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Systematic Literature Review

The Net Benefit of Personalized Medicine: A Systematic Literature Review and Regression Analysis



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ABSTRACT

Objectives: Amidst conflicting expectations about the benefits of personalized medicine (PM) and the potentially high implementation costs, we reviewed the available evidence on the cost-effectiveness of PM relative to non-PM.

Methods: We conducted a systematic literature review of economic evaluations of PM and extracted data, including incremental quality-adjusted life-years (Δ QALYs) and incremental costs (Δ costs). Δ QALYs and Δ costs were combined with estimates of national cost-effectiveness thresholds to calculate incremental net monetary benefit (Δ NMB). Regression analyses were performed with these variables as dependent variables and PM intervention characteristics as independent variables. Random intercepts were used to cluster studies according to country.

Results: Of 4774 studies reviewed, 128 were selected, providing cost-effectiveness data for 279 PM interventions. Most studies were set in the United States (48%) and the United Kingdom (16%) and adopted a healthcare perspective (82%). Cancer treatments (60%) and pharmaceutical interventions (72%) occurred frequently. Prognostic tests (19%) and tests to identify (non)responders (37%) were least and most common, respectively. Industry sponsorship occurred in 32%. Median Δ QALYs, Δ costs, and Δ NMB per individual were 0.03, Int\$575, and Int\$18, respectively. We found large heterogeneity in cost-effectiveness. Regression analysis showed that gene therapies were associated with higher Δ QALYs than other interventions. PM interventions for neoplasms brought higher Δ NMB than PM interventions for other conditions. Nonetheless, average Δ NMB in the 'neoplasm' group was found to be negative.

Conclusions: PM brings improvements in health but often at a high cost, resulting in 0 to negative Δ NMB on average. Pricing policies may be needed to reduce the costs of interventions with negative Δ NMB.

Keywords: cost-effectiveness, net benefit, precision medicine, personalized medicine, QALY, test, threshold.

VALUE HEALTH. 2022; 25(8):1428–1438

Introduction

Personalized medicine (PM), a term often used to describe innovative healthcare interventions that enable improved patient stratification (generally through genetic or genomic testing), may improve health outcomes (eg, by preventing adverse drug reactions in “slow metabolizer” patients) and reduce healthcare costs (eg, by preventing the prescription of treatments to patients who do not benefit from it). Therefore, PM has been subject to high hopes and expectations. Nevertheless, there are concerns about the potentially high costs of (implementing) PM. Among these are worries about the costs of larger-scale gene testing and concerns about the steep pricing of some of the PM interventions that have come onto the market in recent years.^{1,2} Although many countries perform economic evaluations to assess the balance

between health benefits and costs of individual PM interventions coming onto the market, there is limited knowledge about the average net benefit of PM.

Previous reviews have found that cost savings are relatively rare; most economic evaluations of PM show increased costs and higher health benefits.^{3–5} They have also found large heterogeneity in study methods and cost-effectiveness outcomes, sometimes even across different evaluations of the same intervention.^{6–8} The previous reviews focused on incremental cost-effectiveness ratios (ICERs) or binary “cost-effective yes/no” judgments to assess cost-effectiveness. In this study, we aim to build upon previous research by investigating the net monetary benefit (NMB) of PM interventions instead of their ICERs and by performing regression analyses in which we explore the heterogeneity in the cost-effectiveness of PM interventions.

Methods

Systematic Literature Review

We performed a systematic literature review aiming to identify all published economic evaluations of PM between 2009 and 2019. PM was defined as “a medical model that bases therapeutic choice on the result of gene profiling or aims to correct pathogenic gene mutations,” based on a study by Hatz et al.⁷ Given the rapid pace of innovation in PM and changes in its costs over time, studies from before the 2009 cutoff were expected to be less insightful about the current value of PM.

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.⁹ On March 13, 2019, databases Embase, Google Scholar, Medline Ovid, and Web of Science were searched. An additional search for gray literature was performed on May 16, 2019, and included the Centre for Reviews and Dissemination and EconLit databases and the reimbursement dossier sections on the websites of the National Institute for Health and Care Excellence and the Institute for Clinical and Economic Review.

A total of 3 groups of search terms were used, combined with the Boolean operator AND: “economic evaluation”; “modelling”; “personalized medicine” (see Appendix 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2022.01.006>). Studies were included if they fell within our definition of PM, presented a cost-effectiveness model, provided patient-level cost and quality-adjusted life-year (QALY) outcomes, provided the cost year (so that cost outcomes could be inflated to 2020), extrapolated outcomes beyond short-term clinical trial data, and described an existing (ie, nonhypothetical) intervention. Studies also had to compare a PM intervention with a non-PM intervention, given that PM versus PM comparisons would not allow for the assessment of the added value of PM.

Various data items were collected from the included studies, using a Microsoft Excel-based data extraction form. Study details were recorded (first author, year of publication, country, currency), as well as information about the health technology assessment (HTA) methods used (perspective, time horizon, discount rates, cost-effectiveness threshold). Details about the interventions under evaluation (description of the intervention, description of the comparator, disease class according to the International Classification of Diseases, Tenth Revision [ICD-10]), and cost-effectiveness outcomes (incremental costs [Δ costs], incremental QALYs [Δ QALYs], ICERs) were also captured. If studies evaluated multiple interventions or comparators, all 2-way comparisons between PM and non-PM interventions were recorded.

Assessing Cost-Effectiveness

NMB was used as the measure of cost-effectiveness. Although the ICER measure is widely used to measure cost-effectiveness, NMB is better suited for ranking large numbers of interventions (eg, because of issues around interpreting negative ICERs) and for assessing the magnitude to which an intervention is more (or less) cost-effective than another one.¹⁰ Therefore, the NMB measure was deemed more appropriate for our study.

The incremental NMB (Δ NMB) of each intervention i was calculated with the formula $\Delta NMB_{ij} = \Delta h_{ij} * k_j - \Delta c_{ij}$, where $\Delta h_{ij} = \Delta$ QALYs for intervention i in country j , $k_j =$ cost-effectiveness threshold in country j , and $\Delta c_{ij} = \Delta$ costs for intervention i in country j . Δ costs were inflated to 2020 prices using country-specific inflation rates and converted to purchasing power parity using conversion factors from the World Bank Global Economic Monitor.¹¹

Despite the importance of cost-effectiveness thresholds in cost-effectiveness analysis, limited research has been conducted regarding the appropriate threshold value in each country. Indeed, in many countries, the standard cost-effectiveness thresholds applied during HTAs are based on little to no data. Part of the reason for the limited research into cost-effectiveness thresholds may be that there exists conceptual disagreement about what the threshold represents and how it should be calculated.^{12,13} The 2 main views are that the threshold should reflect (1) society's willingness-to-pay for increases in health (v) and (2) the opportunity cost of healthcare spending (k). We opted to use k thresholds, because we were able to find national estimates for all countries included in our data set (apart from Taiwan), whereas v estimates were not available for all countries. In addition, v thresholds might not always be appropriate, especially in studies with a healthcare perspective, given that society's willingness to pay for health benefits may not align with available (healthcare) resources. We explicitly chose not to use the thresholds countries have historically used in our base case analysis. This was partly because several countries do not make use of a specific, single threshold and partly because there are likely inconsistencies in how different countries arrived at their thresholds.

Values for national k thresholds were mostly taken from a 2016 study by Woods et al,¹⁴ which estimates k thresholds for 183 countries. Whenever country-specific studies were available, the estimates from these studies were used. See Appendix 2 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2022.01.006> for an overview of the national threshold values.

Exploring Heterogeneity

Regression analysis was conducted to explore the heterogeneity in the reported cost-effectiveness of PM in the included studies, aiming to identify characteristics of PM that may be associated with higher (or lower) health benefits, costs, and NMB. Generalized linear mixed models were used, with random intercepts at country level to account for national differences in prescribed HTA methods (such as discount rates for future health benefits and costs), healthcare systems, and epidemiology. Restricted maximum likelihood estimation was applied instead of maximum likelihood estimation to avoid bias in the variance estimation. Analysis of variance (ANOVA) was used to assess the benefit of a random intercept at country level. “Variance explained” was assessed using conditional R^2 (following the definitions in Nakagawa and Schielzeth¹⁵) and compared with the adjusted R^2 of a simple linear model with the same specification but without the random intercept. A total of 3 separate models were specified, with Δ QALYs, Δ costs, or Δ NMB as the dependent variables, and all included the same independent variables: “purpose of test,” “type of treatment,” “gene therapy,” “industry sponsorship,” and “disease classification.”

The independent variable “purpose of test” was based on a previous literature review of economic evaluations of PM, which identified broad categories that tests could be classed into and found possible differences in (median) cost-effectiveness between the categories.⁷ The categories were testing to (1) screen for a disease or a genetic marker in an asymptomatic population (eg, genetic testing for LDL receptor mutations in relatives of patients with familial hypercholesterolemia), (2) gain information about disease prognosis (eg, OncotypeDX), (3) identify likely (non)responders to treatment (eg, testing for NTRK gene fusions so that TRK inhibitors can be provided to cancer patients who test positive), and (4) identify patients who may experience adverse drug reactions (eg, CYP2D6 testing to optimize pharmacotherapy).

The variable “type of treatment” indicates for each intervention whether the treatment is pharmaceutical, non-pharmaceutical, or a combination of both (eg, gene-expression

profiling to help diagnose cancers of unclear origin, with subsequent surgical and pharmaceutical treatment). The variable was included based on debate around the affordability and cost-effectiveness of expensive pharmaceuticals in PM.

Literature and initial descriptive analysis showed that genetic therapies tend to be outliers, with sizably higher incremental health benefits and costs than other PM interventions. Therefore, the dichotomous variable “gene therapy” was added to avoid genetic therapies skewing the results for the other variables.

We included “industry sponsorship” as a dichotomous variable to investigate any differences in the reported cost-effectiveness between industry-sponsored and nonindustry-sponsored studies given that previous studies have found that (cost-)effectiveness outcomes tend to be more favorable in industry-sponsored studies than in studies by publicly funded and independent research organisations.^{5,16,17}

Finally, we included a dichotomous variable “disease classification,” which could take on the value “neoplasm” and “non-neoplasm”, depending on whether the intervention was used to treat neoplasms (ie, cancer) or other conditions. This variable accounts for the predictive value of belonging to the largest set of studies found in the literature review. The variable did not further specify the “other” category to avoid multicollinearity with the other predictor variables.

Sensitivity Analysis

In the base case, all studies received equal weight in the regression analysis, only studies with a healthcare perspective were included and Δ NMB was calculated using country-specific k thresholds. Sensitivity analyses were performed where (1) studies were weighted according to their quality score in the Tufts Cost-Effectiveness Analysis Registry, (2) Δ NMB was calculated based on the cost-effectiveness threshold stated by the authors of each study, and (3) studies with a societal perspective were also included. We also repeated the base case analysis in a subsample including only interventions for neoplasms. Finally, because of ambiguity in the definition of genetic therapies, an additional analysis was performed in which the classification of a specific intervention (Spinraza to treat spinal muscular atrophy) was changed from ‘genetic’ to ‘other’.

Results

Study Sample

The systematic search rendered 4774 articles, whose abstracts were screened. Full-text articles were read for 615 studies, of which 128 met the inclusion criteria and were included for data analysis (see [Appendices 3–4](#) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2022.01.006> for the inclusion flow-chart and an overview of included studies). The included articles provided cost-effectiveness outcomes for 279 PM interventions.

Characteristics of Studies, Interventions, and Methods

The distribution of interventions across countries, perspective, disease classes, types of test, types of treatment, and types of funding is presented in [Table 1](#). A total of 23 countries were included in the data set, although most interventions were evaluated in the United States and the United Kingdom (48% and 16%, respectively). All included countries are upper-middle- or high-income economies according to the World Bank country classification,¹⁸ meaning no economic evaluations of PM were identified for lower-middle- or low-income economies. The healthcare

Table 1. Descriptive statistics of the included studies.

Category	Number of interventions (percent of total)
Country	
Canada	10 (4)
China	15 (5)
Germany	15 (5)
The Netherlands	14 (5)
UK	44 (16)
US	135 (48)
Other*	42 (15)
Perspective	
Healthcare	229 (82)
Societal	50 (18)
Disease class	
Diseases of the circulatory system	54 (19)
Endocrine, nutritional, or metabolic diseases	11 (4)
Mental, behavioral, or neurodevelopmental disorders	9 (3)
Neoplasms	167 (60)
Other†	40 (14)
Purpose of test	
Screening	58 (21)
Info prognosis	54 (19)
Identify responders	103 (37)
Identify adverse drug reactions	64 (23)
Type of treatment	
Pharmaceutical	201 (72)
Nonpharmaceutical	70 (25)
Combination	8 (3)
Gene therapy	
Gene therapy	11 (4)
No gene therapy	268 (96)
Industry sponsorship	
Industry sponsorship	90 (32)
No industry sponsorship	189 (68)

UK indicates United Kingdom; US, United States.

*Included in “Other” are Australia (3 interventions assessed), Austria (3), France (5), Hong Kong (1), Italy (3), Japan (5), Malaysia (2), New Zealand (2), Puerto Rico (1), Singapore (4), Slovenia (1), South Korea (2), Spain (3), Sweden (1), Switzerland (2), Taiwan (3), and Thailand (5).

†Included in “Other” are adverse drug reactions (7), diseases of the digestive system (3), diseases of the immune system (6), diseases of the musculoskeletal system or connective tissue (6), diseases of the nervous system (5), diseases of the respiratory system (2), and diseases of the visual system (2).

perspective was the most common perspective (81%). Most evaluated interventions were in the “neoplasms” category (60%). Pharmaceutical treatments allocated based on markers in the tumor DNA were common in this category. Other frequently occurring interventions were gene assays providing risk assessments regarding the aggressiveness of tumors and screening interventions aiming to identify individuals at risk of developing cancer. Common interventions in the “diseases of the circulatory system” category (19%) were pharmacogenomic testing before anticoagulation therapy and genetic screening to identify patients at risk of various heart conditions. Interventions in the “endocrine, nutritional, or metabolic” diseases category (4%) focused on screening for familial hypercholesterolemia and maturity onset diabetes of the young, whereas interventions in the “mental, behavioral, or neurodevelopmental disorders” category (3%)

Table 2. Quantiles Δ QALYs, Δ costs, and Δ NMB.

Variables	Min	5%	25%	50%	75%	95%	Max	Mean
Δ QALYs	−0.76	−0.10	0.00	0.03	0.16	1.08	11.8	0.26
Δ costs (2020 Int\$)	−34 062	−7233	−338	575	3233	282 080	8 095 744	99 777
Δ NMB (2020 Int\$)	−7 997 236	−91 832	−2665	18	3538	21 615	406 277	−77 072

Δ cost indicates incremental cost; Δ NMB, incremental net monetary benefit; Δ QALY, incremental quality-adjusted life-year; Max, maximum; Min, minimum.

mostly involved pharmacogenomic testing before starting antidepressants.

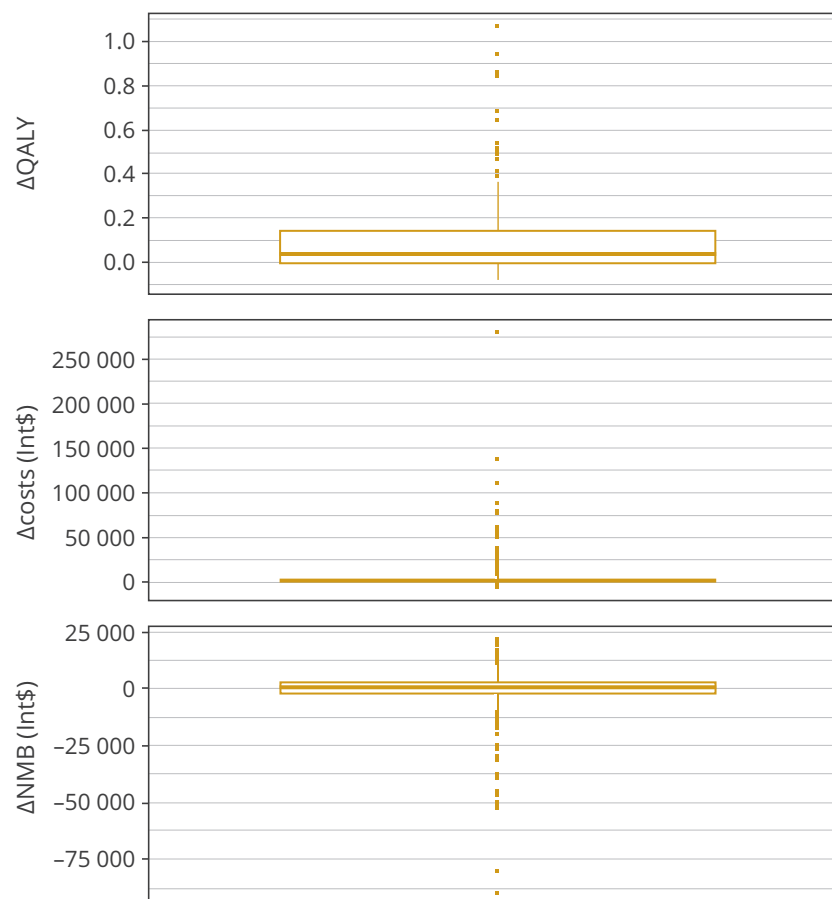
Notably, 21% of the evaluated interventions fell in the “screening” category, 19% in “info prognosis,” 37% in “identify responders,” and 23% in “identify adverse drug reactions”; 72% of the evaluated interventions were pharmaceuticals, 25% non-pharmaceutical, and 3% a combination of both. Non-pharmaceutical interventions consisted mostly of gene tests to determine the appropriate screening interval (eg, increased screening frequency for patients at increased risk of hypertrophic cardiomyopathy or colorectal cancer) and gene tests to determine whether surgery is necessary (eg, preventive surgery for patients with BRCA mutations). Only 4% of evaluated interventions were gene therapies, of which 6 were in “neoplasms” and 5 in “non-neoplasms.” Moreover, 32% of interventions were evaluated in industry-sponsored studies.

Estimated Cost-Effectiveness

The median amount of Δ QALYs of PM interventions relative to their non-PM comparators was 0.03, whereas the mean was 0.26. As can be seen in Table 2, most Δ QALY values are just above 0, with 0.00 Δ QALY at the 25th and 0.16 Δ QALY at the 75th percentile, respectively. Nonetheless, several interventions had larger benefits. Sixteen interventions (6%) rendered > 1 Δ QALY.

Median Δ costs were Int\$575, whereas mean Δ costs were Int\$99 777. Figure 1 shows that a small number of interventions have notably higher Δ costs than the rest.

Median Δ NMB across the included interventions was Int\$18, and mean Δ NMB was Int\$−77 072. Δ NMB centers around 0, with a value of Int\$−2665 at the first quantile and Int\$3538 at the third quantile. As can be seen in Figure 1, extreme negative values are more common than extreme positive values for Δ NMB.

Figure 1. Boxplots Δ QALY, Δ cost, Δ NMB.

For each boxplot, the bottom and top 5% of the distribution were excluded from the figure. Δ QALY indicates incremental quality-adjusted life-year; Δ cost, incremental cost; Δ NMB, incremental NMB.

Table 3. Details for interventions among top 5% of Δ NMB.

Δ NMB	Intervention	Comparator	Country
406 277	CAR-T-cell therapy (tisagenlecleucel) for pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia	Clofarabine	US
265 848	The addition of gene-expression profiling to usual care to identify the tissue of origin and guide therapy choice in adults with metastatic cancer of uncertain origin	Therapy choice based on usual care (including IHC, blood tests, physical examination)	US
208 766	CAR-T-cell therapy (tisagenlecleucel) for pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia	Blinatumomab; clofarabine, cyclophosphamide, and etoposide combination therapy; and clofarabine monotherapy	US
95 175	Gene profiling (mutational load-based) in patients with nondysplastic Barrett's esophagus. Only patients with high risk score receive ablative therapy	Periodic endoscopic surveillance, ablative therapy when high grade dysplasia or esophageal adenocarcinoma are detected	US
78 312	Gene-expression profiling (Mammaprint™) in patients with node-negative, estrogen receptor-positive breast cancer. Only patients with high risk score receive adjuvant chemotherapy	All patients receive adjuvant chemotherapy	NL
62 705	Gene profiling (mutational load-based) in patients with nondysplastic Barrett's esophagus. All patients who test positive for mutational load (high- or low-risk) receive ablative therapy	Periodic endoscopic surveillance, ablative therapy when high grade dysplasia or esophageal adenocarcinoma is found	US
48 518	Gene profiling in children with neonatal diabetes. Patients switch from insulin to sulfonylurea when mutations in the KCNJ11 or ABCC8 genes are found	Insulin treatment for all patients	US
41 885	Gene profiling to identify long-QT syndrome in relatives of index patients. Relatives who test positive are treated with β -blockers	β -blockers for all first-degree relatives	US
37 277	Gene profiling (CPGx™) in treatment-resistant patients with major depressive disorder to guide therapy choice	Therapy choice based on treatment history, physical examination, lab tests that are part of usual care	US
35 604	Gene profiling (assessing IL-28B genotype) of patients with chronic hepatitis C to identify patients who would benefit from the addition of protease inhibitors to standard therapy	Pegylated interferon and ribavirin (standard therapy) for all	US
35 424	Gene profiling (CYP2C19) in patients with acute coronary syndrome. Patients with CYP2C19*2 received prasugrel, all other patients clopidogrel	All patients receive prasugrel	US
26 891	Gene profiling (CYP2C19) in patients with acute coronary syndrome. Patients with CYP2C19*2 received prasugrel, all other patients clopidogrel	All patients receive clopidogrel	US
24 294	Gene profiling (loss of heterozygosity-based) in patients with low-grade oral dysplasia. Patients with a low-risk score return for follow-up every 5 years, patients with an intermediate risk score every 2 years. Patients with a high risk score are referred for surgery	All patients return for follow-ups every 6 months. Patients are referred for surgery when cancer is found	CA
24 052	Gene profiling (IDGx) in patients with major depressive disorder who are treatment-naïve or whose depression is inadequately controlled to guide therapy choice	Therapy choice based on usual care, in which nonresponders to treatment iteratively try alternative options	US

Δ cost indicates incremental cost; Δ NMB, incremental net monetary benefit; Δ QALY, incremental quality-adjusted life-year; ADR, adverse drug reaction; CA, Canada; CAR, chimeric antigen receptor; IHC, immunohistochemistry; IL-28B, interleukin-28B; NL, The Netherlands; Pharm, Pharmaceutical; Ref, reference; US, United States.

Table 3. Continued

Perspective	Disease class	Purpose of test	Type of treatment	Gene therapy	Industry sponsor	ΔQALY	ΔCosts	Ref
Healthcare	Neoplasms	Identify (non) responders	Pharm	Yes	No	7.18	346 163	19
Healthcare	Neoplasms	Identify (non) responders	Pharm	No	Yes	2.65	11 863	20
Healthcare	Neoplasms	Identify (non) responders	Pharm	Yes	Yes	5.17	333 033	21
Healthcare	Diseases of the digestive system	Info prognosis	Nonpharm	No	Yes	0.86	−5260	22
Healthcare	Neoplasms	Info prognosis	Pharm	No	No	1.20	−12 170	23
Healthcare	Diseases of the digestive system	Info prognosis	Nonpharm	No	Yes	0.54	−6115	22
Societal	Endocrine, nutritional, or metabolic diseases	Identify (non) responders	Pharm	No	No	0.32	−14 983	24
Societal	Diseases of the circulatory system	Screen asymptomatic	Pharm	No	No	0.41	1081	25
Societal	Mental, behavioral, or neurodevelopmental disorders	Identify (non) responders	Pharm	No	Yes	0.32	−4161	26
Societal	Certain infectious or parasitic diseases	Identify (non) responders	Pharm	No	No	0.54	20 986	27
Healthcare	Diseases of the circulatory system	Identify ADR	Pharm	No	No	0.01	−34 062	28
Healthcare	Diseases of the circulatory system	Identify ADR	Pharm	No	No	0.12	−14 629	28
Healthcare	Diseases of the digestive system	Info prognosis	Non-pharm	No	No	0.64	−7467	29
Societal	Mental, behavioral, or neurodevelopmental disorders	Identify (non) responders	Pharm	No	Yes	0.17	−6237	30

Nonetheless, there are also some positive outliers, with a maximum ΔNMB of Int\$406 277. Details of the interventions that are among the top 5% in terms of ΔNMB are presented in Table 3.^{19–30}

In Figure 2, median ΔNMB per country (ie, based on all PM interventions evaluated in the country) is plotted against the national k threshold and the (median) author-reported threshold. We see that median ΔNMB of PM is generally close to 0, regardless of the national threshold. This implies that any QALY gains of PM interventions tend to be counterbalanced by their costs to the healthcare system.

Heterogeneity in Cost-Effectiveness

Our data set is inherently heterogeneous, because of the inclusion of studies from many countries and many authors, each with slight methodological differences. This variation is reflected in wide confidence intervals (CIs) (Table 4). Nevertheless, the mean values predicted by the models are close to the observed values.

In Table 4, the regression results for the model with ΔQALYs of PM versus non-PM as the dependent variable are presented first. The regression coefficient for the gene therapy variable is the only coefficient for which 0 is not included in the 95% CI. The coefficient of 3.22 is much larger than any of the other coefficients, suggesting large QALY gains for gene therapies. This may be because most of the gene therapies included in the review focus on early onset conditions with high morbidity and mortality. The conditional R^2 of the mixed model for QALYs was 0.47 compared with an adjusted R^2 of 0.46 of a simple linear model without random intercepts at country level. ANOVA therefore showed that the use of a random intercept did not improve goodness of fit.

For Δcosts of PM versus non-PM, “gene therapy” and “non-neoplasms” have a 95% CI that does not cross 0. The regression coefficient of 1 179 540 for “gene therapy” implies that, on average, the Δcost for gene therapies is 1 179 540 higher than for PM interventions that are not gene therapies. Similarly, the regression coefficient of 386 325 implies that for PM interventions in “non-neoplasm” the Δcost is 386 325 higher than for interventions in “neoplasm.” Conditional R^2 of the mixed model for costs was 0.66 compared with an adjusted R^2 of 0.33 of a simple linear model without random intercepts at country level. Hence, ANOVA showed that using a random intercept improved goodness of fit of the model.

Finally, in the ΔNMB model of PM versus non-PM, the regression coefficients for “gene therapy” has a negative regression coefficient, with the 95% CI again not crossing 0. The coefficient suggests that, on average, gene therapies bring Int\$868 759 less net benefit compared with non-PM interventions, despite offering higher QALY gains. This implies that the costs associated to gene therapies are higher than the monetary value of the QALY gains, leading to a net loss. The coefficient for “non-neoplasm” also does not cross 0 and implies that PM interventions for conditions other than neoplasms render Int\$380 950 less ΔNMB than PM interventions in “neoplasm.” In line with the findings from the regression analysis, the average ΔNMB in the observed data was Int\$–1 287 417 (median Int\$–343 379) for gene therapies, whereas it was Int\$–27 394 (median Int\$49) for the other interventions. Average ΔNMB was Int\$–1161 (median Int\$–426) for neoplasms and Int\$–190 260 (median Int\$164) for other interventions. Conditional R^2 of the mixed model for NMB was 0.53 compared with an adjusted R^2 of 0.23 of a simple linear model without random intercepts at country level. ANOVA showed the model goodness of fit improved by using a random intercept.

Sensitivity Analysis

Results for the sensitivity analysis can be found in Appendix 5 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2022.01.006>. The size and direction of regression coefficients tend to be similar between the analyses using base case assumptions and analyses using the alternative assumptions. In all analyses, gene therapies are associated with significantly higher QALY gains, and PM interventions for neoplasms are associated with lower costs and higher ΔNMB . Within the neoplasm subsample ($n = 167$), conclusions are similar to those reported in the main analysis, although the 95% CI for “gene therapy” now crosses 0. Reclassification of genetic therapy Spinraza to nongene therapy increased the coefficient of “gene therapy” for QALYs to 4.5. After the reclassification, the CI for “gene therapy” crossed 0 in the cost model. The coefficient for “gene therapy” in the NMB model was Int\$777 987. The average ΔNMB for gene therapies remained negative after the reclassification and was Int\$–356 016.

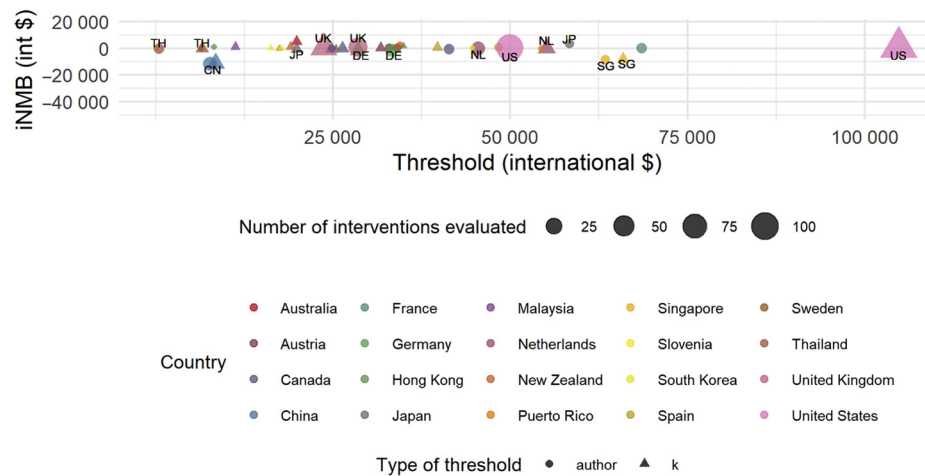
Discussion

Interpretation Results

The median and mean ΔQALYs found in this study (0.03 and 0.26, respectively) are comparable with the QALY gains found by a literature review of cost-utility analyses for all types of healthcare, which identified a median QALY increase of 0.06 (mean 0.31).³¹ We found that 6% of interventions had a QALY increase of > 1 , while this was 8% in the previous study. This suggests that the health benefits of PM tend to be similar to (or possibly slightly lower than) the health benefits of other (new) healthcare interventions.

The median ΔNMB of PM interventions was close to 0 (Int\$18), implying that the health benefits rendered by PM interventions are counterbalanced by the increased costs associated with the interventions. It could be that PM interventions are associated with higher costs than non-PM interventions because of the additional testing needed for the improved stratification in PM. Nevertheless, the costs of testing were often not—or only partially—considered in the studies included in our review.

Gene therapies were found to offer high QALY gains in all analyses. Gene therapies were also found to be associated with high costs and had an average ΔNMB of Int\$–1 287 417 (or Int\$–356 016 after reclassifying Spinraza to nongene therapy). It has been argued that the QALY insufficiently captures the value of gene therapies and that additional value elements, such as the value of a cure (ie, nonhealth-related welfare benefits, such as being able to do more future-planning), should also be considered. Although there may indeed be benefits beyond QALYs to being completely cured of a condition, our findings suggest that, on average, the monetary value of these additional benefits would have to be Int\$–1 287 417 per patient for the ΔNMB to no longer be negative, which arguably is implausibly high, especially in the light of a recent study by Reed et al³² in which much lower figures are found for the “value of hope”. The genetic therapies included in our analysis were treatments for spinal muscle atrophy (Spinraza, Zolgensma) and loss of vision because of inherited retinal dystrophy (Luxturna), and CAR-T cell therapies. Spinraza, an antisense oligonucleotide, is referred to as a “genetic therapy,” yet oligonucleotides are not classified as a “gene therapy” by the Food and Drug Administration or as advanced therapy medicinal products by European Medicines Agency.³³ After reclassifying Spinraza to a nongene therapy, the outcomes for the ΔQALY and Δcost models were largely the same. However, the coefficient for “gene therapy” in the ΔNMB model changed from a negative to a

Figure 2. Median Δ NMB plotted against cost-effectiveness threshold, per country.

Δ NMB indicates incremental net monetary benefit; CN, China; DE, Germany; JP, Japan; NL, New Zealand; SG, Singapore; TH, Thailand; UK, United Kingdom; US, United States.

positive value. Given that the “gene therapy” coefficient is sensitive to single data points, it appears that data are too scarce to draw definitive conclusions on the NMB of gene therapies.

PM interventions in neoplasms were shown to have lower Δ costs and higher Δ NMB. Indeed, average Δ NMB was higher in the “neoplasm” group than in the “non-neoplasm” group (Int\$–1161 vs. Int\$–190,260). However, median Δ NMB is more similar across the groups, with median Δ NMB even being a little lower for neoplasms (Int\$–426 for “neoplasm” and Int\$164 for “non-neoplasm”). This suggests large heterogeneity in the “non-neoplasm” group and precludes a simple explanation of why interventions for neoplasms might render more Δ NMB. The number of interventions per “non-neoplasm” condition are too low to perform condition-specific regression analysis. Different research methods may be needed to further explore the heterogeneity in the benefit that interventions for “other” conditions bring. The addition of a random intercept at country level improved goodness of fit for the Δ cost and Δ NMB models but not for the Δ QALY model, suggesting that the estimation of QALYs is less affected by differences between countries than the estimation of costs and NMB.

The CIs around the regression coefficients other than “gene therapy” and “neoplasm” are wide and cross 0 for all above-mentioned categories. Therefore, no definitive conclusions regarding the association between the different categories and dependent variable Δ NMB can be drawn. Nonetheless, we offer possible explanations for our findings below.

First, a potential explanation for the positive coefficient for “identify ADR” could be that many of the interventions included in this category aim to better stratify patients to existing treatments instead of to new treatments (eg, by offering reduced warfarin dosing to patients with gene mutations that are associated with increased sensitivity to warfarin). Conversely, many interventions in the “identify responders” category stratify toward new treatments. New treatments are generally still patented and may be costly, especially when the target population is small, which has a negative effect on the interventions’ Δ NMB. Nonetheless, in the future, the benefit from new innovations may increase. Decisions on whether to invest in products that currently bring more Δ NMB to the healthcare system or in products that may bring more Δ NMB in the future depend on value judgments on the extent to

which current versus future (uncertain) QALYs should be prioritized.

The regression coefficient for pharmaceutical interventions was positive in the Δ QALY and costs models and negative in the Δ NMB model. This could mean that although PM pharmaceuticals have higher health gains than nonpharmaceuticals, PM pharmaceuticals come at a higher cost than nonpharmaceuticals, causing lower net value (Δ NMB). The higher cost for PM pharmaceuticals compared with PM nonpharmaceuticals could be because of high prices charged by pharmaceutical companies. Nevertheless, the higher cost for pharmaceuticals could also be caused by other factors, such as the nature of the treated diseases.

The positive coefficient for “industry sponsorship” in the Δ NMB could mean that industry-sponsored studies are more likely to have positive cost-effectiveness outcomes, which is in line with previous studies.^{5,16,17} This might be because industry-sponsored studies are often for interventions about to be evaluated for reimbursement and focused on a single promising intervention, whereas nonindustry-sponsored studies may take a wider approach and include several interventions in the evaluation, some of which perhaps less promising. Additionally, authors of industry-sponsored reimbursement studies may have an incentive to limit the included costs (eg, include only testing costs for patients who tested positive as opposed to testing costs for the entire population that received testing) or otherwise make model assumptions to improve cost-effectiveness outcomes. Finally, the issue of publication bias, whereby only studies with positive results are published, may be more prominent for industry- than for nonindustry-sponsored research.

Strengths and Limitations

Previous studies investigating the cost-effectiveness of PM focused on ICERs and descriptive analyses.^{3–8} Our study expands on these studies, by focusing on NMB as opposed to ICERs, given that NMB has been argued to be more appropriate for comparing large numbers of interventions. Our study also adds to the literature by presenting regression analyses, for each of the variables Δ QALYs, Δ costs, and Δ NMB separately. Our study builds on the work of Hatz et al⁷ in particular, by incorporating the types of test they identified into our analysis.

Table 4. Regression results (N = 229).

Variable	Category	Regression coefficient	95% confidence interval	t-value
Dependent variable: Δ QALYs				
Intercept		0.02	[-0.27 to 0.32]	0.16
Purpose of test*	Info prognosis	0.10	[-0.27 to 0.47]	0.55
	Identify responders	0.22	[-0.13 to 0.56]	1.23
	Identify ADR	-0.25	[-0.63 to 0.14]	-1.25
Type of treatment†	Pharmaceutical	0.02	[-0.27 to 0.31]	0.14
	Combination	0.12	[-0.58 to 0.82]	0.33
Gene therapy	Gene therapy	3.22	[2.69 to 3.75]	12.0
Sponsorship	Industry	-0.15	[-0.38 to 0.08]	-1.31
Disease classification‡	Non-neoplasm	0.25	[-0.05 to 0.55]	1.64
Dependent variable: Δ costs				
Intercept		-163 055	[-474 256 to 148 146]	-1.04
Purpose of test*	Info prognosis	137 639	[-190 300 to 465 578]	0.83
	Identify responders	239 144	[-85 158 to 563 446]	1.46
	Identify ADR	-183 129	[-524 414 to 158 156]	-1.06
Type of treatment†	Pharmaceutical	7226	[-254 120 to 268 571]	0.06
	Combination	-96 374	[-687 344 to 494 595]	-0.32
Gene therapy	Gene therapy	1 179 540	[732 527 to 1 626 554]	5.25
Sponsorship	Industry	-92 400	[-292 338 to 107 539]	-0.92
Disease classification‡	Non-neoplasm	386 325	[122 244 to 650 407]	2.91
Dependent variable: Δ NMB				
Intercept		152 210	[-144 118 to 448 539]	1.02
Purpose of test*	Info prognosis	-126 431	[-445 368 to 192 505]	-0.78
	Identify responders	-221 146	[-535 623 to 93 331]	-1.39
	Identify ADR	176 913	[-156 155 to 509 981]	1.06
Type of treatment†	Pharmaceutical	3479	[-251 023 to 257 981]	0.03
	Combination	99 635	[-475 897 to 675 166]	0.34
Gene therapy	Gene therapy	-868 759	[-1 307 289 to -430 229]	-3.94
Sponsorship	Industry	92 109	[-103 308 to 287 527]	0.94
Disease classification‡	Non-neoplasm	-380 950	[-638 867 to -123 032]	-2.94

For values in bold, the 95% confidence interval does not cross 0.

Δ cost indicates incremental cost; Δ NMB, incremental net monetary benefit; Δ QALY, incremental quality-adjusted life-year; ADR, adverse drug reaction.

*Reference category is "screening."

†Reference category is "nonpharmaceutical interventions."

‡Reference category is "neoplasms."

Our definition of PM focuses on genetic and genomic test-treatment combinations. We acknowledge that alternative interpretations of "personalized medicine" exist. Some understand the "personalized" aspect as an increased focus on patient preferences, and some include decision making based on patients' phenotypes in their definition of PM.^{34,35} Our decision to focus on patients' genotypes was based on a study by Schleidgen et al,³⁴ in which a systematic literature review was conducted to understand how the term "personalized medicine" is used in scientific practice. The study finds that most scientific articles on PM focus on the use of gene information in medical decision making. Indeed, Schleidgen et al³⁴ argue that decision making based on phenotype (eg, weight, sex) and patient preferences is part of traditional healthcare. Including these in the definition of PM would blur the distinction between PM and traditional healthcare. Nonetheless, we

acknowledge that this study provides an incomplete overview of the net benefit of PM to those who hold a wider definition of PM.

Although many authors expressed the incremental health benefit of a test-treatment combination "per patient who tested positive," some expressed the health benefit "per patient tested." The health benefit "per patient tested" may be different from the health benefit "per patient who tested positive." For example, when genetic testing has to be applied to a large number of patients to detect a few patients with a rare mutation that determines eligibility for a particular treatment, the average health benefit per patient tested (and treated) may be diluted compared to the health benefit per patient who tested positive. Nonetheless, if outcomes across patients with different test results are expected to be similar, health benefit "per patient tested" and "per patient who tested positive" may be similar. For example, patients with

certain variants in the VKORC1 and CYP2C9 genes require lower warfarin dosing. Once warfarin dosages have been adjusted appropriately, health outcomes for patients who test positive for these gene variants may be similar to health outcomes for patients who test negative for the gene variants and receive normal dosing. Studies of cascade screening often add the health benefit of family members that are identified after an initial index patient tests positive to the health benefit of the index patient, resulting in a single QALY value “per index patient.”³⁶ A single value combining the health gains of multiple patients is likely higher than the benefit “per patient who tested positive.” Therefore, there may be some inconsistency in what is captured in the Δ QALY values that we extracted from the selected studies.

Indeed, our sample has a high level of heterogeneity as a result of the wide scope of our literature search and inconsistency in methods across studies. Therefore, the results of our regression analysis are uncertain. Although we attempted to account for country-level differences by clustering studies according to country, more streamlining of methods across studies may be needed to reduce uncertainty around the cost-effectiveness of PM.

Finally, the countries included in our review were mostly high-income countries (and a few higher to middle income). Therefore, our results do not necessarily apply to low- and (lower-) middle-income countries. Although this was caused by the limited economic evaluations of PM currently available for lower-income countries, we acknowledge the importance of more evidence generation for lower-income countries, given that insights into which interventions offer the highest added value are of critical importance in settings with highly constrained healthcare budgets.

Implications

Our study results show modest health benefits for PM versus non-PM interventions and a median Δ NMB of close to 0. The available evidence therefore seems to contrast the high anticipations that have surrounded PM over recent years. Nonetheless, there are several PM interventions with (very) positive Δ NMB. It appears that the term “personalized medicine” may be too general because it conceals sizable differences in the net benefit of different PM interventions. A more precise division into sub-categories of PM may be needed to uncover the most promising areas for further investment.

Despite the general tendency of PM interventions toward a Δ NMB of 0, we identified various interventions with (very) negative Δ NMB, among which several gene therapies. National and international pricing policies may be needed to reduce the costs of these interventions and ensure that societies are not faced with negative added value when implementing them.

Conclusions

This study has provided evidence that PM leads to additional health gains compared with non-PM but its costs tend to result in 0 to negative Δ NMB. Gene therapies offer high QALY gains and render negative net monetary benefit on average, though data scarcity prohibits drawing firm conclusions on their added value. For PM interventions with negative Δ NMB, the benefit to society may be increased if ways can be found to reduce costs.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2022.01.006>.

Article and Author Information

Accepted for Publication: January 9, 2022

Published Online: March 2, 2022

doi: <https://doi.org/10.1016/j.jval.2022.01.006>

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Supervision: Versteegh, Huygens, Rutten-van Mölken

Conflict of Interest Disclosures: All authors reported receiving grants from European Union Horizon 2020 research and innovation program grant number 824997 during the conduct of the study. No other disclosures were reported.

Funding/Support: The HECoPerMed project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement number 824997.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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