarding the genotype of each patient [57]. The testing protocol suggested that clinicians should prescribe a higher starting dose of azathioprine (for example, 2–3mg/kg/day) to patients at low-risk of ADR, and a reduced starting dose of azathioprine (for example, 25–30mg/day) to those patients at-risk of ADR. In the trial, however, patients at-risk of ADR (heterozygous for the *TPMT* gene) received the same dose as those patients at a lower-risk (wild-type) and, consequently, there was no difference in the rate of azathioprine discontinuation due to ADRs between the arms of the trial ($p = 0.59$) [57,58]. The expected outcomes from the study concluded that TPMT testing to inform azathioprine prescribing decisions, rather than being a dominant intervention, reduced both health care costs by £421.06 and health outcomes by 0.008 QALYs simultaneously [57].

The potential economic case for precision medicine is reliant on the amenability of clinicians to follow a protocol for testing [25,27,59]. Model-based economic evaluations may assume implicitly that diagnostic testing protocols are followed. However, evidence of how diagnostic information, obtained from a test result, is used by clinicians within their routine decision-making is not always clear [60]. For example, clinical decisions may be challenging if the cut point for a continuous test result is disputed or if multiple treatment strategies are possible following a particular test result. In practice, therefore, the imperfect implementation [61] of a testing strategy, through clinicians' prescribing behavior, may contribute to overestimating the net health gain obtained from a precision medicine [20].

3.3. Case study 3: monitoring therapeutic drug levels and/or anti-drug antibodies of tumor necrosis factor-α inhibitors

Monoclonal antibodies that inhibit tumor necrosis factor-α (TNFi), such as adalimumab, are a class of biologic therapies used widely in the management of autoimmune conditions such as rheumatoid arthritis, Crohn's disease, and psoriasis [62]. All medicines require circulating levels of the active drug to remain within a known therapeutic range for treatment effectiveness and safety (and, consequently, cost-effectiveness) [63]. Patients may develop immunogenicity against monoclonal TNFi antibodies, by producing anti-drug antibodies, resulting in drug levels reducing below the minimum required by the therapeutic range to be effective [64,65].

Detecting the presence of anti-drug antibodies and/or measuring the level of TNFi in the serum are two potentially useful sources of heterogeneity in treatment response between patients [66]. The measurement of these biomarkers may be used to inform if, and how, a monoclonal TNFi antibody is prescribed most appropriately in patients with relevant autoimmune conditions [67]. The economic case of using one, or both, of these biomarkers is based on the premise that improved health outcomes and/or reduced health care resource use may be achieved by identifying whether treatment should continue and/or dose adjustment is required. In 2016, NICE conducted a model-based CEA of adalimumab and infliximab anti-drug antibody and drug level testing for patients with Crohn's disease, as part of the Diagnostics Assessment Programme [68]. The assessment concluded that there was insufficient evidence to recommend testing in routine clinical practice, driven by uncertainties in the accuracy, timing, and (health and cost) outcomes derived from testing [68].

Establishing the economic case for measuring more than one biomarker is a challenge, in practice, because different permutations of tests are possible, at different points along a care pathway, resulting in different expected cost and health outcomes [22]. For example, the NICE assessment of TNFi anti-drug antibody and drug level testing evaluated concurrent testing (both biomarkers measured at the same time) and reflex testing (anti-drug antibodies only measured if drug levels were not detected) in patients that had maintained response, or lost response, to their TNFi [68]. Model conceptualization methods may, therefore, be appropriate to inform the relevant comparator strategies and structure of a model-based economic evaluation [69,70].

In addition, the cost of a new test or prescribing algorithm may be unknown if it is not already being used in routine practice. Therefore, microcosting studies, which take a 'bottom-up' approach by measuring and valuing all resources required to use a health technology, can help to estimate the cost of a new diagnostic test in routine clinical practice [71]. For example, one manufacturer of the anti-drug antibody and drug level tests charged approximately £35 per patient for both tests (2015 prices, UK); however, a microcosting study estimated the cost of these tests to approximate £152.52 per patient if all resources to perform testing in routine clinical practice (such as an additional appointment, the analysis of samples, and the time to make a treatment decision) were accounted for [71].

3.4. Case study 4: next generation sequencing panel for inherited eye disease

Massively parallel sequencing technologies have supported the development of a next generation sequencing (NGS)

gene panel test for the diagnosis of inherited retinal dystrophies (IRD) [72]. Historically, IRD were diagnosed by performing a single Sanger sequence test for each gene 'known' to cause vision loss. The single gene tests were subject to national variation in availability and service delivery [73] due, in part, to the cost, technical, and practical complexities of testing [74]. NGS gene panels are now being used to diagnose IRD in clinical practice. The 'Gene Dossier' submitted to the UK Genetic Testing Network estimated that the gene panel test would require a total incremental investment of £5,244 compared to conventional single gene testing. Downstream cost savings may also be possible due to fewer consultant appointments for sequential testing [75]. However, to date, the cost-effectiveness of using gene panels to diagnose IRD has not been investigated.

The use of gene panels facilitates substitution away from time-consuming single-gene testing and, in turn, may enable more individuals to be tested [74,75]. However, short-term capacity constraints within the health care system may impose a limit the number of tests that can be performed. Capacity constraints are, typically, not accounted for within model-based cost-effectiveness analyses [76]. Therefore, in practice, the total net health benefit derived from a precision medicine may be overestimated if the capacity to perform a testing strategy is restricted.

The anticipated benefit of the gene panel test, in the absence of treatments to prevent loss of vision, is the achievement of an accurate and timely diagnosis with information on prognosis and risk to family members [77]. Gene therapies are being developed for subtypes of IRD, which will require an accurate diagnosis for trial participation and eligibility for any subsequent licensed therapy [78]. The gene panel test will also reveal the mutation status of those patients with IRD that are ineligible for gene therapy. This diagnostic information may have value to patients themselves, for example, by improving their own capability to make informed life decisions [79]. In practice, however, if decision-makers were to account for such consequences as a 'benefit' (in addition to health gain) to inform population health care resource allocation decisions, the opportunity cost of those consequences must also be accounted for in terms of the (health) benefit forgone [79,80].

4. Generating evidence to support the economic case for precision medicine

The economic case for precision medicine rests on demonstrating value to decision-makers according to their explicit objectives. Diagnostic tests may improve population health by exploiting patient-level heterogeneity in cost and health outcomes. CEA within an economic evaluation is one method to generate evidence that demonstrates precision medicine may provide an incremental net health benefit. The four case studies, however, highlighted potential challenges when estimating the relative cost-effectiveness of precision medicine in practice.

The decision-making context for any health technology, supported by evidence from an economic evaluation, is inherently uncertain [81]. Limitations in the clinical and economic evidence base, for example, such as those highlighted by the preceding four case studies, serve to increase this uncertainty. The probability of recommending a health technology that is not cost-effective can be expressed as decision uncertainty [82]. The uncertainty present within an economic evaluation has been characterized in the literature as methodological, structural, and parameter uncertainty [83].

Methodological uncertainty describes the uncertainty with respect to the methods of performing an economic evaluation; for example, whether resource allocation decisions ought to account for the non-health outcomes described in Case Study 4 [26]. In practice, methodological uncertainty is resolved by the normative value judgments of a decision-maker, which may be expressed within preferred criteria for performing an economic evaluation, known sometimes as a 'reference case' [10,84]. Structural uncertainty refers to uncertainty with respect to the structure of an economic evaluation; for example, how a de novo decision-analytic model represents the uncertain positioning of the anti-drug antibody and drug level tests (Case Study 3) within an existing care pathway. The choice of decision-analytic model (for example, a Markov model or discrete event simulation) that best addresses the decision problem may itself be uncertain [85]. Methods exist that enable the impact of structural uncertainty on estimates of relative cost-effectiveness to be estimated, such as model averaging and the parameterization of structural assumptions [86]. Parameter uncertainty refers to the uncertainty in the true value of each input of an economic evaluation; for example, the accuracy and clinical effectiveness of the strategies to test for activating mutations of EGFR may be uncertain (Case Study 1). A probabilistic analysis is, therefore, necessary to handle parameter uncertainty by characterizing input parameters as distributions and simulating expected outcomes over these distributions [87,88].

Additional research has the potential benefit of reducing decision uncertainty and 'value of information' methods can provide a quantitative estimate of whether such research has value in reducing uncertainty in the economic evidence base [89,90]. Further research has value, in the context of relative cost-effectiveness, if its expected cost is less than its expected benefit. The upper-bound on the cost of further research can be estimated as the expected value of perfect information (EVPI) [90]. The expected value of partial perfect information (EVPPI) can estimate the upper-bound on the cost of research for specific (sets of) input parameters, such as long-term health outcomes, QALYs, or resource utilization [90]. The expected net benefit of sampling (ENBS) may estimate the value of specific study designs, for example, to inform the sample size of a trial, by accounting for the cost of research itself [91]. The ability of these methods to inform the design of future research may facilitate iterative economic evaluation [92], such that a de novo decision-analytic model may be built during the early development phase of a health technology, and subsequently refined, repopulated, and re-analyzed as more evidence is generated over the life cycle of the health technology [93–95].

Programmes of scientific research, such as biomarker discovery, can support the application of precision medicine and public resources for research have been diverted toward such programmes internationally [96]. Value of information

methods can be used to ensure that the evidence generated to support precision medicine is aligned with demonstrating value to decision-makers responsible for the allocation of limited resources for health care [97]. National funding schemes exist, such as those provided by Genome Canada [98], that encourage the development of an economic case for targeted treatment strategies or new diagnostics. The earlier the economic case for a new precision medicine is considered by manufacturers of diagnostic and pharmaceutical health technologies, and by organizations that fund research, the more likely the subsequent evidence base will be generated to inform health care decision-makers that the example of precision medicine is consistent with their objectives, such as population health maximization, and should be recommended for use in routine clinical practice.

5. Expert commentary

Precision medicine has the potential to improve population health outcomes and the relative cost-effectiveness of health care. The economic case for precision medicine should consider both the cost and consequences of revealing patient-level heterogeneity in a target population. Consideration of cost alone is not sufficient to inform population resource allocation decision-making. The benefits forgone, due to changes in the allocation of resources, must also be quantified. Generating evidence to support the economic case of a precision medicine in practice, however, can be a challenge. Manufacturers, analysts, and funders of research may improve their research and development activities by considering the evidenced required by later-stage decision-makers at an earlier time period in the process of evidence generation.

The economic evaluation of precision medicine, and the generation of further evidence, should be an iterative process rather than a one-time stand-alone activity. Decision-analytic modeling and the prospective collection of data, therefore, both have an important role in estimating the impact of using a diagnostic test in clinical practice on patients' long-term cost and health outcomes. Value of information analyses can be used to prioritize programmes of research, in the presence of competing deficiencies in the evidence base of a precision medicine, according to their potential to reduce decision uncertainty.

6. Five-year view

Precision medicine may evolve further in the future by increasing the utilization of prescribing algorithms that incorporate multiple biomarkers predictive of a specific outcome in clinical practice. Developments in the methods to estimate the accuracy, effectiveness, and cost of testing multiple biomarkers would, in turn, be valuable to estimate the opportunity cost of such algorithms more appropriately. The production and application of genomic-based diagnostics (for example, whole-genome sequencing and whole-exome sequencing) within routine clinical practice may also progress in the future. Substantial investment in capital (for example, laboratory facilities or an IT infrastructure) may be required, or the existing capacity to implement testing may be insufficient, which imposes constraints on the delivery of health care and an opportunity cost on population health. Developments in the methods to

evaluate the economic case for precision medicine, in the context of such capacity constraints, would also likely be informative to decision-makers. Increasing claims on finite resources for health care may also result in decision-makers supporting activities to disinvest in certain health care expenditures, which may be informed by precision medicine strategies. Decision-makers should, therefore, consider exploring social value judgments with respect to resource allocation decisions for health care, informed by members of the public, to support such disinvestment activities.

Key issues

- The economic case for a health technology can be made by comparing its cost and (health) consequences with those derived from a relevant alternative, according to the explicit objectives of a decision-maker responsible for the allocation of health care resources.
- In theory, the economic case for precision medicine can improve the relative cost-effectiveness of care by exploiting patient-level heterogeneity in cost and health outcomes.
- In practice, deficiencies in the (clinical and economic) evidence base, and the plausibility of assumptions, may make the economic case for precision medicine a challenge to demonstrate.
- Early consideration of the requirements expressed by decision-makers can improve the likelihood that appropriate evidence is produced to inform resource allocation decision-making. The economic case for precision medicine can be developed iteratively and the generation of further (clinical and economic) evidence can be prioritized according to the extent to which it reduces the uncertainty expressed by decision-makers.

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