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Title:

The Future of Precision Medicine: Potential Impacts for Health Technology Assessment

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JLK planned the analysis, conducted expert interviews and drafted the manuscript. AP conducted expert interviews and the literature review and drafted the manuscript. JCR and RL developed the original research idea, critically appraised the analysis and drafted the manuscript. KE conducted the literature review. AM & AC critically appraised the analysis and drafted the manuscript. HW conducted the literature searches. MT planned and project-managed the analysis and drafted the manuscript.

Conflicts of interest:

RL and JCR are employed by NICE and AM is a member of a NICE Technology Appraisal Committee. JLK, AP, KE, AC, HW and MT have no potential conflicts of interest that are directly relevant to the content of this article.

Abstract

Objective

Precision medicine (PM) allows healthcare interventions to be tailored to groups of patients based on their disease susceptibility, diagnostic or prognostic information or treatment response. We analysed what developments are expected in PM over the next decade and considered the implications for health technology assessment (HTA) agencies.

Methods

We performed a pragmatic literature search to account for the large size and wide scope of the PM literature. We refine and enrich these results with a series of expert interviews up to one hour in length, including representatives from HTA agencies, research councils and researchers designed to cover a wide spectrum of precision medicine applications and research.

Results

We identified 31 relevant papers and interviewed 13 experts. We found that three types of PM are expected to emerge in clinical practice: complex algorithms, digital health applications and 'omics'-based tests. These are expected to impact upon each stage of the HTA process, from scoping and modelling through to decision-making and review. The complex and uncertain treatment pathways associated with patient stratification and fast-paced technological innovation are central to these effects.

Discussion

Innovation in PM promises substantial benefits but will change the way in which some health services are delivered and evaluated. The shelf-life of guidance may decrease, structural uncertainty may increase, and new equity considerations will emerge. As biomarker discovery accelerates and artificial intelligence-based technologies emerge, refinements to the methods and processes of evidence assessments will help to adapt and maintain the objective of investing in healthcare that is value for money.

Key points

- Three types of precision medicine technologies are likely to become more widespread in clinical practice over the next decade: 'Omics'-based biomarkers; complex artificial intelligence-based algorithms; and digital health applications

- These innovations will require health technology assessment and guideline-producing agencies to adapt their methods and processes
- The fast pace of discovery technological innovation, along with the potentially complex and uncertain treatment pathways patients will be presented with, are at the centre of the new challenges

1. Introduction

Recent technological developments have allowed healthcare to be increasingly tailored toward specific patients and subgroups, a medical model referred to as precision medicine [1]. Broadly this process involves tailoring aspects of the patient pathway (i.e. advice, referral or treatment) based on their disease risk, prognosis or likely treatment response – a process that can yield additional benefits to patients and the wider healthcare system. The ‘precision’ is informed by tools that incorporate genetic, environmental and lifestyle information, and range from risk equations [2] to genetic testing [3].

Technological progress in precision medicine is expected to continue, spearheaded by programmes like the Precision Medicine Initiative [4] and the 100,000 Genomes Project [5]. This innovation will likely change the way that healthcare services are organised and delivered: the creation of new molecular testing infrastructure and the development of ‘learning’ health information systems that analyse molecular and health record data to inform future prevention, detection or treatment strategies are two cited possibilities [6]. This will have consequences for the generation of clinical and economic evidence, meaning that healthcare decision makers, including health technology assessment (HTA) agencies and guideline producers, should consider how their methods and processes will accommodate these new technologies and services.

HTA agencies’ experience of precision medicine has primarily been with diagnostic and companion diagnostic tests, the latter referring to those that identify biomarkers correlated with treatment response such as the HER2 receptor protein for breast cancer pharmacotherapies [3]. Several countries have accommodated the additional complexities of evaluating these tests through new procedures, such as the Diagnostic Assessment Programme at the National Institute for Health and Care Excellence (NICE) in England or the Health Technology Assessment Access Point in Australia [7, 8]. However, additional procedures may be required for other emerging precision medicine technologies.

The objective of this study is to describe the possible landscape of precision medicine over the next decade, alongside the potential implications for HTA. Our analysis is the first to draw together the significant but disparate body of literature on the economics of precision medicine, present the potential issues arising at each stage of the decision-making process, and to anticipate future challenges by consulting with experts in a range of relevant fields.

2. Methods

Our approach consisted of two components: a review of literature on the methodological and empirical challenges of precision medicine with respect to economic evaluation for HTA and a series of interviews with experts in fields related to precision medicine and/or healthcare decision-making. From these we determined the types of precision medicine technologies and services that are expected to emerge in the next decade and the challenges that these and existing technologies create for HTA.

2.1. Literature Review

We conducted searches to identify literature focusing on methodological considerations relating to guideline development, decision-making, and economic evaluation of precision medicine technologies, medicines, and healthcare.

We searched MEDLINE and MEDLINE In-Process, prioritising retrieving relevant records at the expense of sensitivity. This pragmatic approach was taken because of the large size and wide scope of precision medicine literature. The search strategy was not intended to be exhaustive and instead aimed to retrieve those studies most likely to be relevant to the research question, while maintaining manageable numbers of records. A number of pragmatic decisions were made to limit record volume, including using only highly relevant search terms, restricting search terms to the title field, searching for English language publications only, and excluding publication types unlikely to yield study reports (e.g. news items). Rather than use pre-determined cut-off dates for inclusion, a flexible approach was adopted to provide an additional lever to limit record volume. This was anticipated to be from between 2007 and 2012 up to the date the search was conducted (May 2017). We used supplementary search techniques to identify grey literature and unpublished research, with further articles identified through citation searches of included studies and author searches on a preliminary list of 11 expert interviewees. The full search strategy is described in Appendix A.

Articles were included if they (i) presented or assessed of methodological challenges relevant to economic evaluations of precision medicine, or (ii) discussed the implications of new or emerging precision medicine technologies. The number of topics considered relevant to economic evaluation was broad, and included guideline development, trial design, comparative effectiveness and health equity.

Data were extracted from included papers by two reviewers (KE & AP). Consistency of approach was tested by comparing results from an initial single paper and discussing

discrepancies. Findings were tentatively organised into 11 pre-identified topic areas (provided in Appendix B), with new topics added where appropriate.

2.2. Expert Interviews

A list of experts was compiled based on prior familiarity to the authors and preliminary literature searches. Each met one of three criteria: (i) research outputs relating to precision medicine technologies and their evaluation; (ii) experience with decision making in HTA; and (iii) membership of institutes and organisations involving the use or evaluation of precision medicines. A total of 20 experts were contacted, all of whom were based in the UK.

Semi-structured qualitative interviews [9] lasting between 30 to 60 minutes were conducted in person or via telephone by JLK and AP. A standardised document describing the key areas of inquiry was distributed to experts prior to interviews (see Appendix B). Interviewees were not required to contribute to every topic and were encouraged to raise additional relevant issues.

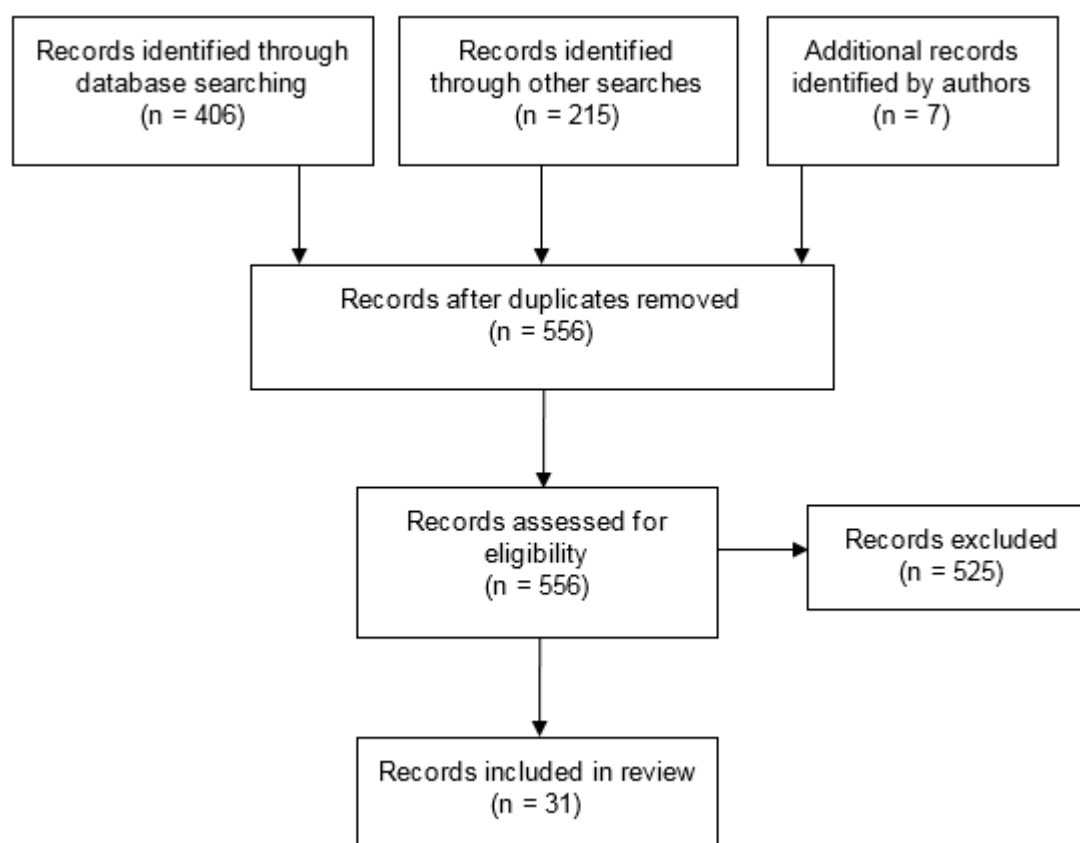
A pattern coding approach was taken with the qualitative data, in which the contemporaneous notes taken during each interview were organised into the initial list of 11 topics, with new topics added where appropriate. Pattern coding was undertaken by one researcher (AP) and validated by a second (JLK), with disagreements resolved deliberatively. These data were then compiled across all interviews using Microsoft Excel. The combined findings from the review and interviews were independently assessed and discussed by three reviewers (JLK, KE & AP).

3. Findings

3.1. Literature search & expert interview results

A total of 549 records were identified from the searches, with an additional seven identified by the authors (Figure 1). In order to restrict the number of records to within our practical limit of 300, articles published before 2011 were not considered for screening. It was assumed that any methodological issues identified in earlier literature would have either been resolved or reiterated in later articles. Screening on the basis of title, abstract and, where necessary, full texts left 31 included papers.

Figure 1: Record flow diagram for pragmatic literature review



Note: Of the 525 records excluded for eligibility reasons, 382 were based on abstract and full text review, with the remaining 143 removed due to being published prior to 2011.

A total of 13 (65%) experts consented to be interviewed. Four represented the scientific affairs, technology appraisal, clinical guidelines and diagnostics assessment programmes at the NICE, and expressed their personal views, rather than Institute policy. Other interviewees

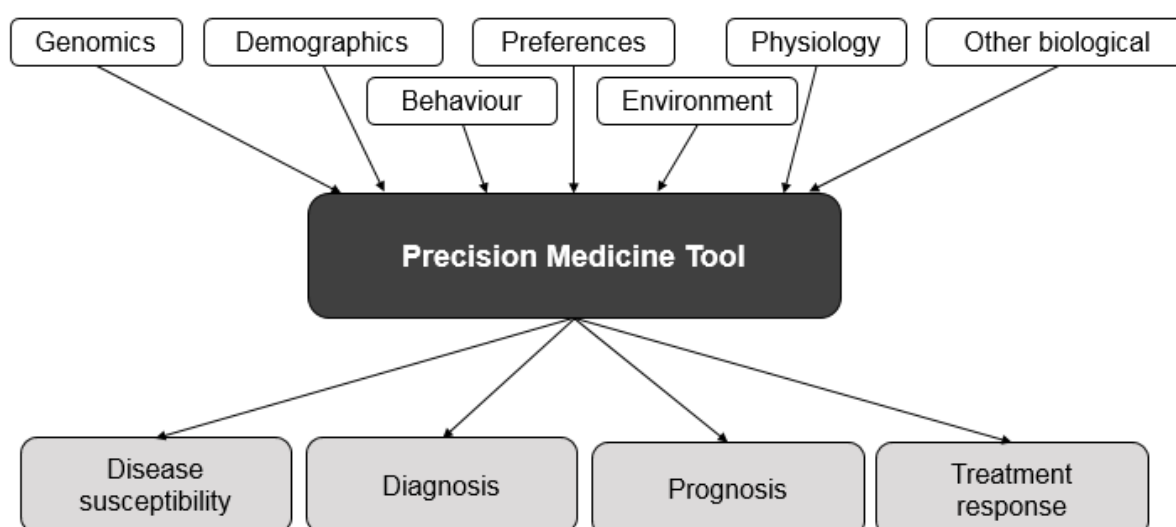
included four senior health economists, two researchers in digital health, a representative of the Medical Research Council (MRC), a specialist from the Precision Medicine Catapult institute and professors of health informatics and primary care sciences. The interviews had an average length of approximately 50 minutes.

3.2. Defining precision medicine

A preliminary consideration for this study was to define the types of technologies and services that precision medicine encompasses. Ten papers from the review provided a definition for precision medicine, as did each of the consulted experts, resulting in a wide range of interpretations [10-12]. Most agreed that precision medicine encompasses more than just pharmacogenetic and pharmacogenomic tests, and the term is now used interchangeably with *stratified medicine*. It is also replacing the term *personalised medicine*, as it also covers technologies that offer unique treatment pathways for individual patients [10, 11].

For the purposes of this study, we consider that a tool falls under the precision medicine 'umbrella' if it can be used to stratify patients to a specific treatment pathway or therapy, based on specific characteristics of the individual. These characteristics vary by tool but go beyond demographic or socioeconomic factors, and include genomic (or other 'omic') information, behavioural traits (including preferences), and environmental and physiological characteristics. Furthermore, tools will usually provide information on disease risk, diagnosis, prognosis or treatment response. This definition is summarised in Figure 2.

Figure 2: Defining precision medicine



Interviewees stressed an additional and important distinction between *prognostic* and *predictive* tests. Prognostic tests indicate the likelihood that an individual patient will have a particular disease course or natural history. For example, the Decipher prostate cancer test, which calculates the probability of metastasis [13]. Predictive tests provide an estimate of the expected disease response to specific treatments, such as tests identifying the human epidermal growth factor receptor (HER2) gene to determine treatment allocation for patients with breast cancer. This distinction has direct implications for HTA: a senior health economist highlighted a recent instance in NICE Diagnostics Guidance in which the committee's discussions focused on whether the technology could be considered predictive as well as prognostic, since this had an impact on the cost-effectiveness of the test [14].

3.3. Technological developments

Three major types of precision medicine technology likely to emerge over the next decade were identified: complex algorithms, digital health applications (“health apps”), and ‘omics’-based tests. These are summarised in the following sections and, alongside existing precision medicine tools, in Table 1.

Complex algorithms

Experts anticipated increased use of algorithms that use artificial intelligence (AI) to aid clinical decision-making over the next decade [15]. These algorithms require large data sets (“knowledge bases”) that include a large number of variables, such as genetic information, sociodemographic characteristics and electronic health records. Using this information, the algorithms provide clinicians and patients with predictions on expected prognosis and optimal treatment choices using patient-level characteristics. Algorithms update regularly as new information is added to the knowledge base, an approach termed “evolutionary testing”. The first approaches of this type for clinical use are already being established [16-20]. AI-based technologies will also be combined with advances in imaging to develop algorithms that incorporate scan results into knowledge bases to offer more accurate information [21].

Health apps

Health apps include a wide range of tools that provide disease management advice, receive and process patients-inputted data and record physical activity and physiological data such as heart rate. A subset of apps will likely fall under precision medicine, with the most advanced also utilising AI-based technology described above. Numbers of health apps are expected to increase significantly over the next decade. Digital health experts predicted that principal developments in this area would involve apps that analyse social or lifestyle determinants of health such as socioeconomic status or physical activity in order to stratify patients, including

apps linked to activity monitoring devices (or wearable technologies). In March 2017 NICE began to publish briefings on mobile technology health apps, known as “Health App Briefings”. One of the first to be published concerned *Sleepio*, an app shown in placebo-controlled clinical trials to improve sleep through a virtual course of cognitive behavioural therapy [22].

‘Omics’-based biomarkers

Many current precision medicine tools use genetic and genomic information to estimate disease prognosis and predict treatment response [23]. A senior health economist predicted the use of other ‘omics’-based biomarkers, such as proteomics, metabolomics and lipidomics would become more common and partially replace genomics over the next decade.¹

‘Omics’-based testing is expected to increase in complexity and scope, with single tests informing treatment pathway, therapy choice or disease risk for multiple diseases simultaneously [24]. This was described by one expert as “multi-parametric testing”. Whole-genome sequencing is at the broadest end of this scale and could feasibly provide information on risks and treatment decisions for hundreds of diseases [25].

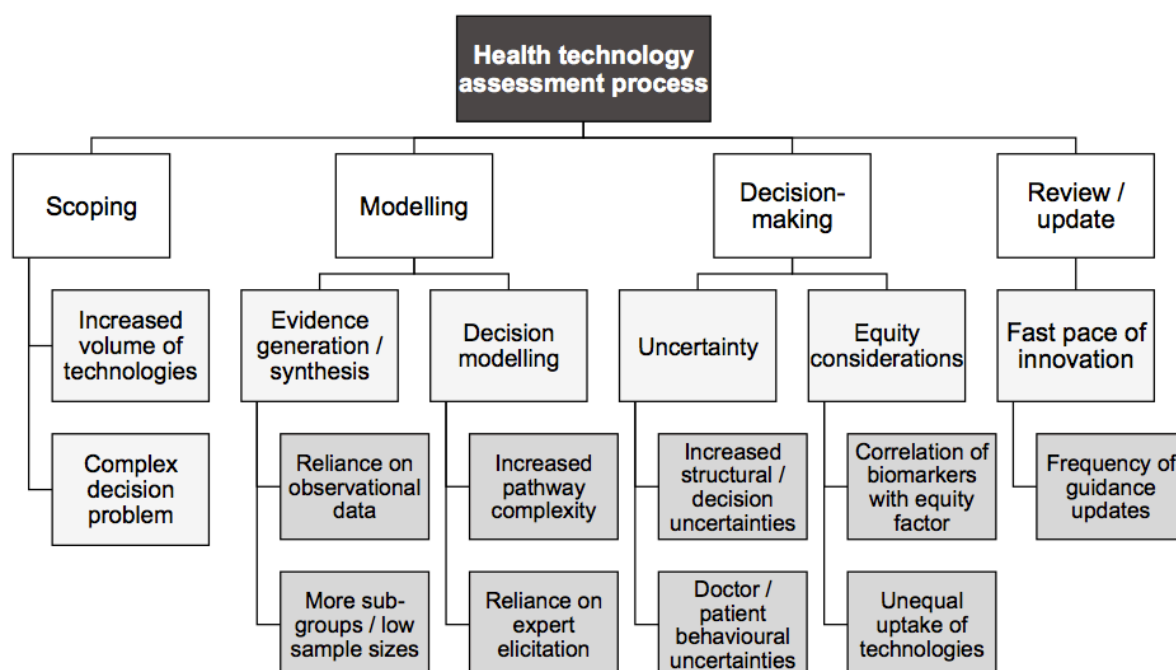
Table 1: Types of precision medicine technologies

Type of technology or service	Relevance to precision medicine	Estimated timescales for use
<p>Tests for prognostic biomarkers Example: Decipher tests [13] - indicate risk of disease progression after prostate cancer diagnosis.</p>	<p>Biomarkers indicate disease course and inform the patient treatment pathway.</p>	<p>Genomic biomarkers are already in use. Rapid discovery of proteomic and metabolomic biomarkers is expected in the next five years.</p>
<p>Tests for disease susceptibility biomarkers Example: Tests for BRCA1 gene - indicates risk of breast and ovarian cancer [26].</p>	<p>Biomarkers indicate risk of developing a particular condition and inform the patient treatment pathway.</p>	
<p>Tests for predictive biomarkers Example: HER2 protein tests – predicts response to breast cancer treatment [3].</p>	<p>Biomarkers predict treatment response and inform therapy choice.</p>	<p>An increasing number are being evaluated by HTA agencies – a review found NICE had evaluated seven by 2014 [8]</p>

¹ These refer to fields of study that can identify biomarkers using proteins, metabolites and cellular lipids. These can be used instead of or in combination with genetic and genomic information.

Type of technology or service	Relevance to precision medicine	Estimated timescales for use
		Expected to expand rapidly in next five years.
<p>Diagnostic services Including genetic, genomic and molecular testing services but also other types of diagnostic support for clinicians e.g. Computerised Decision Support [27].</p>	Services inform diagnoses and the patient treatment pathway.	Some of these services are already in use.
<p>Complex algorithms Example: Sapientia [18] – combines genomic sequencing with clinical phenotyping to inform treatment decisions.</p>	Clinical, genomic, behavioural (and more) data are utilised by these algorithms to inform diagnosis, recommendations for patient treatment pathways and therapy choices.	Several are being developed and trialled – expected to be in clinical practice within the next decade. Expected to be artificial intelligence-based as the field progresses (e.g. AI Biocomputing [28]).
<p>Digital health applications Example: MyHeart Counts [29] – records and analyses data on activity, risk factors and haematology, providing suggestions on improving heart health.</p>	Apps draw on clinical and behavioural data and aim to influence patient behaviour, healthcare use and/or choice of treatment.	Apps are already available but numbers are expected to increase dramatically in next decade.
<p>Risk prediction tools Example: QRISK [30] – static algorithm that determines risk for cardiovascular disease and informs statin prescribing.</p>	Patient histories and characteristics (e.g. BMI, co-morbidities) are used to calculate disease risk, informing the patient treatment pathway.	Currently available for a wide range of clinical areas.
<p>Patient decision aids Example: MAGIC [31] – produces dynamic decision aids that update based on published guidelines</p>	Instruments support patients in making decisions tailored to their preferences.	Currently available for a wide range of clinical areas.

Figure 3: Challenges for health technology assessment agencies raised by precision medicine



Note: The first-tier categories (scoping to review) relate to the four principal stages of a typical health technology assessment appraisal, such as that used by National Institute for Health and Care Excellence in England for traditional pharmaceutical technologies [32].

3.4. Issues for HTA

Precision medicine interventions will pose challenges at each stage of the HTA process, from scoping through to review (Figure 3).

3.4.1. Scoping

The nature of the decision problem presented to HTA agencies and guideline developers will become more difficult to define when dealing with some precision medicine technologies and services. The emergence of multi-parametric tests, for instance, is expected to increase the number of relevant interventions, comparators and populations encompassed by a single assessment by providing information on multiple diseases simultaneously. The number of care pathways under consideration will also increase because tests (i) may not have a defined place in the care pathway and could potentially be used at a range of time points and (ii) may be used in combination with other tests [33-37]. Evaluating all of the relevant pathways, populations, and comparators could be practically and computationally infeasible, and will likely necessitate increased use of expert opinion [11, 33, 38, 39, 34, 35]. One expert noted

that these issues are particularly relevant for whole-genome sequencing, which can be performed at any point during an individual's lifetime, inform care pathways for a wide range of diseases, and be analysed using many different methods [37].

The fast pace of innovation in precision medicine may also mean that assessment bodies face higher volumes of evaluations. Mixed views on how to address this emerged from expert interviews. A NICE analyst stated that scoping workshops, in which clinicians and other consultees determine which technologies should be evaluated, may be sufficient for technology appraisal. With respect to health apps, researchers agreed that new systems would need to be put in place to manage the burden of assessment. This could involve (i) a preliminary self-assessment phase, (ii) appraising classes of (rather than individual) apps, or (iii) setting priority areas using clinician input. Each present their own difficulties: classes would need to contain apps that are relatively homogenous, whilst any priority setting process would require a clear and transparent decision-making framework.

Experts highlighted that adaptive AI-based algorithms would present a unique challenge in terms of regulation and evaluation. As more data are processed and the algorithm becomes more effective over time, evaluators would need to decide how frequently and exactly when to assess safety and clinical and cost-effectiveness [40]. Interviewees also highlighted that technical validation of complex algorithms could be a challenge [41].

3.4.2. Modelling

Measuring value

A number of studies stated that the value placed on knowing diagnostic test results may need to be included in economic evaluations of precision medicine [42, 43, 39, 44-47, 35, 48-50]. This could be positive if such knowledge benefits patients and their families: directly in the case of hereditary conditions [12], or indirectly through enhanced autonomy or changes in lifestyle and screening behaviours [50]. Conversely, unintentional harms may also occur, for example due to psychological stress for patients and families.

Experts highlighted that the health-related quality of life instruments typically used in economic evaluations are unlikely to capture this value of knowing and that decision-makers may instead consider these factors through deliberation, taking into account the patient perspective, when making recommendations. Three studies [12, 44, 35] suggested that discrete choice experiments could be used to value patient preferences for increased knowledge, over and above any specific QALY gains deriving from subsequent treatment decisions. Quantifying these benefits separately (or in monetary terms) would be consistent with a welfarist

framework but not the extra-welfarist one adopted by some agencies such as NICE [51]. Furthermore, incorporating these additional aspects of value on the benefits side of the cost-effectiveness equation also requires that they be incorporated when accounting for opportunity costs [52]. Incorporating non-health benefits into the evaluative framework of HTA would therefore require knowledge of (i) the extent to which society is willing to trade-off health and non-health benefits and (ii) what type of services might be displaced in order to fund a new intervention, and their associated non-health benefits.

Evidence evaluation and synthesis

Precision medicine presents numerous challenges for evidence evaluation. The stratification of patients to increasingly small subgroups will reduce sample sizes [10, 44, 53] and result in only certain subgroups (i.e. ones with specific biomarkers) being included in individual trials. Obtaining head-to-head estimates of comparative effectiveness for treatments and subgroups will become more difficult and will result in evidence networks being incomplete in cases where no common comparator links together the available trials. One study and several of the interviewees concluded that expert opinion will be needed more regularly to fill gaps in the evidence [12], along with suitably robust methods for eliciting these judgements [46]. Interviewees also noted that new trial designs are being developed that may be more compatible with precision medicine, including basket, umbrella and adaptive trials [54-56]. These designs, which are yet to contribute to any value dossiers submitted to HTA agencies, allow for trials to be adapted in terms of inclusion criteria and treatment response.

Nevertheless, the need to analyse multiple subgroups and more complex treatment pathways in decision models for precision medicine interventions is likely to necessitate additional sources of evidence [12], in terms of both cost and clinical data [39, 34, 38, 33, 53, 36, 35]. An absence of relevant data recently resulted in the discontinuation of a diagnostic service delivery guideline being developed by NICE [57]. Regulatory efforts are being made to encourage the generation of clinical evidence, including the introduction of the In Vitro Diagnostic Device Regulations (IDVR) in 2017 by the European Commission [58]. However, as the new clinical evidence requirements for approval of the IDVR will not apply until 2022, evidence paucity is likely to be an issue in Europe in the medium term.

There was consensus that use of observational data for assessing precision medicine interventions will increase over the next decade [11, 36, 39, 44, 33], including registry data, cohort studies and electronic health records [59, 16, 60]. Experts noted that advanced statistical methods (and accompanying technical guidance) would be required to identify causality while controlling for the risks of selection bias and confounding in observational data.

Decision analytic modelling

Multiple studies predicted that the complexity of clinical pathways in precision medicine could render traditional Markov-type model structures insufficient for capturing long-term costs and benefits [42, 61, 43, 12, 10, 35]. For example, multi-parametric testing may lead to secondary findings unrelated to the original test, as well as spill-over effects on family members and future generations [48]. A number of studies concluded that more research is needed to establish best practice guidelines for modelling precision medicines [43, 60, 33, 12], while others suggested approaches that could handle complex structures more adequately, such as microsimulation and discrete event simulations [35, 12, 62].

3.4.3. Decision-making

Uncertainty

The stratification of a patient population may result in smaller sample sizes recruited to trials for precision medicine interventions. Combined with more complex and variable treatment pathways, this could increase levels of uncertainty associated with cost-effectiveness estimates presented to decision makers.

Higher standard errors for estimates of treatment effect were raised as a concern [42, 61, 36, 11, 43, 60, 35, 46]. Several experts believed, however, that this concern is overstated. First, treatment effect variation between patients should be lower when therapies are targeted towards responders, thereby reducing standard errors. Second, any reduction in sample sizes could be compensated for in time through the use of large, linked observational datasets [16]. Value of information analysis, a technique for quantifying the value of reducing decision uncertainty, was also identified as key technique that could be beneficial to decision making [12, 33, 44, 60, 63, 64]. Along with more typical factors such as patient population size, the key determinants of value of information in precision medicine will include the sensitivity and specificity of tests and predictions, and the intervention context (i.e. if it is used in combination with other tests).

Another source of uncertainty will be the unit costs, for example of 'omics'-based tests, which vary by laboratory [36]. Such tests may also yield continuous results, meaning that thresholds must be set to determine the outcome of testing [11]. Thresholds will impact on the cost-effectiveness of tests and, therefore, it was argued that determination of thresholds should go beyond analysis of receiver operating characteristic curves [12].

Complex clinical pathways will generate substantial uncertainties over model structure in economic evaluations of precision medicine interventions. Many experts and studies

highlighted this as a critical aspect of decision modelling that would need to be addressed [35, 39, 33, 43, 11, 36]. Whilst it was agreed that the current approach of extensive sensitivity and scenario analyses should continue, interviewees expressed a desire for coherent frameworks for analysing and quantifying structural uncertainties. Approaches highlighted in the literature included multi-parameter evidence synthesis, although this approach may also be impeded by sparse data [65]. Value of information-type approaches can help to quantify the extent of this uncertainty and the value of reducing it, through techniques such as expert elicitation [66].

An additional consideration is uncertainty around the behaviour of clinicians and patients. Decisions made by these individuals, for example whether to follow the treatment pathway indicated by the result of a diagnostic test, could influence how clinically effective the intervention is and, thus, impact cost-effectiveness [12, 43, 33, 38, 44, 34, 39]. In terms of clinician behaviour, low compliance to genotype-specific dosing recommendations has been observed [33]. Steep learning curves for some stratification tools have also been suggested as a cause of variability [67]. On the patient side, adherence remains an important yet under-researched determinant of effectiveness [36]. The development and application of evidence-based computerised decision support and patient decision aids could be a way to tackle these challenges.

Equity and equality

When generating guidance that recommends different courses of treatment for different groups of patients, HTA agencies and other public bodies should aim to ensure that principles of non-discrimination and equality of opportunity are advanced [68, 69]. The main challenge lies in the specific instances where there are small numbers of patients in rare biomarker-stratified groups, for whom there is greater uncertainty around treatment effects [70]. An equality issue arises when the biomarkers used for stratification are correlated with factors such as ethnicity [53, 36]. In the NICE appraisal of sofosbuvir for treating chronic hepatitis C [71], low levels of evidence were available for some genotypes that were more common in minority ethnic patients. In this instance, a “pragmatic” approach was explicitly taken on the grounds of equity, high unmet need and the lack of treatment options; evidence was extrapolated from genotypes where the treatment’s effectiveness was well-supported and the therapy was recommended for the rarer genotypes.

Stratifying patients to different treatment pathways based on measures of physiological dysregulation (such as blood pressure or cortisol level) may also introduce equity concerns. A significant, negative association between these measures and socioeconomic status has been established in the literature [72]; differential treatment recommendations may therefore result in individuals from low socioeconomic groups having a lower probability of receiving the

most effective treatments. Concerns were also raised with respect to the differential uptake of some precision medicine interventions that require patient engagement. This is particularly true in digital health, where experts reported that use of health apps was much more common in younger age groups and those with higher social and educational status. If traditional (i.e. GP-delivered) services were to be withdrawn in favour of digital-only access, the benefits of precision medicine may be unevenly distributed.

3.4.4. Review / update

Experts working for HTA agencies noted that the rate of discovery of biomarkers means that the specificity and sensitivity of companion diagnostic tests is expected to steadily improve. Similarly, health apps and AI-based algorithms are regularly updated and upgraded, meaning that certain treatment pathways might become more cost-effective over time. Although beneficial, this could reduce the 'shelf-life' of guidance issued by HTA agencies and necessitate more frequent reviews and updates [35]. NICE have already begun addressing this issue with innovations to fast-track some evaluations [73] and increase the capacity of the technology appraisals programme [74]. Similar combined approaches to streamlining processes and increasing capacity will help the HTA community keep guidance up-to-date and useful while keeping the overall cost of HTA manageable.

4. Discussion

This study aimed to take a forward-looking view of precision medicine, considering what challenges are likely to be faced by HTA and guideline producing agencies as precision medicine technologies and services become more prevalent (see Appendix C for a brief demonstrative case study).

We identified three key areas of precision medicine that are expected to expand in the next decade: complex algorithms, health apps and 'omics'-based tests. The potential benefits to patients from these technologies are substantial, particularly as the costs of 'omics' testing are likely to decrease and manufacturers will be able to develop targeted therapies with greater efficiency. Complex algorithms and health apps will utilise AI and large, linked datasets to adapt all aspects of healthcare to patient sub-groups and individuals in order to improve health outcomes. Additional technologies that were not discussed by experts or in the literature, such as the genome editing technique CRISPR [75], are also likely to fall under the umbrella of precision medicine as their application in healthcare is developed.

These new technologies will inevitably present challenges to decision makers. Researchers and clinicians should remain aware that it will not always be beneficial or ethical to use biomarker information to inform treatment decisions. Examples are already emerging of instances where a seemingly informative biomarker has not added predictive power to risk equations [76].

Early consideration of the evidence required by decision-makers can improve evidence collection and analysis for precision medicine technologies and services in very early stages of development [77]. Innovative approaches for evidence generation to facilitate this are currently being developed: new trial designs [55] and robust statistical methods for analysing observational data [78] will help fill evidence gaps and improve trial recruitment numbers. Additionally, increasing use of health apps can improve the quality, frequency and accuracy of data collection.

Clear and transparent processes and principles will also be necessary to ensure equitable decision making, particularly in cases where biomarkers are correlated with factors such as ethnicity and sociodemographic status. As with interventions such as vaccination and cancer screening [79, 80], unequal uptake of some precision medicines is also an area of concern that policy makers may want to consider and design strategies to counteract, such as targeting programmes.

Furthermore, it is not yet clear if any European agencies will be responsible for evaluating the safety, clinical- and cost-effectiveness of health apps and AI-based technologies. Addressing this regulatory and assessment vacuum is necessary to promote the uptake of safe and effective products. Evaluating these types of tools not only requires a new technical expertise within HTA agencies, but perhaps even a different system altogether given (i) the pace of innovation and (ii) the regularity with which apps and algorithms are updated, which can alter their effectiveness and cost-effectiveness. Historical examples of assessments of these technologies by HTA agencies are sparse; developing a better understanding of the most appropriate approach for robustly evaluating AI-based technology should therefore be a valuable area of further research.

Resolving some of the issues presented in this paper, such as scoping increasingly complex treatment pathways, may require a thorough and balanced evaluation of the strengths and potential shortcomings of normative choices within an HTA framework,. Any departure from current established frameworks will require considerable deliberation and co-operation between a wide range of stakeholders from across the health system. An appropriate solution will be dependent upon on (i) the decision-making context within which the HTA agency exists, (ii) the stated objectives of the health system as a whole and (iii) the practicality of the assessment and (iv) the relevance of the framework to the technology type [81].

A number of European organisations, such as ICPeMed, EUnetHTA and Horizon 2020, have identified the health economic evaluation of precision medicines as an important area of research [82-84]. The conclusions of these initiatives, which are at this point undetermined, can help to seeking to address some of the other methodological issues we have highlighted, such as evidence generation and synthesis.

Strengths and limitations

Whilst other studies have analysed the potential consequences of precision medicine on HTA processes [60, 38], the focus has been restricted to diagnostic and companion diagnostic tests. The more expansive definition of precision medicine adopted in this review, which includes technologies substantively different to diagnostics, therefore highlights a number of novel issues on the horizon for HTA agencies that will be realized in an evolving regulatory landscape.

However, our findings are limited by several factors. First, our qualitative interviews were conducted with UK-based experts only. Although the wider scope of the literature review also

helps to relax the UK-centricity of the findings, future research should look implications in other settings. This need aligns with the research objectives of the cross-country initiatives noted above.

Second, for practical reasons we made several pragmatic decisions when conducting the literature review. This may have resulted in relevant articles that being excluded from our analysis, resulting in overlooked insights and issues.

Our review also primarily focused on the implications of precision medicine technologies on HTA rather than identifying those expected to come into practice in the decade. We were therefore more reliant on expert opinion for this aspect of the results.

5. Conclusion

Precision medicine interventions are likely to proliferate over the next decade and will change the way services are delivered and evaluated. It is possible to speculate that such changes will be driven firstly by the complexity and uncertainty around delivering therapies that use biomarker data and, secondly, by the innovative, evolutionary nature of AI-based technologies. Healthcare systems around the world will need to consider adjusting their evaluative methods and processes to accommodate these changes in such a way that they can continue to robustly assess the value-for-money of new treatments and services.

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