Adapting HTA frameworks for precision medicine: methodological advances in the UK and EU4

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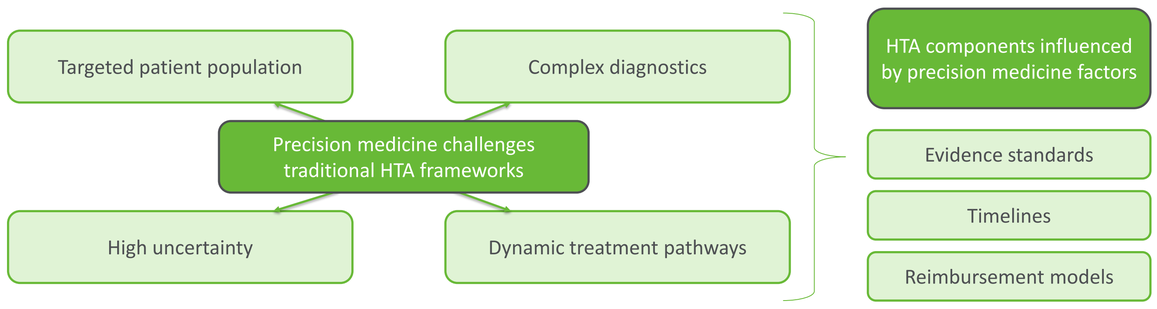
HTA21

Introduction

Precision medicine refers to therapies tailored to the patient, based on genetic, molecular, or other biological characteristics, to optimize treatment effectiveness and safety.[1] Through targeting specific populations based on underlying genetic or biomarker profiles, precision medicine necessitates complex diagnostics and leads to limited sample sizes for clinical trials, making it difficult to generate robust evidence and potentially increasing uncertainty in safety and efficacy (Figure 1). Additionally, precision medicine treatment pathways are not static as they can involve combination therapies and sequencing strategies. Therefore, traditional HTA frameworks may not be appropriate to ensure timely and equitable access to these therapies. We aimed to summarize how HTA methodologies have evolved to accommodate precision therapies, highlighting key innovations and implications.

Figure 1. Challenges associated with precision medicine can impact HTA considerations



Methods

A targeted review of HTA guidance documents and published literature was conducted*, which focused on methodological considerations related to evidence requirements, appraisal processes, and frameworks for precision therapies. Findings relevant to four European (EU) countries and the UK (Table 1) were then organized based on the level of policy advancement regarding precision medicines, split into four levels of implementation/usage (limited, being considered/exploring, ongoing/under development, strong/advanced implementation).

Table 1. Countries included within the review with their associated HTA agencies

Country	HTA agency (abbreviation)
UK	National Institute of Health and Care Excellence (NICE)
France	Haute Autorité de santé (HAS)
Germany	Institute for Quality and Efficiency in Health Care (IQWiG)
Italy	Agenzia italiana del Farmaco (AIFA)
Spain	Ministerio de Sanidad

*Local language documents were translated to English with an open-use website

Note: Countries are colour coded by implementation level as in Table 2 throughout the poster.

Results

HTA policy areas/ features applicable (but not exclusive) to precision medicine were identified and categorized into eight distinct topics following review of the guidance documents to standardize the assessment. The country's position on each of the policy areas/ features was subsequently determined and split into four levels of implementation (Table 2).

Country-level differences in policies regarding precision medicine were notable; the UK demonstrated the greatest adaptability in HTA, including managed access schemes, real-world data, and flexible pathways. Italy is also increasingly flexible in their methodology specific to innovative therapies, starting with reforms on its pricing and reimbursement framework in 2020 followed by merging HTA entities to streamline evaluations and negotiations (Scientific and Economic Commission). Conversely, France and Germany generally maintained standard methods, emphasizing clinical endpoints with limited use of adaptive tools. Spain showed mixed, variable approaches with certain regions acknowledging particularities of precision medicine.

Table 2. Comparison of themes identified by manual analysis and AI

Policy Area / Feature	UK (NICE)	France (HAS)	Germany (GBA/IQWiG)	Italy (AIFA)	Spain
Horizon scanning/innovation	✓	□	□	△	△
Early dialogue/scientific advice	✓	△	□	△	✗
Flexibility for surrogate endpoints	△	□	□	△	✗
Genomic medicine integration	✓	✓	□	△	□
HTA influence (centralised)	✓	✓	✓	△	□
Multi-criteria decision analysis	□	□	□	□	□
Adaptive/conditional pathways	✓	✗	✗	✓	△
Real-world data use	✓	✗	□	✓	□

HTA: Health technology assessment.
✓: Strong/advanced implementation (clear guidance and supporting infrastructure with routine application)
△: Ongoing/under development (active but not yet mature; partial integration)
□: Being considered/exploring (concepts are recognized and feasibility is being discussed)
✗: Limited (ad hoc implementation with isolated cases and initiatives)

Horizon Scanning

Horizon scanning supports early identification of precision therapies:
> In the **UK**, NICE, led by the NIHR Innovation Observatory, uses horizon scanning to prepare for complex technologies.[3]
> In **Italy**, AIFA publishes reports on EMA PRIME and ATMPs to track pipeline innovations.[4]
> In **Spain**, RedETS (Spanish Network for Health Technology Assessment of the National Health System) informs IPTs (Institute for Prospective Technological Studies) through scanning of emerging non-pharmaceutical technologies.[6,7]
> **France** and **Germany** rely primarily on EU-level coordination, with less formalized national processes for horizon scanning.

Early dialogue/ scientific advice

HTA agencies can offer confidential consultations to help align clinical development plans with HTA evidence expectations. Early scientific advice is increasingly available to support precision medicines, though maturity varies.
> The **UK** offers a range of interactive scientific advice in collaboration with NICE, while AIFA is less commercialized than NICE's model.[20,21]
> **Italy** provides formal advice from AIFA linked to innovative products specifically, though this service is currently suspended.
> Early Dialogue opportunities with HAS exist in **France** but these are limited to certain products and engagement is now offered only in written format.[22]
> **Germany** and **Spain** lack a national process but are joining EU-level consultations.[23]

Results (continued)

Flexibility for surrogate endpoints

Surrogate endpoints, which are often used in precision medicine where traditional endpoints are harder to measure, enable earlier assessment of treatment effects and faster access due to shorter trials:
> While final clinical outcomes (direct measures of patient survival, symptom improvement, or quality of life) are preferred, agencies like NICE and AIFA in **UK** and **Italy**, offer structured guidance and flexibility, often supported by real-world data (e.g., monitoring registries).
> **France** and **Germany** are more conservative, requiring strong validation.
> **Spain's** acceptance is limited and regionally variable.

Overall, methodological advances reflect a trend toward clearer guidance and conditional use to accelerate access while managing uncertainty.[2]

Genomic medicine integration

Genomic testing, with companion diagnostics for example, is a crucial step in identifying eligible patients for precision therapies, therefore HTA agencies should evaluate both therapy and diagnostic costs together.[10] Integration ensures reimbursement decisions reflect complete treatment pathways, aligning policy with personalized care models.
> The **UK** and **France** have structured processes in place (e.g., the NHS Genomic Medicine Service and newly launched Plan France Médecine Génomique 2025).[11,12]

HTA influence

Differences in HTA influence including decision-making and implementation levels across countries can create opportunities for early engagement or, conversely, lead to variability and delays in patient access (Table 3). The influence of recent EU collaborations such as the JCA, where precision medicine is important for both oncology and rare indications, is still to be determined.

Table 3. Implication for precision medicines of current national HTA influence

Country	Decision	Implementation	Implication for precision medicines
UK	NICE positive recommendations are legally binding for NHS England.	Nationally implemented via NHS England within 90 days (TA and HST programmes).	Conceptually national access, however, remains dependent on availability of infrastructure (e.g., testing facilities).
France	P&R decision by HAS is binding and leads to inclusion on LPPR.	Hospitals may have specific access pathways (e.g., 'Liste en sus' and retrocession lists).	Centralized evaluation with variations due to special funding mechanisms.
Germany	Nationally binding under AMNOG process (led by G-BA supported by IQWiG). => Decision leads to statutory health insurance coverage.	Sickness funds and providers may affect uptake.	Strong methodological rigor based on RWE, variability in uptake of precision medicines due to variety in health providers.
Italy	P&R decision by AIFA are binding => Product is reimbursed under the SSN [NHS].	Regional health authorities control budget allocation, formulary inclusion, procurement and access.	Delayed or uneven regional implementation due to variations in specialized infrastructure and resources for high-cost therapies.
Spain	P&R decisions can be made nationally by the CIPM. Some regions require additional HTA evaluation for local adoption.	Autonomous communities control healthcare budgets and decisions influenced by organizational feasibility and clinical protocols.	Regional autonomy leads to variability due to delays or restrictions in regional formularies and procurement.

CIPM: Comision de Precios de Medicamentos; HAS: Haute Authorité de Santé; HST: highly specialized technologies; LPPR: liste des produits et prestations remboursables; NHS: national health system; P&R: pricing and reimbursement; RWE: real world evidence; TA: technology appraisal.

Multi-criteria decision analysis (MCDA)

The MCDA is a structured decision-making approach that evaluates a variety of weighted factors (disease severity, innovation, equity) which are combined into an overall score to support balanced HTA decisions.[16] Including multiple considerations in HTA decision-making may help address the uncertainty of evidence inherent in precision medicine while ensuring that stakeholder priorities are reflected.
> MCDA principles are not formally embedded but are currently being explored especially in research, pilots and early dialogues (e.g., Advance Value Frameworks) the **UK**, **France** and **Spain** (specifically Andalusia).[17-19]

Adaptive/conditional pathways

HTA agencies are exploring flexible mechanisms to accelerate access to high-cost precision medicines.
> In the **UK**, NICE applies Managed Access Agreements and conditional approvals (e.g., Cancer Drugs Fund).[5]
> **Italy** widely implements risk-sharing agreements such as outcome-based contracts to manage uncertainty and budget impact.[8]
> **Spain** has also shown willingness to use adaptive pricing and access schemes.[9]
> In contrast, **France** and **Germany** currently lack established adaptive pathways for precision medicines, resulting in more traditional approaches to market access and reimbursement in these countries.

Real world data use

HTA agencies increasingly rely on real-world data to address evidence gaps in precision medicine.
> The **UK** promotes registries and digital health records to supplement limited trial data.[13]
> The AMNOG process in **Germany** accepts real-world data when linked to clinical trials, especially in oncology.
> In **Italy**, AIFA mandates post-marketing registries for certain drugs, while **Spain** shows growing interest in leveraging health system data, both aiming to generate real-world evidence for post-launch evaluations.[14,15]

EU HTA regulation[24]

New EU HTA regulations: Introduced as of January 2025 aim to harmonize evidence requirements across the EU and particularly relevant to precision medicine as new molecular entities for oncology and advanced therapy medicinal products (ATMPs) are in current scope, which will broaden to include orphan medicines in 2028. ATMPs include cell and gene therapies which are inherently personalised to the patient and therefore require flexible assessment frameworks which consider broader value elements such as long-term outcomes.

Joint Clinical Assessments (JCA): single clinical evaluations of new medicines
Joint Scientific Consultations (JSC): early dialogue to align trail design and endpoints

These mechanisms improve predictability, support surrogate endpoints and facilitate coordinated use of RWE, by sharing infrastructure for evidence generation. These aspects will facilitate evaluation of precision medicines.

Conclusions

HTA methodologies in the UK and EU4 are evolving, to meet the unique demands of precision therapies; such as adaptive trial designs due to limitations of randomized trials in rare or biomarker-driven patient populations, and to meet stakeholder expectations of faster access to innovative therapies. As there are variations in current implementation of flexible HTA (which impacts patient access to these newer therapies), continued innovation, international collaboration (such as Joint EU HTA activities: JCA and JSC), and adaptation of value frameworks are essential to ensure equitable, efficient access to personalized treatments across Europe.

Abbreviations

AIFA – Italian Medicines Agency (Agenzia italiana del farmaco); AMNOG – Pharmaceutical Market Reorganisation Act (Arzneimittelmarkt-Neuordnungsgesetz; ATMP – advanced therapy medicinal product; EU4 – Europe (France, Germany, Italy, Spain); UK – United Kingdom; HTA – Health Technology Assessment; JCA – Joint Clinical Assessments; JSC – Joint Scientific Consultations; MCDA – Multi-criteria decision analysis; NICE – National Institute for Care and Excellence; NHS – National health system; HAS – Haute Autorité de Santé; RedETS – Spanish Network for Health Technology Assessment of the National Health System; IPTs – Institute for Prospective Technological Studies; NIHR – National Institute for Health Research; EMA – European Medicines Agency; PRIME – PRIority Medicines; G-BA – Federal Joint Committee (Gemeinsamer Bundesausschuss); IQWiG – Institute for Quality and Efficiency in Health Care

References

1. Love-Koh J, Peel A, Rejon-Parrilla JC, et al. The Future of Precision Medicine: Potential Impacts for Health Technology Assessment. Pharmacoeconomics. Dec 2018;36(12):1439-1451. doi:10.1007/s40273-018-0686-6; **2.** Radu P, Kumar G, Cubi-Molla P, et al. Navigating Change: How have HTA agencies evolved their methods over time? OHE. 2024;3. Khan SK, Gonzalez-Moral SG, Lanyi K, Ogunbayo D, Craig D. Closing the loop between horizon scanning and health technology assessment – an overview of topics submitted for appraisal in England. International Journal of Technology Assessment in Health Care. 2023;39(1):e64. e64. doi:10.1017/S0266462323000491; **4.** AIFA. Horizon scanning. https://www.aifa.gov.it/en/horizon-scanning; **5.** NICE. Managed access. 2025. https://www.nice.org.uk/what-nice-does/patient-access-schemes-and-pricing-agreements/managed-access; **6.** Ministerio de Sanidad. Plan estrategico RedETS. 2022. https://redets.sanidad.gob.es/Presentacion_PlanEstrategico/Archivos/PLAN_ESTRATEGICO_RedETS.pdf; **7.** NHS. Cancer Drugs Fund. https://www.england.nhs.uk/cancer/cdf/; **8.** Capuozzo M, Celotto V, Zovi A, Langella R, Ferrara F. Recovery of suspended reimbursements of high-cost drugs subjected to monitoring registries and negotiated agreements (MEAs): a tool for governance and clinical appropriateness in the Italian reality. The European Journal of Health Economics. 2024;25(1):1-5; **9.** El Real Decreto 5/2024 por el que se regula la ETS (2024); **10.** Mitchell C, Kumichel A, D'Ausilio A, Gibbs KL. HTA114 How Are Companion Diagnostics Evaluated and Reimbursed in Europe? Comparative Analysis of the EU-4 and UK. Value in Health. 2023;26(12):S340. doi:10.1016/j.jval.2023.09.1798; **11.** NHS. NHS Genomic Medicine Service. 2025. https://www.england.nhs.uk/genomics/nhs-genomic-med-service/; **12.** Aviesan. France Medicine Genomique. 2025. https://pfmg2025.fr/wp-content/uploads/2024/02/plan_france_medecine_genomique_2025.pdf; **13.** NICE real-world evidence framework (2022); **14.** AIFA. Monitoring registries. 2025. https://www.aifa.gov.it/en/registri-farmaci-sottoposti-a-monitoraggio; **15.** Ministerio de Sanidad. Programme for the use of real world data in health and technology assessment. 2025. https://www.iacs.es/wp-content/uploads/2025/03/00_IACS_RWD-HTA_E3_DEF_EN.pdf; **16.** Thokala P, Devlin N, Marsh K, et al. Multiple Criteria Decision Analysis for Health Care Decision Making—An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value in Health. 2016/01/01/ 2016;19(1):1-13. doi:https://doi.org/10.1016/j.jval.2015.12.003; **17.** NICE. Guide to the methods of technology appraisal: Appraisal of the evidence. https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making#appraisal-of-the-evidence; **18.** Angelis A, Linch M, Montibeller G, et al. Multiple criteria decision analysis for HTA across four EU member states: piloting the advance value framework. Social Science & Medicine. 2020;246:112595; **19.** Ghabri SJ, Jean-Michel; Le Maux, Benoit Could or should we use MCDA in the French HTA process? **20.** NICE. NICE Advice service. 2025. https://www.nice.org.uk/what-nice-does/life-sciences-how-to-get-your-product-to-market/nice-advice-service; **21.** AIFA guidance for applicants requesting national scientific advice (2012); **22.** HAS. Early dialogues. https://www.has-sante.fr/jcms/c_1625763/en/early-dialogues; **23.** Urbina I, Adams R, Fernandez J, Willemsen A, Hedberg N, Rüther A. Advancing cooperation in Health Technology Assessment in Europe: insights from the EUnetHTA 21 project-mindst the evolving legal landscape of European HTA. International Journal of Technology Assessment in Health Care. 2024;40(1):e75. e75. doi:10.1017/S0266462324004689; **24.** Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance) (2021);