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SYSTEMATIC REVIEW

# Financing and Reimbursement Models for Personalised Medicine: A Systematic Review to Identify Current Models and Future Options

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## Abstract

**Background** The number of healthcare interventions described as 'personalised medicine' (PM) is increasing rapidly. As healthcare systems struggle to decide whether to fund PM innovations, it is unclear what models for financing and reimbursement are appropriate to apply in this context.

**Objective** To review financing and reimbursement models for PM, summarise their key characteristics, and describe whether they can influence the development and uptake of PM.

**Methods** A literature review was conducted in Medline, Embase, Web of Science, and Econlit to identify studies published in English between 2009 and 2021, and reviews published before 2009. Grey literature was identified through Google Scholar, Google and subject-specific webpages. Articles that described financing and reimbursement of PM, and financing of non-PM were included. Data were extracted and synthesised narratively to report on the models, as well as facilitators, incentives, barriers and disincentives that could influence PM development and uptake.

**Results** One hundred and fifty-three papers were included. Research and development of PM was financed through both public and private sources and reimbursed largely through traditional models such as single fees, Diagnosis-Related Groups, and bundled payments. Financial-based reimbursement, including rebates and price-volume agreements, was mainly applied to targeted therapies. Performance-based reimbursement was identified mainly for gene and targeted therapies, and some companion diagnostics. Gene therapy manufacturers offered outcome-based rebates for treatment failure for interventions including Luxturna®, Kymriah®, Yescarta®, Zynteglo®, Zolgensma® and Strimvelis®, and coverage with evidence development for Kymriah® and Yescarta®. Targeted testing with OncotypeDX® was granted value-based reimbursement through initial coverage with evidence development. The main barriers and disincentives to PM financing and reimbursement were the lack of strong links between stakeholders and the lack of demonstrable benefit and value of PM.

**Conclusions** Public-private financing agreements and performance-based reimbursement models could help facilitate the development and uptake of PM interventions with proven clinical benefit.

## 1 Introduction

Healthcare interventions falling under the umbrella term of personalised medicine (PM) include tests that provide information on patient genotypes, or those which enable drugs to be targeted to patients' genetics. This information can be used to help predict disease predisposition, suggest preventive actions or stratify treatments [1]. Gene therapies

**Key Points for Decision Makers**

Appropriate models for financing and reimbursement of personalised medicine are vital to stimulate the development and uptake of these interventions if they are able to show demonstrable clinical benefit.

Public-private financing agreements and performance-based reimbursement models could help facilitate the development and uptake of PM interventions with proven clinical benefit.

Defining and measuring performance that reflects the value of PM for the involved stakeholders is still a hurdle to realise the full potential of performance-based reimbursement.

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and companion diagnostics are examples of PM interventions that were made possible by the decoding of the human genome and subsequent technological developments [2]. The volume of PM interventions, including gene and cell therapies, is increasing rapidly, and the diagnostics to guide treatment have become a reality. Consequently, United States (US) Food and Drug Administration (FDA) approvals of PM increased from 21 to 39 % during 2014–2020 [3], while the European Union (EU) invested €3.2 billion in PM research in just one year (2017) [4]. International and national initiatives have been launched (e.g., International Consortium for Personalised Medicine) [5] to support research and translation of PM, and government investment in genetic research and development (R&D) and translation was over US$4 billion in 14 countries in 2019 [6]. Furthermore, a personalised approach may yield substantial health benefits and slow healthcare expenditure growth [1, 7]. Given this, governments and public institutions have recently expanded their involvement in the R&D of PM [4, 6].

Despite such initiatives, the translation of PM into clinical practice has been variable [8, 9]. For example, the gene therapy Glybera® was adopted in Germany, but not in France, the UK, Italy or Spain [10]. Reimbursement challenges contribute to these varied adoption rates [11]. Reimbursement agencies make complex investment decisions about PM interventions, with substantial budget impacts, yet the evidence on effectiveness and cost-effectiveness that underpins these decisions is often limited. For example, in the UK the use of histology-independent cancer drugs, such as Vitrakvi® (larotrectinib), is an example of complex reimbursement decisions [12]. The standard approach in oncology is to treat tumours based on their type. However, targeted therapies based on a tumour's genetic information have recently been developed. Larotrectinib is indicated for any solid tumour with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion. Because many tumour types respond to it, the drug is considered to be 'tumour-agnostic' or 'histology-independent'. The National Institute for Health and Care Excellence (NICE) ultimately approved the use of this therapy, but found the process of appraising a histology-independent treatment to be extremely challenging, because existing assessment methods require technologies to be assessed one at a time. A further example is the withdrawal of several gene and cell therapies from the European market due to high prices (partly related to high R&D costs) and weak evidence of effectiveness [13]. In addition, the misaligned reimbursement for companion diagnostics and medicines has led to the reimbursement of companion tests being dependent on national or local tariffs and hospital budgets, if reimbursed at all [14].

Given this clear variability and the challenges associated with financing and reimbursing PM interventions, it is crucial that appropriate financing and reimbursement models that share financial risk and benefits between stakeholders are identified to stimulate the development and uptake of PM interventions, if proven to be effective and cost effective. An important first step in this work is to describe the current landscape in this context and identify promising examples of models that could support decision makers when faced with reimbursement decisions.

Therefore, the aim of this paper is to review financing and reimbursement models for PM, summarise their key characteristics, and describe their ability to influence development and uptake of PM.

## 2 Methods

This systematic review adhered to our published protocol [15] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. We defined a financing model as a mechanism to fund R&D, and a reimbursement model as a mechanism for purchasing and providing PM. Personalised medicine was defined according to the European Council Conclusion on personalised medicine for patients (2015/C 421/03) as "*a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.*" [1] The term PM in this review is synonymous with other terms such as precision medicine, individualised medicine, tailored therapy, personalised health care, etc.

### 2.1 Search Strategy

The search was conducted in Medline, Embase, Web of Science, and Econlit. Grey literature was identified through Google Scholar, Google and subject specific webpages [5, 17–23]. Search syntaxes and selection criteria are presented in Appendix 1. As the most recent developments in the landscape of financing and reimbursement of PM are relevant for current decision making, our searches were restricted to the period 2009–2019 and were updated to include studies published up to October 2021. This matches the timing of the emergence of novel genomic tests and the increase in submissions to health technology assessment agencies. To ensure all potentially relevant publications were captured, we applied our search strategy to identify reviews on this topic published before 2009 and examined resulting hits.

### 2.2 Selection Process

Search results were de-duplicated in EndNoteX9 [24], and split equally between three reviewers (AT, JB and RKK)

for title, abstract and full text review. To ensure consistency in the selection process, each reviewer screened the titles, abstracts, and full texts of 10 % of the articles screened and selected by the other reviewers as per a previous study [25]. The target for inter-reviewer agreement was 95 %. References and citations of included studies were crosschecked for additional studies using the (reverse) snowballing method [26]. Articles published in English that described models for the financing and reimbursement of PM interventions were included. No restrictions were applied to study location, delivery setting or type of PM. Financing models for the development of non-PM interventions were also included to enable the identification of promising examples that can be potentially applied to fund R&D for PM interventions, but reimbursement models for non-PM were excluded.

### 2.3 Data Extraction

Data were extracted on the characteristics of the financing and reimbursement models; the type of PM (or non-PM for financing models) considered; country and healthcare system; and the facilitators, incentives, barriers and disincentives to financing and reimbursement that could influence the development and uptake of PM. Facilitators and barriers were factors that were defined as enablers or obstacles, originating from the type of financing/reimbursement model, which in combination with health system, regulatory arrangements, or other factors, could enable or impede the development and uptake of PM interventions. Incentives and disincentives were defined as factors that could motivate or discourage. Stakeholders were defined as representatives of academia, industry, pharmaceutical manufacturers, government agencies, health payers, healthcare provider organisations, patient representatives, e.g., people and organisations with vested interest in PM financing and reimbursement. Extracted data on facilitators, barriers, incentives and disincentives were based on reports in the relevant papers. Facilitators, barriers, incentives and disincentives were classified according to whether they related to evidence generation, financial risk, reimbursement models, health technology assessments (HTAs) or regulatory frameworks. All data were recorded in a standardised Excel form.

### 2.4 Data Synthesis

Data were synthesised narratively according to the type of proposed or used financing and reimbursement models. We summarised the facilitators, incentives, barriers and disincentives related to financing and reimbursing of PM. Financing models were grouped by source of research funding to identify differences between publicly and privately funded studies. Reimbursement models were grouped into non-risk sharing (or traditional) and either financial-based or performance-based risk-sharing models [27–29].

## 3 Results

After screening 23,877 records, 150 publications and reports were included in the qualitative synthesis process (Fig. 1). Three additional papers were identified through reference and citation screening. The characteristics of the included studies are presented in Table 1. The target set for inter-reviewer agreement of 95 % was achieved. Only four of the included papers were published before 2009, the remainder were published in the period 2009–2021. Thirty-three papers (21.5 %) reported on financing models for research and product development [30–62], 87 papers (57 %) reported on reimbursement models that had been proposed [63–82] or used [10, 13, 79–81, 83–147] for PM (Fig. 2) and 33 (21.5 %) were discussion papers [148–180]. Fifty-four papers reported on Europe, 88 on North America, 5 on Australasia and 3 on Asia; the remainder either had an international perspective or did not report a specific country or region. The predominant disease area in which reimbursement was reported was cancer.

### 3.1 Financing of PM Research

Personalised medicine research is financed through various public and private sources, and public-private collaborations [30–62] (Table 2). Public financing is provided by the National Institutes of Health in the USA, Medical Research Councils in the UK, dedicated research funds, governments (e.g., Genome Canada funded by the Canadian government), and by different initiatives and programmes of the EU [30, 33, 38, 43, 58, 61, 62]. Private financing includes industry, venture capital and philanthropic funding [35, 40, 42, 55, 59, 60], and mixed public-private financing includes collaborations between academia, government, pharmaceutical and diagnostic companies, charities, and small and medium enterprises [32, 34, 37–39, 43–49, 52, 56, 57]. Two financing models unrelated to PM were identified. In the first model, venture capitalists, called "high-net-worth individuals" [50], privately funded and managed research in areas of their vested interest. In the second model, a specially developed health currency (Healthcoin) was exchanged between payers as a risk-sharing agreement in which future health insurers paid Healthcoins to the previous health insurers of their insured population for engaging in research that would benefit the insured [51].

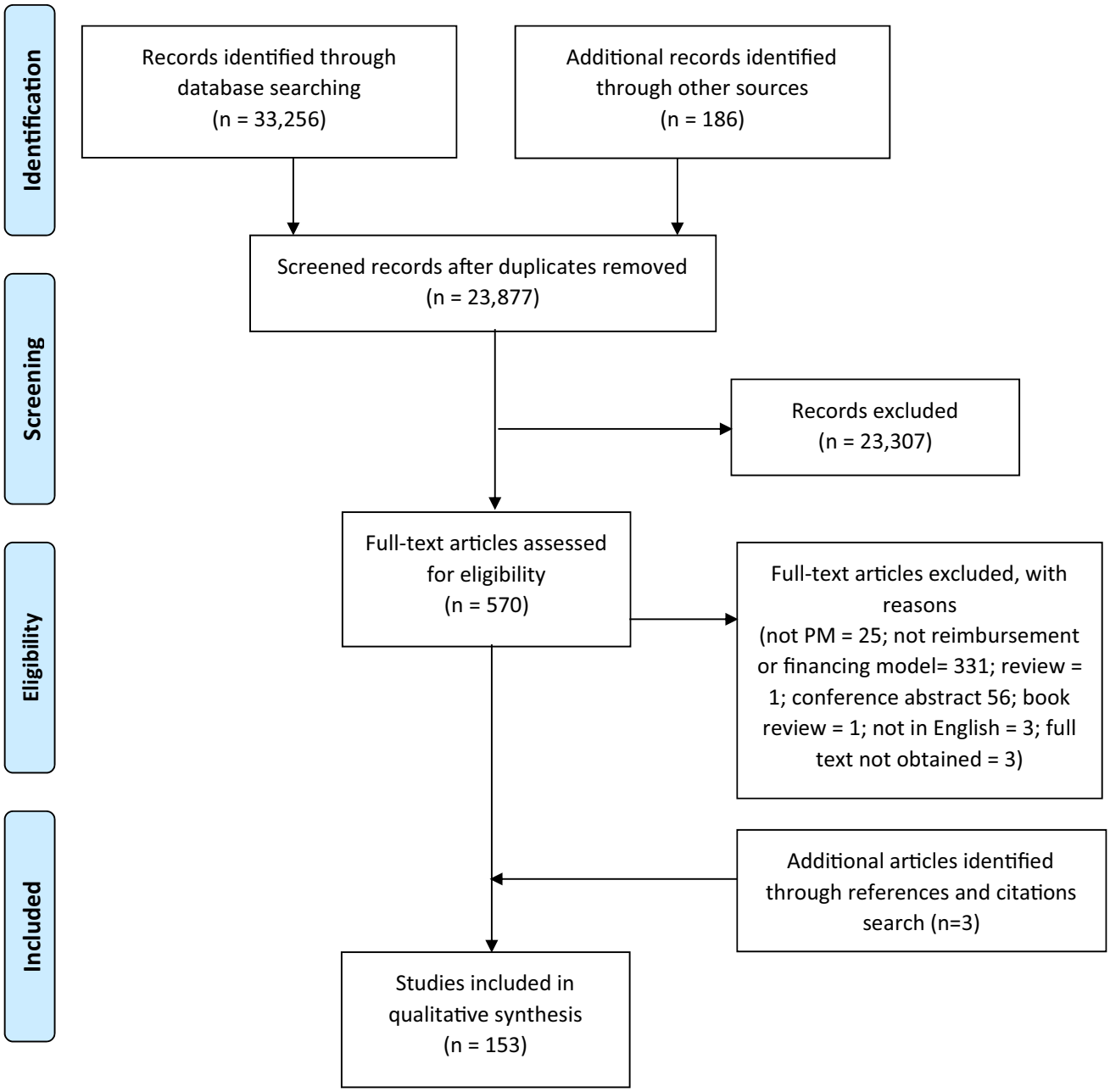


**Fig. 1** PRISMA Flow Diagram

### 3.2 Facilitators and Incentives for Financing PM Research

Partnerships between funding organisations, academic institutions, and pharmaceutical companies were described as having the potential to facilitate funding streams and collaborations by providing support and access to non-marketed compounds [31] (Table 3). It was also noted that virtual and venture variants of partnerships could facilitate the financing of new business areas by spreading the capital initially required, and enabling strategic outsourcing and investment instead of costly mergers and acquisitions [46]. It was proposed that "Open source innovation" [39, 56]—the exchange of internal and external ideas and knowledge to advance technology—could replace the traditional in-house-focused approach and incentivise new collaborations [39]. However, it was noted that this required an organisational framework, clarifying factors such as financial and intellectual contributions and asset rights, while maintaining scientific independence [39].

Risk-sharing financing agreements between governments and manufacturers—such as using government

**Table 1** Characteristics of the included studies

| Sub-groups of papers (*n*) | | Type of personalised medicine (*n*) | Publication period | Region (*n*) | Conflict of interest (Y/N) (*n*) | Study funding (*n*) |
|---|---|---|---|---|---|---|
| Financing models (33) | | – | 2004–2021 | North America (14), Europe (8), international (3), Asia (1), not reported (8)* | Y (4), N (29) | Publicly funded (5), privately funded (1), mixed funding (2), not reported/not received (25) |
| Reimbursement models (87) | Applied models (71) | Gene/cell therapy (19) | 2016–2021 | Europe (9), North America (13)** | Y (6), N (13) | Publicly funded (1), privately funded (1), not reported/none received (17) |
| | | (Molecular) biomarkers including genotyping and phenotyping and/or targeted therapy (52)**** | 2010–2021 | Europe (22)<br>North America (31), Australasia (3), Asia (2), international (1)*** | Y (20), N (32) | Publicly funded (7), privately funded (6), mixed funding (3), not reported/not received (36) |
| | Proposed models (16) | – | 2010–2019 | North America (7), not specified (3), Europe (4), international (2) | Y (3), N (13) | Publicly funded (2), privately funded (1), mixed funding (2), not reported/not received (11) |
| Discussion papers (33) | | – | 2008–2021 | North America (15), Australia (2), Europe (7), international (2), not reported (8)**** | Y (10), N (23) | Publicly funded (5), privately funded (7), not reported/not received (21) |

*N* no, *Y* yes

*Numbers add up to more than 33 as some papers reported on different regions

**Numbers add up to more than 19 as some papers reported on different regions

***Numbers add up to more than 52 as some papers reported on different regions

****Numbers add up to more than 33 as some papers reported on different regions

*****Different types of cancers are the predominant disease area in which reimbursement was reported and only 17 papers reported on other conditions and diseases (inherited retinal disease, lipoprotein lipase deficiency, trisomies, cardiovascular diseases, mental diseases, neurological diseases (Alzheimer), spinocerebellar ataxia, hereditary pulmonary disease, cystic fibrosis, foetal aneuploidy (nuchal translucency), karyotype, factor V Leiden, prothrombin G20210A, primary or secondary clonal eosinophilia, systemic mast cell disease without eosinophilia, spinal muscular atrophy, transfusion-dependent β-thalassemia

**Table 2** Financing models

| | |
|---|---|
| Public sources | Research institutes [30, 33, 38], national scientific centres, universities and institutes of health, charities [31, 37, 38, 44, 53, 58, 61], medical research councils [31, 33, 38], non-for-profit organisations [41] |
| | Dedicated research funding calls: Precision Medicine Initiative [36, 37], Canadian Microbiome Initiative, International Human Microbiome Consortium [43] |
| | European Commission/Union programmes [38, 43, 62] |
| | Governments [38, 43, 62] |
| Private sources | Pharmaceutical industry [38, 40, 42, 53] |
| | Insurance providers (Healthcoin) [51] |
| | Philanthropy [54] |
| | Venture capital: high-net-worth individual [50], biotechnology industry [55] |
| | Mergers and acquisitions between pharmaceutical/development/diagnostic companies [35, 53, 59, 60] |
| Public-private mix | Collaborations between academia, government, pharmaceutical industry, charities, including:<br>– Distribution of public funding to small businesses to encourage development of new radiation-effect modulators and collaboration with academia [32]<br>– Public private partnerships between National Cancer Institute funded by National Institutes of Health (NIH) American Recovery and Reinvestment Act (ARRA) funds and venture capital–backed companies through the Small Business Innovative Research (SBIR) programme [34].<br>– Collaboration between the American Heart Association, academic medical centres, patient advocacy groups, and private partnerships (Health eHeart Alliance) for cardiovascular research [37]<br>– AstraZeneca's Open Innovation Initiative, GSK's Centre for Therapeutic Target Validation (CTTV) and the Eisai University College London (UCL) collaborative drug discovery alliance [38]<br>– Dedicated centres for oncology research connecting academic, clinical and industrial partner, small and medium enterprises (Oncotyrol) [39]<br>– Network of Centres of Excellence (academia, industry, government and non-profit organisations) [44]<br>– Cancer genome-sequencing initiatives which used different sources of funding (governmental, charities, government combined with academic/professional, industry, charities combined with industry and academic/professional societies, or hybrid combinations) [45]<br>– Government funding and policies, and research entities for rare and intractable diseases [47]<br>– Network of separate entities (universities, hospitals, technology suppliers, contract research organisations and manufacturing, data analysis firms and key opinion leaders from numerous countries; independent research sites) [46, 56] |
| | Collaborations between government and pharmaceutical industry, including:<br>– federated business models promoting open innovation to develop cancer vaccines [46];<br>– pharmacogenetics/PM research in Europe, utilising core funding from governments, small industrial contracts and funds from charitable foundations, EU Sixth Framework and FP7 Programme with opportunities for industry to access [48, 52]<br>– coordinated industry-academia funding Innovative Medicines Initiative (IMI), a partnership between the European Community and the European Federation of Pharmaceutical Industries and Associations [43, 48, 52]<br>– "Grant-and-Access" programme for developing drugs for rare diseases, based on risk-sharing agreement, e.g., using federal grant to subsidise drug development in return for cap on the price [49]<br>– International Immuno-Oncology Network (collaborations between Brystol Myers and the Netherlands Cancer Institute, Dana-Farber Cancer Institute, The Royal Marsden NHS Foundation Trust, the Institute of Cancer Research, and Johns Hopkins Kimmel Cancer Centre; Pfizer, Eli Lilly, AstraZeneca, and the National Institutes of Health's National Clinical and Translational Sciences programme for funding preclinical and clinical feasibility studies for new uses of shelved compounds) [43]<br>– European commission programmes (H2020) for Research and Innovation to support innovative small and medium-sized enterprises in the diagnostic area [57] |

grants to subsidise the direct cost of clinical drug development in return for reduced market prices—were suggested as an approach to facilitate innovation, quicker access to, and translation of new products into clinical practice [49]. Similarly, risk-sharing agreements between payers, such as Healthcoin [51], were suggested as means that could incentivise research financing of cures that produce benefits throughout patients' lifetimes.

Furthermore, it was noted that creating a system based on conditional approval could facilitate R&D funding by decreasing the size of preapproval trials, the capital required for initial development, and the time from trial initiation to approval [49]. It was also suggested that R&D of companion diagnostics could be incentivised by payment of royalties on drug sales or at sales-based milestones—which facilitates sharing of the long-term value of the drug-diagnostic combination—or by compensating diagnostic research companies for the risk of the drug not being approved or not meeting sales targets [53].

Achieving a balance between cost-sharing, risk-sharing, benefit-sharing, and scientific independence was noted to be essential to maintaining public-private partnerships [39].

**Table 3** Financing models—facilitators, incentives, barriers and disincentives

| Facilitators and incentives | Barriers and disincentives |
|---|---|
| **Public research institutes:**<br>– Co-funding and public-private partnerships [30]<br>**Collaborations between academia, government, pharmaceutical industry, charities:**<br>– A cooperative ''win-win'' model: R&D cost already borne by academia and the government, thus clinical translation more attractive to pharma since the cost of development and risk of late-stage failure is likely to be reduced [32]<br>– Balance in cost-sharing, risk-sharing and benefit-sharing [39]<br>– Strong organisational framework, clarifying financial and intellectual contributions, distribution of rights on assets, intellectual property rights and knowhow [39]<br>– Maintenance of scientific independence [39]<br>– Open Innovation concept involving crowd science through "crowd sourcing" and "crowd funding" [56]<br>**Healthcoin:**<br>– Incentivise private payers to invest in research for a cure [51]<br>– Feasibility of introducing Healthcoin dependent on new legislation [51]<br>**Public funding through national scientific centres, universities, medical research councils and institutes of health:**<br>– New trends toward innovative partnerships among funding organisations, academic institutions, and pharmaceutical companies [31]<br>**Collaborations between government and pharmaceutical industry:**<br>– Virtual and venture federated models [46]<br>– Risk sharing financing agreement: using federal grants for research in return of a cap on the price of marketed products [49]<br>– Establish a system based on conditional approval [49]<br>**Private funding through manufacturers:**<br>– Royalties on sales of the drug or sales-based milestones [53]<br>**Private funding through venture capital:**<br>– Decrease in R & D costs on niche market-directed therapeutics [55] | **Public research institutes:**<br>– Performance requirements, unclear assessment criteria [30]<br>**Collaborations between academia, government, pharmaceutical industry, charities:**<br>– Operationalisation and streamlining of research are made on a national level, while healthcare decisions are made within provincial boundaries [44]<br>– Financial support for data sharing, bioinformatics concerns (lack of conformity and interoperability of pipelines), and clinical data availability [45]<br>– Lack of expertise and legal issues, privacy/ethics and international legislation [45]<br>**Collaborations between government and pharmaceutical industry:**<br>– Lack of strong links between academic researchers and private endeavours [48]<br>– Strategic and confidentiality reasons related to intellectual property rights [48]<br>**Public funding through national scientific centres, universities, medical research councils and institutes of health:**<br>– Remaining patent life of the drug/compound, additional research cost, unclear return on investment [31]<br>**Private funding through manufacturers:**<br>– Variation in revenue between drugs and diagnostics [53]<br>– Intellectual property protection of diagnostics [53] |

It was also noted that when most costs are already borne by academia and the government, this could create incentives for pharmaceutical companies to finance and engage in clinical translation as the risk of costly late-stage failure is reduced [32].

## 3.3 Barriers and Disincentives for Financing PM Research

Barriers to financing research in PM were identified that related to the discordance between research prioritisation decisions on national and local levels [44] (Table 3), legal, intellectual property rights and privacy/ethics issues (such as lack of harmonisation of legal and ethical guidelines concerning data and sample sharing, as well as licensing concerns which require dedicated policies to help overcome them) [45, 48]. Other reported barriers included the lack of strong links between potential industry and academic partners [48] and performance requirements focused on direct practical applicability rather than scientific advancement [30]. Several factors were identified as disincentives associated with financing research to repurpose and reposition drugs using genome-wide approaches, or involving genomic research in early clinical development of drugs. These included the remaining patent life of the drug, and the additional costs for research coupled with an unclear return on investment [31]. The variation in revenue between drugs and diagnostics, and the inadequate intellectual property protection of diagnostics, was also highlighted as a potential disincentive to invest in laboratory developed tests [53].

## 3.4 Reimbursement Models Used in PM

### 3.4.1 Traditional Models

Non-risk–sharing reimbursement (i.e., traditional) models are used to reimburse gene, cell and targeted therapies, biomarkers, genetic and genomic tests (Fig. 2, Table 4). For example, Spinraza®, used to treat spinal muscular atrophy, has been reimbursed in the USA on the basis of wholesale acquisition price in the first year and an annual instalment for the duration of patients' life without considering the

performance of the drug [147]. CAR T therapies, Kymriah® and Yescarta® for B cell cancers, have been reimbursed in the outpatient setting on the basis of the wholesale acquisition cost supplemented by additional payment of 6 % of that cost [126, 146]. In the inpatient setting, these therapies have been reimbursed in the USA via a higher-weighted diagnosis-related group (DRG) or the "autologous transplant" DRG supplemented by an add-on payment for new technology, or bundle payment. In Europe they received confidential rebates [85, 126–128, 133, 146] (Table 4). DRGs have also been applied in Europe to reimburse Kymriah®, Holoclar®, used to treat moderate to severe limbal stem cell deficiency, and Spherox®, used to treat articular cartilage defects [133]. Imlygic®, used to treat melanoma patients, has been reimbursed in the UK with a narrow indication and at a discounted price [10, 13].

Existing fee-based payment models are usually used to reimburse tests. As companion diagnostics and genetic tests do not usually have a dedicated code for reimbursement, existing Current Procedural Terminology (CPT) codes were used to reimburse KRAS, PDL-1, EFGR, HER2-testing, gene panel oncology testing and genetic testing for spinocerebellar ataxia in the USA [88, 92, 119, 124, 137–139]. Code-stacking (i.e., use of multiple codes, which are commonly based on the performed laboratory procedures), was applied to reimburse the Mammostrat® and eXagenBC™ tests, as well as molecular pathology tests in the USA [95, 113]. Unit fees were applied to reimburse BRCA1/2 tests in Australia [89] and codes were usually used to reimburse companion diagnostics in France [91, 109]. Molecular diagnostic tests were also reimbursed by incorporating them into existing DRG- and locally and nationally negotiated tariff-based payments (e.g., in EU5 countries: Germany, France, Spain, Italy and UK) [14, 115, 121, 123, 125, 140, 142], or diagnostic costs were covered by state and hospital budgets or pharmaceutical companies [140]. Molecular diagnostics, genetic and genomic tests were also offered as direct-to-consumer tests by online companies and private health providers [90], or covered by third party payers (e.g., social security institutions) [115, 121].

Medicare Part B and D plans in the USA, which provide outpatient medical and prescription drug coverage, are used to reimburse targeted therapies, e.g., ibrutinib, trastuzumab, cetuximab, imatinib, abacavir, etc., but patient co-payments for the specialty-drug tiers, in which these drugs are placed, are high [111, 119]. In Europe (Netherlands and Scotland), targeted cancer therapies (e.g., afatinib, axitinib, bevacizumab, etc.) are reimbursed through existing policies to fund expensive hospital and orphan drugs, and patient access schemes [118].

#### 3.4.2 Risk-sharing Reimbursement Models

Performance-based models are applied to reimburse gene and cell therapies, and some companion diagnostics [83–85] (Fig. 2, Table 5). For example, Luxturna©, a gene therapy for inherited retinal disease, has been reimbursed through a risk-sharing pay-for-performance arrangement, which provides rebates if the drug fails to deliver agreed outcomes at 30 days, 90 days and 30 months, including coverage with evidence development [79, 83, 85, 132]. Kymriah®, a CAR-T therapy, has also been reimbursed via a 30-day outcome-based rebate related to achieving complete remission in the paediatric population group in the USA [85, 129, 131]. In European markets, coverage with evidence development and outcome-based rebates or payments in instalments were applied for Yescarta® and Kymriah® [80, 130, 132–134]. Strimvelis®, used to treat severe combined immunodeficiency, received reimbursement coverage by the Italian Medicines Agency, supplemented by a limited risk-sharing outcome-based model that provides a rebate in case of treatment failure [10, 13, 86, 87]. The manufacturer of Zynteglo®, a gene therapy for beta-thalassemia, has proposed an outcomes-based model that spreads five equal payments over five years for the key EU markets, including coverage with evidence development in France, Germany and England [80, 132]. Outcome-based and retroactive rebates were also offered in Europe for Zolgensma®, used to treat spinal muscular atrophy [79, 80, 132], and Holoclar® was reimbursed via payment by result in some European countries. ChondroCelect®, applied in treating cartilage defects of the knee, was reimbursed via a risk-sharing outcome-based agreement with yearly rebates for 3 years post-treatment [13] before being withdrawn from the market. OncotypeDX®, a genetic test that predicts the risk of recurrent breast cancer to inform chemotherapy treatment, is an example of a diagnostic test that achieved value-based pricing and reimbursement. The manufacturer entered into a coverage with evidence development (CED) agreement with payers in the USA, offering a discounted price while data were collected. When subsequent evaluations demonstrated the economic and clinical benefits of the test, OncotypeDX® kept its price, which was higher than the price the test would receive had code-stacking been used [84, 104, 105, 122].

Some of the risk-sharing agreements (Table 6) for targeted therapies in the UK and Italy are purely financial and involve partial rebates, free cycles of treatment and discounted schemes, while others consider outcomes of treatment and involve partial costs covered by manufacturers in case of treatment failure (money-back guarantee) [114, 144]. In Italy, the drug bevacizumab is reimbursed on an indication basis depending on the cancer type with an additional discount for advanced colorectal cancer [81]. Targeted cancer therapies were reimbursed in Europe through different

**Table 4** Classification of reimbursement models—non-risk sharing (traditional)

| Type of model | Description | Personalised medicine category | Ref |
|---|---|---|---|
| Fee based payment (including CPT codes, unit fees, code stacking) | Fixed price usually based on laboratory codes or performed procedures. Used to reimburse companion diagnostics and genetic/genomic tests | (Molecular) biomarkers including genotyping and phenotyping) and/or targeted therapy | [14, 88, 89, 91–95, 100, 101, 106–109, 112, 113, 115, 116, 119, 121, 123–125, 137–140, 142] |
| Higher weighted DRGs (or incorporated in existing DRGs, tariffs, block contracts) | Including additional funds to cover the cost of adding a new drug/technology/test to existing DRG payments. | Gene/cell/targeted therapy | [66, 85, 123, 126–128, 133, 146] |
| Add-on payments for new technologies/therapies | Additional top-up payments are provided alongside traditional hospital funding (DRG, HRG, budgets) to account for innovation and compensate for the costly price of the new technologies/therapies based on lists of medicines not covered in the existing reimbursement schemes (usually licensed ATMPs). Sometimes supplementary funding is intermediate for a defined period of time until DRGs are updated | Gene/cell therapy | [66, 85, 126–128, 146] |
| Health funds | Financial-based schemes which define producer's contributions to the cost of a therapeutic or diagnostic based on financial thresholds | | [77] |
| Direct to consumer (out-of-pocket) | Out-of-pocket payments for tests that are sold online | | [90] |
| Bundled payment/episode-based payment | A single payment to providers or healthcare facilities (or both) for all services provided to treat a given condition or provide a given treatment, including hospital procedures, care after discharge, etc., usually for a time period not exceeding 90 days.<br>Covering of all services including genetic test within an episode of care (e.g., pregnancy) | | [76, 96, 103] |
| Upfront payment | Lump sum of full cost of treatment coming at substantial budget impact to health provider who is baring solely the risk of treatment failure | Gene therapy | [77, 86, 147] |

**Table 4** (continued)

| Type of model | Description | Personalised medicine category | Ref |
|---|---|---|---|
| American Society of Clinical Oncology's Clinical Practice Committee (CPC) model | Payments are based on monthly episodes of care defined by the disease continuum: new patient, patient in treatment, transition-of-care, and under surveillance or non-treatment. Categories of treatment may be expanded with acuity and complexity of care and disease. Treatment months are paid at four levels based on disease complexity and patients' regimen. Reimbursement takes into account mode and mean of care costs, as some patients are more costly than others, and each core payment is tied to a medical inflation index. Risk corridors with parallel billing systems could be considered. The CPC plan has two levels of bundles for the patients not receiving treatment: a higher level of payment for patients who have recently been treated, and a lower level for curative or adjuvant therapies after some period of time. With personalised medicine risk of relapse and received treatment would define patients' follow-up and level of payment. Each core bundled payments could be adjusted by adopting value-based pathways and quality-improvement activities | | [65] |

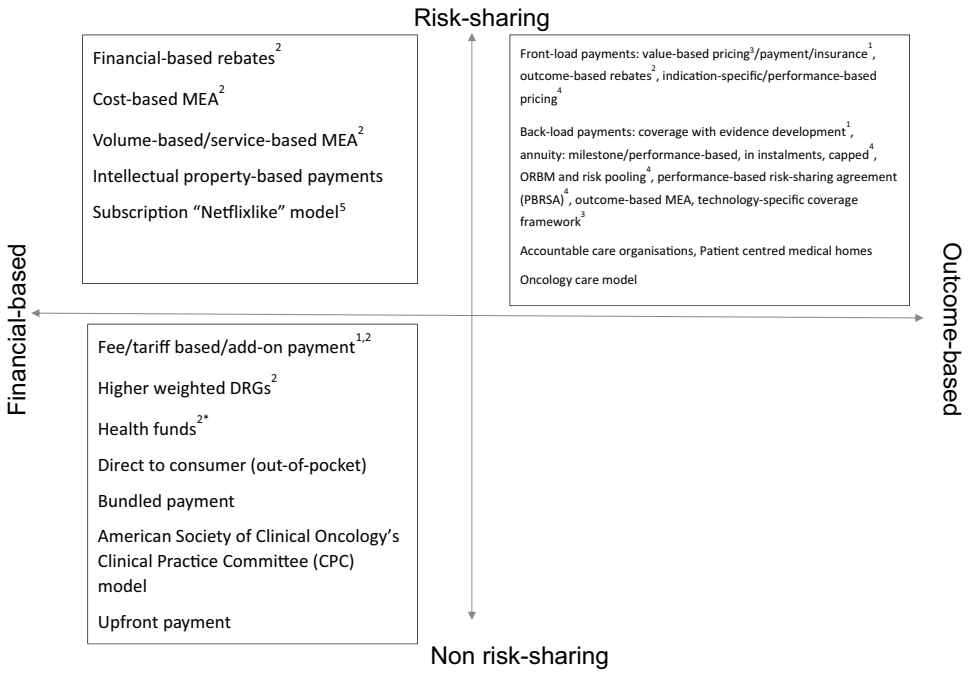


**Fig. 2** Reimbursement models for personalised medicine. *There are also risk-sharing health funds; *MEA* managed entry agreement; *ORBM* Orphan Reinsurer and Benefit Managers; *PBRSA* Performance-based risk-sharing agreement.[1]Used in reimbursing (Molecular) biomarkers including genotyping and phenotyping) and/or targeted therapy;[2]Used/proposed in reimbursing gene/cell therapies/targeted therapy;[3]Proposed for reimbursing (Molecular) biomarkers including genotyping and phenotyping) and/or targeted therapy;[4]Proposed for reimbursing gene/cell therapies/targeted therapy;[5]Mentioned as a potential application for reimbursing gene/cell therapies/targeted therapy

financial-based models and managed entry agreements, including discount rebates, price volume agreements and price cap freezes [135, 136].

### 3.5 Reimbursement Models Proposed for PM

Models that were proposed for reimbursing PM were either financial- or outcome-based [63–82], (Fig. 2, Tables 5, 6). Performance-based contracts can be short- (one year) or long-term (multi-year), with payments made either upfront (lump sums with rebates paid in case of underperformance), or in instalments (based on the achievement of agreed milestones) [63–82]. Performance-based models could decrease the financial risk to payers as producers would share the cost in case of treatment failure or underperformance, thus overcoming the shortcomings of traditional payment models that are usually based on a one-off upfront lump sum. Value-based reimbursement was proposed as an alternative payment model for companion diagnostics that will allow the clinical utility of the tests to be assessed for a specific use, and a tiered rate then assigned [82].

In financial-based models (Table 6), producers contributed to the cost of PM to reduce the financial uncertainty surrounding the introduction of a new therapy on the basis of agreed financial thresholds and price volumes [76], provision of rebates and discounts, or a certain number of treatment cycles for free, and utilisation caps that limit the number of reimbursed doses per patient [74]. Subscription-based, also referred to as Netflixlike, models that are based on lump sum payment to manufacturers in return for unlimited access for patients over a defined period, have been mentioned in the literature discussing potential reimbursement schemes for PM [78, 80], as well as in papers describing reimbursement of interventions that are not PM [182, 183]. However, their current implementation is limited to reimburse direct-acting antivirals for hepatitis-C virus in Australia and the state of Louisiana so far [182, 183]. Expanded risk pool models have been proposed for reimbursing PM as means to reduce financial burden as third-party public or private payers will cover some of the payment for expensive treatments, e.g., gene and cell therapies [79].

### 3.6 Facilitators and Incentives for PM Reimbursement

It was frequently asserted that early pre-approval dialogue to agree on outcomes to be assessed and necessary evidence, and the application of performance-based agreements, could facilitate the reimbursement process and incentivise payers to cover PM [83, 86, 162, 165] (Table 7). Coverage with evidence development was often identified as a potential facilitator for reimbursement and adoption of companion diagnostics as it could tackle the issues of generating adequate evidence, improving access for patients, addressing regulatory concerns, simplifying reimbursement decisions, and improving the likelihood and timing of financial gains [84, 93, 119, 122]. Financial-based models, including rebates and volume caps, were pointed out as means to reduce the budget impact of new treatments and improve affordability [13]. Lists of "approved for reimbursement" tests (such as "Palmetto") [88, 107, 156, 160, 171], and caps on out-of-pocket contributions from patients [92, 111], as well as

**Table 5** Classification of reimbursement models—performance-based

| Type of model | Description | Personalised medicine category | References |
|---|---|---|---|
| Coverage with evidence development (CED) (evidence-based schemes) | Provision of insurance/payment coverage for promising but unproven medical technologies conditional on evidence generation. This temporary transitional status is granted until the product developer provides or fails to provide sufficient evidence, resulting in full coverage or non-coverage | (Molecular) biomarkers including genotyping and phenotyping), gene/cell/targeted therapy | [68, 74, 80, 84, 93, 102, 105, 122, 130, 132, 134] |
| Rebates based on outcomes | Discounts negotiated between payers and providers based on pay-for-performance or other outcome-based mechanism (also referred to as payback for treatment failure). Outcomes can be assessed at a single or multiple time measurement points | Gene/cell/targeted therapy | [10, 13, 79, 80, 83, 85, 87, 114, 129–132, 134, 144] |
| Value-based pricing/payment/insurance<br>Indication-specific pricing/performance-based pricing | Paying for interventions with higher levels of evidence and better outcomes, while discouraging use of off-evidence interventions or those that provide marginal benefit. Tiered rates can be assigned depending on clinical utility<br>Paying in accordance with the drug performance in each indication or a weighted price for all indications to alleviate the burden of high costs in some indications | (Molecular) biomarkers including genotyping and phenotyping) and/or targeted therapy | [72, 81, 82, 104, 105, 110] |
| Milestone-based annuity<br>Performance-based annuity/payment by instalments/outcome-based contract/capped annuity risk-sharing | Performance-based contract between provider/payer and developer/specialty pharmacy/wholesaler in which an up-front payment consisting of 100 % of the agreed price of the product occurs at the time of treatment. Outcomes are assessed at a specified time post-treatment and a rebate is paid in case of treatment underperformance<br>The contract can be a multi-year payment schedule as well. In this case an up-front payment of a part of the product cost is made and yearly payments in instalments are agreed on the basis of achieving outcomes. After the first outcomes failure, no further outcomes assessment would be done, and future payments would be terminated | – | [70, 71, 73, 75, 77, 79, 85, 86, 129, 130, 133, 134] |

**Table 5** (continued)

| Type of model | Description | Personalised medicine category | References |
|---|---|---|---|
| Orphan Reinsurer and Benefit Managers (ORBM) and risk pooling | ORBMs carve-out and pool risk across orphan diseases for which potentially curable/durable gene therapies exist. ORBMs contract developers and providers to establish provider networks, and healthcare plans/insurers to cover treatment. Patients contribute premiums and co-payments to payers. Developers are contracted on value-based agreements (financial or outcome-based). Expanded risk pool models are means to reduce financial burden as third party public or private payers will cover some of the payment for expensive treatments, e.g., gene and cell therapies | Gene/cell therapy | [75, 79] |
| Performance-based personalised reimbursement scheme<br>(Performance-based) risk-sharing agreement (PBRSA)<br>Outcome-based managed entry agreements/Health funds for reimbursing costs of medicines against their health gain | Risk-sharing can be based on outcomes and evidence, where the price level, reimbursement, or revenue received is linked to the performance of the product in the real world. These agreement are also called pay-for-performance, outcomes guarantee, disease management schemes, and coverage with evidence development | – | [13, 63, 64, 67–69, 74] |
| Technology-specific coverage framework | A coverage framework focused on a specific technology (e.g., next generation tumour sequencing, with different coverage criteria being recommended on the basis of the number of genes. Standard-of-care drugs as well as off-label therapies may be covered if supported by evidence. The drug manufacturer pays for the first 3 months of the off-label therapy, and the payer reimbursement starts thereafter if positive or stable results are observed | (Molecular) biomarkers including genotyping and phenotyping) and/or targeted therapy | [68] |
| Accountable care organisations (ACOs) | ACOs manage and coordinate care for a specified group of patients through shared governance from a variety of stakeholders. The two main models in Medicare are the Medicare Shared Savings Program (MSSP) and the Pioneer ACOs. ACOs can enter into two-sided risk arrangements and are given a target spending benchmark based on historical costs. ACOs can earn "shared savings" based on the amount of Medicare spending below the benchmark in a given year. If ACOs cannot contain costs beneath their target amount, they may be required to pay back the Medicare programme | | [76] |

**Table 5** (continued)

| Type of model | Description | Personalised medicine category | References |
|---|---|---|---|
| Patient-centred medical homes | Coordinates care across all elements of the broader healthcare system, including specialty care, hospitals, home, and community services. The Patient-Centred Oncology Medical Home (PCOMH) model includes a fixed, per member per-month (PMPM) care management fee on top of the normal fee-for-service payment. The initiation of the payment model starts with a patient's diagnosis, when the practice assumes primary responsibility for the coordination of all services related to the cancer and coordination with other providers for any non-oncologic care, extending through to the survivorship phase | | [76] |
| Oncology care model | Coordinates oncology care across physician practices to improve quality and lower costs. The payment arrangement is based on financial and performance accountability for episodes of care | Targeted therapy | [141] |

dedicated pathways for drug-test evaluation and funds were also suggested to facilitate reimbursement and improve clinical utilisation [101, 149]. Co-development of companion diagnostics and drugs was proposed as an approach that could potentially improve test-drug reimbursement by improving the clinical evidence base, but which may also delay market access as R&D and clinical trials could take longer [154, 169]. It was noted that reimbursement of companion diagnostics could potentially be further facilitated by improving coding terminology [107, 112, 113, 119, 156, 160, 161], providing evidence for clinical and cost effectiveness, and inclusion in guidelines [94, 116, 161, 176]. As value-based reimbursement models for companion diagnostics are not widely used in healthcare systems, it was proposed that aligned reimbursement processes of precision mechanism and subsequent treatment based on evidence and HTA could facilitate the reimbursement of such tests [175, 178, 179]. Refinement of value assessment frameworks to include wider economic analyses of direct and indirect costs and benefits, as well as broader value concepts and using financial markets valuation methods were proposed to help achieve the implementation of value-based reimbursement for targeted cancer therapies [173]. It was proposed that innovation should be rewarded on the basis of value and should be flexible with the generation of new evidence and the emergence of competing technologies. Finally, it was noted that the core value elements should include length and quality of life; however, value of knowing should also be incorporated into the paradigm for PM [174].

### 3.7 Barriers and Disincentives for PM Reimbursement

A key barrier to reimbursing gene and cell therapies was said to be the lack of demonstrable benefit [10, 13] (Table 7). Existing HTA frameworks evaluate these interventions in a similar way to other therapies and reimbursement models are not adapted to reflect the effectiveness of one-off treatments; data for the sustainability of long-term benefits and improvements in quality of life that could be achieved in chronic conditions are uncertain or lacking [10, 87]. In addition, regulatory requirements (e.g., Medicaid Best Price in the USA) were identified that may pose a barrier to introducing annuities [85], as a single instalment may be regarded as "the best price" to which Medicaid will be entitled.

Among the barriers and disincentives for value-based reimbursement of targeted cancer therapies are the lack of differentiated criteria for assessing and recommending these therapies that include wider economic analyses of direct and indirect costs and benefits, and additional elements of value. Thus, positive reimbursement decisions depend on the availability of financial managed entry agreements, including usually confidential discounts [173].

Key barriers for the reimbursement and adoption of molecular and genetic/genomic testing were noted to be the use of existing CPT codes for other tests (cross-walking), the use of code-stacking, and prolonged service codes that were rarely reimbursed [104, 106, 109, 110, 116, 119, 121, 137, 138, 148, 151, 154–156, 160, 161, 171, 172]. Variations

**Table 6** Classification of reimbursement models—financial-based

| Type of model | Description | Personalised medicine category | Ref |
|---|---|---|---|
| Rebates non-outcome-based | Discounts negotiated between payers and providers based on financial risk-sharing and not related to outcomes | Gene/cell/targeted therapy | [10, 81, 114, 135, 136] |
| Free of charge/discounted cycles of treatment/ Cost-based managed entry agreements | Agreement in which developer agrees to provide a number of cycles of treatment free of charge or at a discounted price. Cost-based agreements are financial and do not linking coverage to health outcomes (e.g., price–volume agreements, rebates, discounts, and utilization caps) | Targeted therapy | [13, 74, 114, 135, 136, 143–145] |
| Volume-based managed entry agreements | Restriction to the highest- value patient groups and limiting the number of patients eligible for treatment to improve affordability | - | [13, 74, 135, 136, 143, 145] |
| Intellectual property-based payments | Type of payment that rewards innovation and removes the burden from manufacturers to seek high costs for their treatments. It can include prizes for patents, out-licensing of technology rights or prolonged patent rights | Gene therapy | [77] |
| Subscription-based "Netflixlike" model | Lump sum payment to manufacturers in return for unlimited access for patients over a defined period | Gene therapy | [78, 80] |
| Service-based MEAs | Arrangements that can be conducted between manufacturers and payers, or healthcare providers that include services dedicated to facilitate patient management from different perspectives: patients, healthcare professionals, healthcare providers to ensure better use and improved outcomes of expensive therapies | - | [145] |

**Table 7** Reimbursement models—facilitators, incentives, barriers and disincentives

| Facilitators and incentives | Barriers and disincentives |
|---|---|
| **Evidence:**<br>➤ Performance-based models:<br>– Value-based reimbursement in oncology could reduce financial barriers to selected services [72, 84]<br>– Collection of reliable data (real world) and comparative effectiveness [63, 64, 70]<br>– Product design with the best possible long-term benefit-risk structure [73]<br>➤ Non-risk-sharing (traditional) models:<br>– Patient protection plans and caps on out-of-pocket payments [92, 111]<br>– Inclusion in guidelines [94, 116, 161, 176], validation in dedicated clinical trials (Tailorx, Mindact), proven cost-effectiveness [95]<br>➤ General:<br>– Co-development of companion diagnostics could enhance drug authorisation but may delay market access [154, 169]<br>– No penalisation for pharmaceutical firms investing in research and development of biomarkers when applying pay-for-performance agreements to drugs initially lacking a biomarker [169]<br>– Increasing usage of test-pathway strategies can accelerate the diffusion process [101] | **Evidence:**<br>➤ Performance-based models:<br>– Inability to obtain accurate/credible data to measure outcomes (related cost barriers to implementing data collection technologies) [71]<br>– Lack of demonstrable benefit/value [10, 13, 152]<br>– Clear evidence of the clinical utility of diagnostic tests [63, 101, 120, 149, 161–163] |
| **Financial risk:**<br>➤ Performance-based models:<br>– Value-based reimbursement could incentivise use of interventions with higher quality (and possibly lower cost) and contain costs [72, 151, 157]<br>– Risk reduction for providers as rebates are paid in case of outcomes not achieved at the evaluation points [83]<br>– Risk-sharing agreements likely to improve sustainability and avoid unnecessary expenses [64]<br>➤ Financial models:<br>– Using patient access schemes to improve the cost-effectiveness and reduce the budget impact of new treatments [13]<br>– Improving affordability through restricting the high-value therapies to patient subgroups based on cost-effectiveness and clinical considerations [13]<br>– Reinsurance for health payers covering high-quality cancer therapeutics [74] | **Financial risk:**<br>➤ Performance-based models:<br>– (Increasing) co-payments by patients reduces access/use of treatment [72]<br>– Affordability issues of PM [126–128, 168] (even for therapies with proven cost-effectiveness) and costly new therapies (gene/cell/cancer therapies) [13, 126–128, 150, 152]<br>– Future private payers have incentives to avoid patients with accrued liabilities due to past treatment [73]<br>– Switch to insurance providers to those with a history of coverage [10]<br>– Distort incentives for payers if the current payer can shift payment disproportionately toward future payers [73]<br>➤ Non-risk-sharing (traditional) models:<br>– Budget capping with limitation on the number of tests performed [97, 98]<br>– Budgetary consequences of reimbursing testing for every eligible member of the population [149]<br>– Insufficient reimbursement levels for the acquisition costs of the therapy in weighted DRGs [85]<br>– Direct-to-consumer tests' results may lead to indirect risk selection, migration of good risks to private insurance companies, increase of expenses, and thus an increase of additional contributions [90] |
| **Reimbursement models:**<br>➤ Performance-based models:<br>– Progressive risk-sharing agreements (coverage with evidence development, rebates) can be used to ensure value-based pricing [166] of novel diagnostics [84, 93, 119, 122], facilitate the access to off-label products [93] and quicker/early access to medicines [64, 70, 102] and re-evaluate reimbursement decisions [84, 93, 149]<br>– Advantages of progressive (accelerated) or adaptive (CED, managed entries) regulatory and reimbursement frameworks, in which initial approval is conditional upon further study, over a binary approval model [122]<br>➤ Non-risk-sharing (traditional) models:<br>– Developing appropriately granular coding terminology for tests [107] and application of new coding systems [112, 161], tier-based coding [82, 112, 113, 119, 156, 160]. | **Reimbursement models:**<br>➤ Performance-based models:<br>– Lack of established value-based pricing pathway for novel diagnostics [121]<br>– Pay-for-performance models face implementation challenges due to a lack of accessible endpoints [86]<br>– Lack of clear governance structure to outline financial flow, ensure stakeholders' engagement and resolve administrative [132] and financial issues around data collection [102], linking of outcomes with payments, payment duration and spread of instalment amounts [177]<br>➤ Financial-based models:<br>– Financial penalties for test ordering [103]<br>➤ Non-risk-sharing (traditional) models:<br>– Prolonged service codes and billing for genetic counselling rarely reimbursed [100]<br>– Lack of reporting and billing codes for hospital services [85]<br>– Pricing and reimbursement systems for diagnostics focused on the expected cost of making and conducting the test (which may depend on the technology platform used) and not the value delivered, e.g., the price of a new diagnostic is often based on the price of existing tests ("cross-walking", "code-stacking") with similar clinical use or with similar characteristics or based on production cost based on analytic steps (often leading to under-reimbursement) [104, 106, 109, 110, 116, 119, 121, 137, 138, 148, 151, 154–156, 160, 161, 171, 172]<br>– Preference for an upfront, lump-sum payment by producers [73] |
| **HTA and regulatory frameworks:**<br>➤ Performance-based models:<br>– Early pre-approval engagement between payers and manufacturers [83, 86, 162, 165].<br>– Novel regulatory routes [87].<br>– Aligned reimbursement processes of precision mechanism and subsequent treatment [175, 178, 179]<br>➤ General:<br>– Use of lists of approved genetic and genomic tests and dedicated technology assessment programme (e.g., "Palmetto") [88, 107, 156, 160, 171]<br>– Regulatory reforms to streamline access to diagnostics, dedicated funding [123].<br>– Use of value of information to define who should bear the cost of precision medicine value [170]<br>– Refinement of value assessment frameworks to include wider economic analyses of direct and indirect costs and benefits, and additional element of value [173, 174] | ➤ General:<br>– Considerable variation and inconsistency across clinical conditions and types of insurance coverage of tests and treatments, cost-sharing and preauthorisation requests, large out-of-pocket payments, lack of or different funds for tests and drugs, fragmented reimbursement process for diagnostics [14, 88, 92, 94, 97–101, 108, 109, 115, 117, 119, 121, 123, 151, 159, 161, 162, 176, 178, 179]<br>– Unilaterally set reimbursement levels could disincentivise development of a pipeline of innovative tests that require substantial risk-based research (defined as the uncertainty of the investment in innovation) [167] |
| | **HTA and regulatory frameworks:**<br>➤General:<br>– Inability of health systems to implement risk-sharing agreements [70]<br>– Considerable practicalities of administering rebates over a longer period of time [83]<br>– Regulatory requirements (Medicaid Best Price—lowest price and rebate for Centres for Medicare and Medicaid Services) may discourage instalment-based payments [85]<br>– Current assessment paradigms (including HTA) and reimbursement systems [10, 87, 105, 107, 109, 121, 151–153, 155, 158, 162, 168, 180]<br>– Unregulated direct to consumer (DTC) online market [90]<br>– Data privacy, information disclosure regulations, health regulation compliance [71]<br>– No common assessment of drug and diagnostic as treatment package [115]<br>– Potential replacement of the patent system with a prize system and dedicated government contracts for specified drug innovations [164]<br>– Lack of differentiated criteria for assessing targeted therapies and specific mechanisms for attributing added benefit [173] |

and inconsistencies in insurance coverage of tests, including whole genome sequencing, and treatments, cost-sharing (e.g. co-payments), varying insurers' contributions and preauthorisation requests, financial penalties for test ordering and budget capping on number of tests performed [14, 88, 92, 94, 97–101, 108, 109, 115, 117, 119, 121, 123, 151, 159, 161, 162, 176, 178, 179] were also identified as barriers.

Coverage with evidence development in cancer care was rarely applied in some health systems, partly due to a lack of clarity regarding the threshold for coverage initiation, the coverage mechanisms and the increased costs of evidence generation [102]. Performance-based agreements were suggested as a way that may facilitate earlier and quicker access to costly therapies [64, 70, 102], or technologies with yet unproven benefit, but were reportedly difficult to implement in current healthcare systems due to data requirements, high administration costs, and perverse incentives due to switching among payers [70, 86]. In addition, performance-based agreements could disincentivise producers who prefer an upfront, lump-sum payment [73]. The lack of a clear governance structure that outlines the financial flow of the performance-based agreements, ensures the engagement of multiple stakeholders and resolves administrative [132] and financial issues was pointed as barrier to implementing outcome-based reimbursement [177]. If current payers could shift payments towards future payers, this might disincentivise these payers from accepting patients with accrued liabilities due to past treatments [73], and prompt patients to choose insurance providers with a history of coverage [10]. In general, unilaterally set reimbursement levels [167] and infrequent assessments of drugs and diagnostics as treatment packages [115] were identified as the key disincentives for developing a pipeline of innovative tests that require substantial risk-based research.

## 4 Discussion

Personalised medicine interventions are currently financed through public and private sources, and largely reimbursed through traditional payment models, not specific to PM. Performance-based agreements are used for gene and cell therapies, and some companion diagnostics. The main barriers and disincentives to PM financing and reimbursement that were identified in the literature were the lack of strong links between public and private stakeholders and the lack of demonstrable benefit and value of PM in health technology assessments.

Across multiple papers, there was a degree of confidence that public-private agreements could facilitate financing for R&D of PM and provide opportunities for partners to share and access research facilities, databases, expertise and experience. Traditionally, early R&D in PM was undertaken in academia and small and medium enterprises, with large pharmaceutical companies organising translation [32]. However, this approach to research is evolving, with larger research consortia now pooling research funds, sharing expertise, data and resources. To keep the momentum and scale-up public-private partnerships, it was suggested in the literature that cost-sharing, risk-sharing and benefit-sharing should be carefully balanced, and efforts should be made to maintain scientific independence [39]. This will require clear and widely accepted organisational, financial, and legal frameworks to be in place. Public-private partnerships could serve as a platform for engaging in risk-sharing and outcome-based reimbursement models that improve early access to and uptake of PM, as data sharing agreements could be signed and early-phase evidence could be shared during the R&D phase [181]. However, alternative approaches to partnership were highlighted. These include vouchers or subscriptions for private investors and patients [182] that can be exchanged against healthcare when needed as well as contracts between individual investors and small and medium enterprises similar to social impact bonds that aim to improve social outcomes, are traded in markets [184–186] and are increasingly promoted by governments (e.g., in the UK) [187].

Although subscription-based models have been mentioned as potentially suitable to reimburse gene therapy [78, 80], it is unclear how they could be implemented in practice to pay for these one-off, very expensive therapies. It would also be challenging to set the level of the subscription fee to reflect the value of the gene therapy and the uncertainty in the expected outcomes, determine the prescriber (e.g., the patient, their insurer, or the state), and the duration of the subscription. Even if these challenges were overcome, it is still unclear how subscription models could actually solve the affordability issues surrounding gene and cell therapies.

To achieve risk-sharing outcome-based reimbursement agreements, the barriers identified in this review must be overcome. In particular, evaluation frameworks are required that can accurately assess the value of PM interventions. Although value frameworks are in "prime time" [188], it is currently challenging to distinguish the value of diagnostics and their accompanying therapies and to incorporate the benefits of one-off treatments and diagnostics that can alter treatment pathways into reimbursement models in the assessment of PM interventions. The adoption of outcome-based models will depend on establishing systems to collect and analyse necessary data, and on agreeing evaluation outcomes that may go beyond health outcomes to incorporate value elements related to decreased uncertainty, hope, real options, and insurance [189]. Capturing these additional value elements will require consideration of the scope of these studies, and treatment interactions that capture synergy

effects between tests and therapies may need to be included [190].

Coverage with evidence development could be an intermediate step to introduce outcome-based models by facilitating access to promising new technologies with unproven benefits while permitting data collection to inform future reimbursement decisions [83, 86, 162, 165]. However, if evidence of effectiveness and health benefits is ultimately unconvincing, it might be difficult to withdraw reimbursement and delist PM interventions [191]. Basing reimbursement on outcomes and agreeing future rebates linked to underperformance could also incentivise payers to provide coverage and access to new PM.

Aligning reimbursement of companion tests and treatments [14] could further incentivise the establishment of value-based care pathways [96, 120, 121], by facilitating the use of cost-effective PM and incentivising the investment in R&D for companion diagnostics. However, at a societal level, value-based pricing might be both unaffordable and unacceptable—especially for highly priced curative therapies and orphan drugs—despite the generated benefits [192].

Global differential pricing of PM across countries with different ability and willingness to pay for both new medicines and diagnostics coupled with reimbursement based on performance could be a potential solution to reimbursement issues [154]. However, this approach is not without its challenges as manufacturers could be disincentivised to offer differential pricing in cases where transparency of pricing is required.

Ideally, financing and reimbursement models should ensure that any surplus that is generated is distributed fairly among stakeholders, however, this is hard to achieve. Another challenge when establishing value-based care pathways based on next-generation sequencing tests (e.g., in the context of tumour agnostic drugs) is whether and how to attribute the cost of testing to existing treatments in cases when more than one actionable mutation is detected.

Theoretical models on financial incentives, rooted in behavioural economics, could be used to support the development of financing and payment models for PM by providing: (a) insight into the risk preferences of individual providers and organisations, (b) arguments about the use of sticks (e.g., penalties) or carrots (e.g., rewards), and (c) an informed perception of the appropriate size of financial incentives [193] and their potential intended and unintended consequences. This theory-based information could be used alongside existing evidence about the effectiveness of financial incentives to select the stakeholders to be involved in the financing or payment model, choose the type and level of the incentive, and construct an optimal risk structure.

On the applied side, financing and payment models should be (a) clear on how to spread the benefits and respective costs of testing, especially of extended gene panel, whole genome and exome sequencing, to different preventive measures and gene and targeted treatments, (b) propose ways to engage multiple stakeholders from the very early stages of R&D to achieving reimbursement coverage, to allow for fair pricing and sharing of value, and (c) incorporate a roadmap for their successful implementation.

Large markets and leading innovators, such as the USA, that contribute more than one-third of the global annual pharmaceutical revenues and produce a large share of PM [3, 194], are key in realising the full potential and value of PM globally. Therefore, international efforts to increase the development and uptake of PM may prioritise the implementation of appropriate financing models for R&D accompanied by payment models that reward innovation and achievement in such countries. It is often these countries that experiment and establish innovative models for financing and reimbursement of healthcare that are later adopted by other countries [132].

Approval and market access do not always guarantee reimbursement coverage and R&D costs of PM may not be adequately reflected in reimbursement. This financial risk may reduce the interest of manufactures to invest in PM and evidence generation through large RCTs. According to our findings, weak evidence is in turn a barrier for successful implementation of performance-based reimbursement models. Therefore, it was argued in the literature that a new paradigm that aligns financing of R&D and reimbursement for PM intervention is needed. This could facilitate the distribution of uncertainty and financial risk of investments between stakeholders and incentivise investment in R&D. A possible way to achieve this is to expand the scope of public-private financing agreements to include the terms of reimbursement in case the PM intervention proves to meet the expectations of the involved parties.

Reimbursement challenges that are barriers to clinical implementation and adoption, and provide disincentives for research, development and innovation, are not unique to PM. New expensive antibiotics have faced reimbursement issues, albeit for different reasons such as the caps on prescription and prices, and the well-established generic market [195].

The strengths of our review included the extensive search of scientific databases and grey literature, and the detailed data extraction that allowed us to identify promising models for PM. The main limitation was that we did not assess the quality of the included studies, as our aim was to summarise options for financing and reimbursement of PM, rather than judging the quality of individual studies.

## 5 Conclusion

Our study shows that current barriers in the implementation of appropriate financing and reimbursement models for PM challenge the translation of PM interventions into clinical practice. Policymakers and other stakeholders around the world could concentrate their efforts in removing these barriers to stimulate public-private financing of PM R&D and achieve performance-based reimbursement agreements of PM with proven clinical and cost effectiveness.

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## Declarations

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**Conflict of interest** Sarah Wordsworth and James Buchanan are co-applicants of a project funded through Genome British Columbia's GeneSolve programme and Illumina and have received travel support from Illumina to attend conferences in Baltimore (USA), Barcelona (Spain), and Basel (Switzerland). Heleen Vellekoop, Simone Huygens, Matthijs Versteegh, Maureen Rutten-van Mölken, László Szilberhorn, Tamás Zelei, Balázs Nagy, Rositsa Koleva-Kolarova, and Apostolos Tsiachristas have no conflicts of interest that are directly relevant to the content of this article.

**Ethics Approval** This study did not require approval by a medical ethics committee.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Availability of Data and Material** Search strategies used for the systematic literature review and the selection criteria are available in the supplementary files. The Excel file used for the data extraction during the systematic literature review can be made available upon request.

**Code Availability** No programming was used in this study.

**Author contributions** AT and SW outlined the concept and broad methods for this study. AT, JB and RKK conducted the literature review and together with SW wrote the manuscript. All authors provided multiple rounds of critical feedback.



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