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Commentary

An Economic Reference Case for Precision Medicine – Are We There Yet?

Comment on "Development of the PICCOTEAM Reference Case for Economic Evaluation of Precision Medicine"

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Abstract

Precision medicine interventions challenge the conduct of health economic evaluations. Precision medicine often targets small benefitting populations, which results in complex direct and indirect consequences for patients, health systems, and society. These complexities are not directly addressed by existing reference cases guiding the economic evaluation of health technologies. Chen and colleagues sought to address this gap. Through a multi-stage process involving expert consultation, literature review, and consensus seeking, they developed the PICCOTEAM (Population, Intervention, Comparator, Cost, Outcome, Time, Equity and ethics, Adaptability, and Modelling) reference case specifying 46 recommendations for conventional economic evaluations of precision medicine, and 30 additional recommendations for early-stage evaluations. This commentary discusses the contribution of the PICCOTEAM recommendations and identifies opportunities to strengthen future development of an economic reference case for precision medicine. Our recommendations include clarifying institutional purpose and values, broadening technological scope, and considering how the reference case could be applied across the technology life cycle to support iterative, evidence-informed healthcare decision-making.

Keywords: Precision Medicine, Genetic Test, Reference Case, Economic Evaluation, Cost Effectiveness

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Introduction

Precision medicine raises important considerations for the economic evaluation of health technologies. By using genomic and other molecular information to tailor healthcare to patient pathophysiology and familial risk, precision medicine divides health and disease into smaller, biologically defined populations. This results in interventions with complex and cascading testing and treatment pathways that are frequently evaluated outside randomized controlled trials.[1] Together, these conditions create substantial decision uncertainty for health technology assessment (HTA) bodies globally. The PICCOTEAM (Population, Intervention, Comparator, Cost, Outcome, Time, Equity and ethics, Adaptability, and Modelling) reference case developed by Chen and colleagues offers a useful contribution with guidance on economic evaluation during early technology development and for reimbursement decision-making.[2] Its recommendations would be strengthened by greater clarity regarding alignment with institutional purpose and values, the technological scope for evaluations, and relevance for life-cycle evaluation to support iterative healthcare decision-making.

What Is a Health Economic Reference Case?

Engaging with the PICCOTEAM reference case starts by clarifying what an economic evaluation reference case is intended to achieve. Normatively, a reference case specifies the set of methodological standards that addresses the objectives of the institution for which it is developed.[3,4] For health economic evaluation, the objective is often to allocate finite healthcare resources to maximize population health gains.[3,5] In the United States, the Second Panel on Cost-Effectiveness in Health and Medicine recommends two reference-case analyses: one conducted from the healthcare sector perspective and the other from the societal perspective.[4] The latter broadens the evaluation to include relevant consequences occurring beyond healthcare. In both the healthcare and societal perspectives, the set of prescribed methodology should translate the relevant institutional objective into analytical requirements, including specifying the decision problem, target population, comparators, analytic perspective, type of economic evaluation, health outcomes and their valuation, resource use and costs, time horizon, discounting, analytic modelling, equity effects, characterization of decision uncertainty, and presentation and interpretation of results.[3,4]

The stated purpose of the PICCOTEAM's reference case

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is to ensure transparency, consistency, bias minimization, and standardization. These are important qualities because they reduce avoidable analytic discretion and enhance interpretability, reproducibility, and comparability. They do not, on their own, establish the objective of the economic evaluation. That objective must be defined by the institution using the reference case. Nor can standardization determine whose outcomes should count, how equity should be valued, or when departures from aggregate health maximization are justified, such as through use of the societal rather than healthcare sector perspective or through distributional cost-effectiveness analysis. These normative choices, and the fairness, legitimacy, and accountability of the resulting decisions, extend beyond the economic reference case.[5]

The authors recognize that reference case recommendations must be adapted to local context. Although primarily recommending a societal perspective, they allow comparison across perspectives where the societal viewpoint is not locally prioritized. Relevant societal outcomes include labour-force participation and productivity, intergenerational effects, social value, and health and financial consequences for family members. Genomic information can also provide value, for example by identifying the cause of disease, informing prognosis and treatment, clarifying hereditary risk, ending prolonged diagnostic odysseys, identifying relatives who may benefit from surveillance or prevention, and generating knowledge for future patients.[6] Preference studies in precision medicine consistently find that patients and members of the public value genomic information even when it does not directly improve health status.[6,7] Capture of these valued non-health outcomes are congruent with the recommended societal perspective,[4] yet similar to published good practice guidelines,[8,9] the PICCOTEAM reference case misses an opportunity to provide guidance on how precision medicine health and non-health outcomes should be valued and aggregated in economic evaluation. A quality-adjusted life-year-based economic analysis can aggregate effects on health status, including those experienced by family members, but it does not usually incorporate the value of non-health outcomes such as value of disease diagnosis.

In precision medicine, the value of non-health outcomes, such as identifying cause of disease or ending a diagnostic odyssey, has long been examined through preference-based studies, predominantly through discrete choice experiments.[6] When the cost of a precision medicine intervention is considered, preference-based studies can generate estimates of willingness to pay for health and non-health outcomes, which can be incorporated into cost-benefit analysis.[10] For example, when the primary effectiveness measure of a precision medicine economic evaluation is an intermediate or non-health outcome, such as diagnostic yield, the estimated willingness to pay for an additional diagnosis can be used for calculating net monetary benefit.[11] The PICCOTEAM reference case should clarify whether health and non-health consequences should be valued through patients' willingness to pay or some other measure of preference-based utility. Different approaches reflect different objectives and may produce different conclusions. Consensus on a societal perspective economic reference case that includes both health and non-health outcomes and explicates methods for aggregation remains an active opportunity for research.

The explicit inclusion of equity in the PICCOTEAM reference case is an important contribution. Precision medicine may improve outcomes for narrowly defined populations while also widening inequalities through differences in representation in background variant libraries, access to testing, and opportunity to benefit from genomic information.[12,13] PICCOTEAM recommends applying principles of non-discrimination and equality of opportunity and, where relevant, incorporating health inequality through distributional cost-effectiveness analysis. This recommendation is welcome. Its application requires future guidance concerning which measures of equity matter, how relevant population groups should be defined, and whether or how distributional consequences should be weighted to reflect societal preferences for equity. The PICCOTEAM reference case would be strengthened by including specific recommendations for developing guidance on equity measures. In precision medicine, the data required to conduct equity analyses are not well described or routinely collected. This limits the feasibility of conducting equity-focused analyses and risks further masking existing inequalities.

The Scope of Precision Medicine

The PICCOTEAM reference case is primarily developed for genetic screening, diagnosis, and pharmacogenomic testing. These are important applications, but they do not encompass the full range of precision medicine, such as the evaluation of new targeted treatments, disease-agnostic treatment or testing strategies, or competing testing platforms. PICCOTEAM recommendations can apply to treatment selection, but comprehensive molecular profiling raises distinct issues. For example, a single platform may identify multiple actionable alterations, direct patients toward several competing treatments, and be reinterpreted as biomarkers and treatment evidence evolve. This means the value of the test itself cannot readily be separated from the availability, effectiveness, sequencing, and cost of the downstream treatments identified. While the PICCOTEAM reference case can allow for this complexity, specific recommendations on handling interconnected care pathways in an economic evaluation are warranted.

Economic evaluation may also need to account for heterogeneity of costs and outcomes across disease areas, repeat testing, access to clinical trials, and the health system capacity required to interpret and act on results. While one testing platform may be cost-effective in a single indication, an alternative platform may be less cost-effective in that indication yet be more favourable across disease areas. This is a different decision problem from evaluating a discrete screening, diagnostic, or pharmacogenomic test in a single indication. The PICCOTEAM reference case contains recommendations relevant to platform evaluations within the cost domain, but further guidance on how the reference

case applies across the broader range of competing precision medicine technologies that can be used across diseases is needed.

Connecting Economic Evaluation Across the Technology Life Cycle

O'Rourke and colleagues redefine HTA as a multidisciplinary process using explicit methods to determine the value of a health technology at different points in its lifecycle, with the purpose of informing decisions that promote an equitable, efficient, and high-quality health system.[14] HTA is relevant before market entry, during regulatory review and market authorization, at reimbursement, following adoption, and through to disinvestment. Life-cycle evaluation is integral to the contemporary definition of HTA and has direct relevance to economic evaluation.

PICCOTEAM importantly recognizes that the reference case needs to move toward life-cycle economic evaluation. The authors emphasize the necessity of iterative modelling for addressing evolving clinical pathways and changing populations, highlighting that ongoing interactions between researchers, innovators, clinicians, patients, and decision-makers are central to iterative evaluations. They make specific recommendations for economic evaluations conducted at an early stage and at time of market access, but do not explicitly consider post-market economic evaluations that can inform disinvestment.

Iterative evaluation is particularly relevant to precision medicine. Eligible populations may be redefined as new biomarkers are discovered, testing and treatment pathways may change, indications may expand, sequencing prices can fall, variant interpretation may be updated, and comparative evidence may emerge only after implementation. Germline testing may also generate information with lifetime and intergenerational consequences, meaning that relevant time horizons, comparators, and downstream pathways can evolve long after the initial evaluation is complete. There remains an opportunity to connect these elements within a life-cycle economic evaluation reference case. Conducting early and conventional economic evaluations at different points in development does not, by itself, constitute life-cycle HTA. Early HTA can inform decisions about subsequent development, research, and/or investment.[15] Evaluation at reimbursement should build on early economic evaluations, incorporating the evidence generated during development while identifying uncertainties that warrant post-adoption evidence generation. Reassessment should use the resulting evidence to determine whether coverage should be continued, expanded, restricted, repriced, or withdrawn. We recommend that the PICCOTEAM reference case be extended to post-market evaluations to support life-cycle HTA and management.

A life-cycle economic evaluation reference case for precision medicine can specify how evolving evidence can support appraisal, reappraisal, and disinvestment within a learning healthcare system.[16] In learning healthcare systems, real-time evidence is routinely generated and interpreted to support serial decision-making. PICCOTEAM recognizes key time points in technology development, but the reference case can further discuss how uncertainty identified during early evaluation can shape subsequent evidence generation, how evidence generated during development should inform reimbursement, and how residual uncertainty at reimbursement should be linked to post-adoption evidence collection and reassessment.

The PICCOTEAM reference case emphasizes deterministic and probabilistic analyses to characterize uncertainty at a particular decision point. A life-cycle reference case would in turn ask how unresolved uncertainty should shape the current decision, subsequent evidence generation, and reassessment criteria.[16] Formal methods like value of information analysis may help prioritize whether further research should resolve decision uncertainty and should be recommended in both early and conventional reference cases. The central requirement is that decision-relevant uncertainty determines the trajectory of what evidence is generated and collected, when it is reviewed, and how the decision may change.

Jurisdictional Adaptation and Transferability Require Institutional Grounding

PICCOTEAM's emphasis on jurisdictional adaptation is well placed, particularly for health systems with limited capacity to commission bespoke economic evaluations. The reference case also advances the worthwhile goal of facilitating the transferability of economic evidence across jurisdictions and reducing duplication, particularly in low- and middle-income countries. A common framework can improve reporting, align analytic approaches, and allow jurisdictions to reuse relevant evidence and model components. It can facilitate transferability, which is a qualitative judgment of whether evidence can be used for deliberation. Such judgments need clear alignment with institutional purpose and values, and a first step would be to understand whether and how jurisdictions currently make adaptations so that future recommendations can build on feasibility demonstrated in practice. Quantitatively establishing whether evidence can be used in different settings, ie, transportability, requires careful assessment.

Transferability is assessed in relation to the local decision problem. Economic evaluations commonly combine clinical and economic inputs from several jurisdictions,[17] yet healthcare systems differ in their prices, service bundles, diagnostic practices, and definitions of outcomes, such as what constitutes a genetic diagnosis. These differences affect model structure, comparators, resource use, costs, and ultimately cost-effectiveness. Precision medicine is subject to further variation in variant prevalence and penetrance, genetic ancestry, test performance, clinical pathways, and access to downstream interventions. There is a persistent need to determine which inputs are transportable, which require local estimation or recalibration, and whether the model structure adequately represents local practice.

Conclusion

Economic evaluations of precision medicine face unique complexities. Testing and treatment pathways involve cascading uncertainties that produce direct and indirect consequences for patients, health systems and society. The PICCOTEAM reference case represents a step towards addressing these challenges. For conventional and early-stage economic evaluations of genetic screening, diagnosis, and pharmacogenomics, PICCOTEAM specifies a set of recommendations that highlight the necessity of expert engagement, iterative evaluation, decision-relevant outcomes measurement, uncertainty analysis, and equity assessment. While these recommendations contribute to more consistent economic evidence, opportunities remain for achieving a broad fit-for-purpose economic reference case for precision medicine. These include clarifying the institutional purpose it is intended to serve, ensuring that recommended study perspectives and outcomes align with institutional objectives, broadening the technological scope, and considering life-cycle applicability for precision medicine appraisal, reappraisal, and disinvestment.

Disclosure of artificial intelligence (AI) use

Not applicable.

Ethical issues

Not applicable.

Conflicts of interest

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Authors' contributions

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