Advancing the development and use of diagnostic target product profiles for cancer

June 2024

CANCER RESEARCH UK

Together we are beating cancer

Contents

About this report

This report, and the research conducted to inform it, has been undertaken by researchers at RAND Europe and the Office of Health Economics.

RAND Europe is a not-for-profit policy researchorganisation that helps to improve policy and decision making through research and analysis.

The Office of Health Economics supports better health care policies by providing insightful economic and statistical analyses of critical issues.

About Cancer Research UK

We're the world's leading cancer charity, dedicated to saving and improving lives through research. We fund research into the prevention, detection and treatment of more than 200 types of cancer through over 4,000 scientists', doctors' and nurses' work. In the last 50 years, we've helped double cancer survival in the UK, and our research has contributed to around half of the world's essential cancer drugs. Our vision is a world where everybody lives longer and better lives, free from the fear of cancer.

Our values

Our values help guide our behaviour and culture in an ever-changing world, building on the best of what we do today and what we aspire to be in the future. They unite and inspire us to achieve our ambitious plans and mission of beating cancer together.

Our values are:

Bold
Act with ambition, courage and determination

Human
Act to have a positive impact on people

Credible
Act with rigour and professionalism

Together
Act inclusively and collaboratively

Reference

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List of acronyms

ABHI	Association of British Healthtech Industries
AG:	Advisory Group
AHSN	Academic Health Science Network
AI	Artificial Intelligence
ARF	Academics (including clinical academics)) and Research Funders
BIVDA	British In Vitro Diagnostics Association
CDSA	Clinical Decision Support Algorithm
CLSI	The Clinical and Laboratory Standards Institute
CRUK	Cancer Research UK
DHSC	Department of Health and Social Care
EEE	Early Economic Evaluation
EEM	Early Economic Modelling
EVPI	Expected Value of Perfect Information
FIT	Faecal Immunochemical Test
GP	General Practitioner
HP	Healthcare Professionals and Pathlab Managers
HPV	Human Papillomavirus Infection
HRA	Health Research Authority
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IND	Industry
IVD	In Vitro Diagnostics
MHRA	Medical and Healthcare Products Regulatory Agency
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OHE	Office of Health Economics
PAG	Public Advisory Group
PATH	Program for Appropriate Technology in Health
PCPC	Patient, Carer and Public Voice and Charities Perspectives
PPI	Patient and Public Involvement
PPIE	Patient Public Involvement and Engagement
PRHE	Policy, Regulators, Health Research Authority, and Health Economists
PSA	Prostate Serum Antigen
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
R&D	Research and Development
REC	Research Ethics Committee
SBRI	Small Business Research Initiative
SME	Small or Medium-Sized Enterprise
ToR	Terms of Reference
TPP	Target Product Profile
UK	United Kingdom
UKAS	The UK Accreditation Service
UNICEF	United Nations Children's Fund
VOI	Value of Information
WHO	World Health Organisation
WTP	Willingness to Pay

Foreword

Improving cancer outcomes is a priority for health system decision-makers. Earlier and timelier cancer detection and diagnosis are central to improving long-term patient prognosis and outcomes. The ability to achieve timely and accurate diagnosis depends, in part, on the development, adoption and implementation of innovative diagnostic tests.

Providing innovators with a clear steer on the requirements for novel diagnostic tests for cancer can aid and expedite their development and adoption. Diagnostic Target Product Profiles (TPPs) are product specification documents that can serve as tools to help provide such clarity. They enable those who might use and pay for diagnostic tests to provide innovators with a clear demand signal about the types of tests needed, helping innovators respond appropriately to areas of unmet need. To the best of our knowledge, TPPs in the diagnosis space primarily focus on infectious diseases, rarely cancer. Therefore, Cancer Research UK commissioned this research following recommendations outlined in the Early Detection and Diagnosis (EDD) Roadmap[i] that highlighted TPPs as a critical action needed for overcoming hurdles and accelerating cancer EDD progress.

The project sought to produce a general (tumour-site agnostic) guide for developing cancer TPPs that can serve as a tool and resource for future efforts to develop bespoke TPPs for specific cancers, test types and use cases.

This report's findings will help decision-makers develop diagnostic TPPs for cancer in carefully considered, efficient and effective ways. The insights gained highlight the complexity of TPP development, the multifaceted considerations regarding features to include in a TPP, and the possible approaches and methods. We hope this research's practical and actionable focus will help those developing bespoke diagnostic TPPs for specific cancer use cases navigate this complexity.

TPPs are an essential tool that can help signal the types of cancer tests a health system may need. However, TPPs alone cannot solve broader challenges in incentivising innovation and its adoption in the NHS. The overarching aim of any TPP development effort is to engender innovative diagnostic tests that reach the health service and benefit patients. However, a TPP alone cannot align innovative diagnostic development and supply with demand and willingness to pay, and efforts to develop it must avoid the pitfalls of being everything to everyone. Therefore, those developing diagnostic TPPs for cancer must carefully consider how to maximise a TPP's traction and impact as part of a broader collaborative and connected community of practice.

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i Cancer Research UK. 2023. *Early Detection and Diagnosis of Cancer Roadmap*. As of 22 March 2024: https://www.cancerresearchuk.org/funding-for-researchers/research-opportunities-in-early-detection-and-diagnosis/early-detection-and-diagnosis-roadmap

Executive summary

The context

Tackling cancer is a priority for health system decisionmakers. Early and improved cancer detection and diagnosis are central to improving long-term patient prognosis and outcomes. Achieving timely and accurate diagnosis depends, in part, on developing and adopting innovative diagnostic tests.

Innovators need a clear steer on the diverse requirements for novel diagnostic tests for cancer. Diagnostic Target Product Profiles (TPPs) help provide such clarity. Those who might use and pay for diagnostic tests must give innovators a clear demand signal on test types needed so they can respond to areas of unmet need. Diagnostic TPPs are product-specification documents that can serve as a tool to achieve this. There is growing interest in their use to support the development of novel diagnostic tests for cancer. To the best of our awareness, TPPs in the diagnosis space have been developed in other areas (most notably infectious diseases) but not in cancer.

Research aims and approach

Cancer Research UK commissioned RAND Europe and the Office of Health Economics (OHE) to research and establish a guide for developing diagnostic TPPs for cancer. The research aimed to advance practical knowledge on approaches to developing diagnostic TPPs for cancer, focusing particularly on the UK context. Cancer Research UK commissioned the research in light of the growing interest in supporting innovation to improve cancer diagnosis.

The project sought to produce a 'general' (tumour-site agnostic or for cancer generally regardless of where it started in the body) guide for developing cancer TPPs that can serve as a tool and resource for future efforts to design bespoke TPPs for specific cancers, test types and use cases. We used a mixed-methods approach combining scoping desk research and interviews, workshops with diverse stakeholder communities and an early economic modelling tool to inform the requirements of a TPP for cancer and develop the guide.

Key findings: the guide for developing diagnostic TPPs for cancer

The guide covers the following aspects relevant to developing diagnostic TPPs for cancer: (a) the *features that need to be considered, (b) the stakeholders to involve, (c) considerations for TPP prioritisation, and (d) the process in terms of approaches and methods.*

What features need consideration in diagnostic TPPs for cancer?

Identifying the core features and feature combinations driving the central value proposition (i.e. improvement offer) for a novel test and associated specifications for them is key to TPP development. The specifications can include minimal, preferred or optimal requirements (where possible), undesirable characteristics, and an accompanying rationale for the chosen specifications. Identifying and integrating the key features within diagnostic product development can help increase (though not guarantee) the chances of developed tests' successful adoption and innovators considering more than just technical performance criteria. TPPs must provide specifications for a diverse range of features because the latter should reflect the appropriateness of any test developed for eventual real-life use.

Thus, we have outlined features covered as part of TPP development to increase understanding of features and key considerations relating to them.

Drawing on a systematic review by Cocco et al. (2020),[1] and refining it through our research, we found that the types of features that TPPs can provide specifications for broadly fall into nine core categories, each of which can include multiple features:

Unmet need: The unmet need a diagnostic test should respond to and its application scope (e.g. its intended use, the medical decision(s) supported, use setting, target user and target population). It is also important to clarify how it should interact with other tests and care decisions a patient may encounter.

Analytical performance: Requirements relating to the test's accuracy. It is important to consider how the context of real-world use might differ from that of experimental laboratory settings.

Clinical validity: Requirements reflecting how far a test will measure an appropriate disease marker in a specific population;

Clinical utility: Requirements related to the test's influence on downstream care outcomes, such as patient survival and quality of life. Proxy diagnostic measures may be required because it can be challenging to link a diagnostic test with patient outcomes.

Human factors: Requirements relating to individuals' interaction with the test. Examples for healthcare professionals include specifications for training needs, test preparation and administration, and interpreting results to ensure effective use. It is also important to specify requirements related to patients as end users, e.g. patient acceptability, accessibility and experience, and how the test may affect inequalities.

Infrastructure: Requirements related to facilities, equipment, supplies, IT systems or other operating conditions that need to be established and maintained.

Cost and economic considerations: Requirements related to economic and commercial matters (e.g. the test's price and commercial routes to market). It is vital to consider cost-effectiveness, for which early economic modelling can help.

Regulation: Features related to regulatory (i.e. safety and efficacy) requirements.

Environmental impact: Requirements about the test's environmental impact.

TPPs are typically formatted as tables detailing the desired specifications for each relevant feature. Additional contextual information helps ensure the TPPs are clear and transparent. At a minimum, this should cover the TPP's purpose and target audience, a glossary of terms to ensure accessibility, a list of those who helped develop the TPP and adequate justification for its final specifications.

Who needs to be involved in developing diagnostic TPPs for cancer?

Given the issues needing consideration when developing a TPP, multiple stakeholder groups play important roles. Such stakeholders include **academic, clinical-academic and research communities; healthcare professionals and diagnostic laboratory experts; industry; patient, carer and public representatives; research and innovation funders in the public sector and charities; and regulators, Health Technology Assessment (HTA) and policymaker perspectives** (in consideration of procurement realities). We cover how the TPP development process can involve stakeholders throughout and key considerations concerning particular groups. In part, relevant stakeholders will be represented via engagement in **a core working group** leading the TPP development effort. However, the process also needs a consultation with a broader range of individuals across stakeholder groups.

What should be considered when prioritising which TPP to pursue?

TPPs can be helpful in multiple contexts, but health system decision-makers must prioritise which use cases to develop a TPP for in the future. Thus, prioritisation is a critical aspect of TPP development. We aim to support this process by outlining some of the considerations that can impact prioritisation and mechanisms for achieving this. Based on stakeholder consultation, relevant considerations include (a) ***epidemiology*** (e.g. cancer incidence and prevalence, including considerations around rarity or significant incidence differentials between groups), (b) ***early diagnosis challenges*** (especially when linked with poor survival), (c) ***existing test performance*** (e.g. inadequate test performance on technical, accessibility or acceptability fronts), (d) ***health services organisation and capacity*** (e.g. where existing tests are a poor fit with workforce capacity or skills, health systems infrastructure, or provide poor economic value) and (e) ***prevention-potential*** (e.g. where testing for risk factors for cancer, such as human papillomavirus, can help with cancer prevention aims).

How to develop a diagnostic TPP for cancer: Approach and guiding principles

Developing a TPP is a complex endeavour for which no established protocol yet exists. However, **developing a TPP typically involves two key stages**: (a) ***the inception stage***, which establishes a core working group, governance and coordination arrangements and an action plan, and (b) ***implementing TPP development***. Using our research to build on a conceptualisation from the recent systematic review by Cocco et al. (2020),[1] the TPP implementation stage of TPP development comprises three phases:

- **Scoping the unmet need and key requirements for the novel test.**
- **Drafting the TPP** to provide information on relevant features for a novel test and, where applicable, specifications for them.
- **Consensus building**, exploring and seeking consensus on a final TPP draft.

However, these phases are not linear. For example, drafting and consensus-building often happen iteratively. TPP development can employ diverse methods, and it is essential to consider each type's rigour and feasibility. Relevant methods include:

- **Desk research**, e.g. systematic reviews or rapid literature assessments, diagnostic test and patent database analysis, and policy and clinical guideline analysis to understand unmet needs and key test requirements.
- **Stakeholder consultation**, e.g. workshops, interviews with experts, core working group meetings, TPP draft reviews and Delphi (a method for consensus surveys and workshops).
- **Modelling**, e.g. early economic modelling to help model the care pathway, explore a test's health economic value with a specified set of features, and test the features with the most influence on the value proposition.

The methodologies and rigour applied to TPP development can vary, and 'rate-limiting' factors **influence the most appropriate methods and approaches**. Examples include the new test's urgency (based on need), policy impetus, financial resources, stakeholder engagement within the specified timeframe, and the strength of the pre-existing evidence on feature specifications. Decisions must ultimately balance optimal methods with real-world pragmatism while ensuring sufficient rigour. **We identified four overarching principles that can help support 'fit for purpose' approaches. These apply to all TPP development phases and should be used to guide the process**. These are:

1. **Inclusiveness** – engaging the right stakeholders in feasible and accessible ways.
2. **Clarity on a novel test's value proposition** – including specifying which features matter most (and must be specified in the TPP) and which can be omitted at the innovator's discretion.
3. **Balancing methodological rigour with pragmatic considerations** while ensuring objectivity.
4. **Considering a TPP's local relevance alongside the global nature of incentives for innovation** – this has implications for TPP developers considering the relevance of a TPP's specifications beyond a UK-only market.

The guide for developing diagnostic TPPs resulting from this research will help decision-makers to develop diagnostic TPPs for cancer in carefully considered, efficient and effective ways. The insights gained have highlighted TPP development's complexity, showing the multifaceted considerations necessary for deciding which features to include and the optimal methods and approaches to utilise. We hope that this research's practical and actionable focus will help those who might develop bespoke diagnostic TPPs for cancers navigate this complexity.

Future TPP development efforts will also likely help refine our insights.

Our work also identified important avenues for a future research agenda. Such avenues include approaches to prioritising which TPPs to develop, clarifying the terminology used to describe desired diagnostic test features, improving understanding of features relevant to diverse diagnostic technologies, and optimising the governance and management of TPP development.

TPPs are an important tool that can help identify the types of cancer tests a health system needs. However, TPPs alone cannot solve wider challenges in incentivising innovation and its adoption in the NHS. Any TPP development effort's overarching aim is to yield innovative diagnostic tests that reach the health service and benefit patients. However, a TPP cannot align innovative diagnostics' development and supply with demand and willingness to pay and cannot please everyone. Therefore, those developing diagnostic TPPs for cancer must carefully consider how to maximise a TPP's traction and impact as part of a broader collaborative community of practice.

This study is unique in exploring diagnostic TPPs in the cancer field, where they have not yet (to the best of our knowledge) been used to signal the demand for innovation and thus present a novel approach to aligning supply and demand. It is a robust and timely analysis combining diverse research methods and harnessing many peoples' expertise across diverse stakeholder communities. The results are relevant to a wide range of individuals, groups and organisations interested in improving cancer diagnosis and patient outcomes.

Organisation of the report

This document's contents are organised as follows:

Section 1 **('Introduction'**, pg. 13–15) outlines the study's background and broader context. It introduces the need for earlier cancer detection and diagnosis, the importance of developing innovative diagnostic tests, and the need to clarify to innovators the requirements novel tests must meet. Section 1 also explains what demand-signalling diagnostic Target Product Profiles (TPPs) are, why they matter and how they can help inform novel diagnostic tests' development to increase their likelihood of effectively responding to unmet needs and demands.

Section 2 **('Research aims and objectives'**, pg. 16–17) describes the aim of the research and who it is most relevant to. It also explains the purpose and scope of the completed guide to TPP development.

Section 3 **('Methods'**, pg. 18–22) summarises the methods that informed the project, chosen based on desk research and stakeholder consultation. It introduces six associated work packages (described in sections 3.2–3.7).

Section 4 **('Results',** pg. 23–56) presents the research findings and is divided into nine subsections:

1. **Insights on feature-related considerations likely to be important** in developing diagnostic TPPs for cancer (subsection 4.1).
2. **Insights on stakeholder considerations**, i.e. who should be involved in developing diagnostic TPPs for cancer and why (subsection 4.2).
3. **Prioritisation considerations** that could help inform future decisions about which TPPs to develop given multiple needs across use cases, cancer sites, use settings and test types (subsection 4.3).
4. **Results regarding establishing an early economic modelling tool** to inform TPP feature specifications (subsection 4.4).
5. **A guide for TPP development processes** (sections 4.5–4.9). This subsection briefly overviews the development process and its key guiding principles (Subsection 4.5) before focusing on the key stages for TPP development: inception (subsection 4.6), scoping (subsection 4.7), drafting (Subsection 4.8) and consensus-building (subsection 4.9).

Section 5 **('In reflection and towards a future research agenda',** pg. 57–62) considers the broader implications of this work's findings, including how efforts to develop TPPs must consider the broader cancer-innovation and policy landscape, alongside presenting concluding thoughts and identifying avenues for future studies to consider.

Throughout the report, we provide practical tips that complement the core findings to help those developing a diagnostic TPP for cancer in the future (see Boxes 1–18).

A series of annexes accompany this core report, detailing the methods and findings from each of the project's core work packages:

- **Annexes A and B** detail insights from the early scoping activities (Work Package 1). Annex A describes the scoping research for an initial understanding of diagnostic TPP development processes and features and their enablers and barriers. Annex B expands on the features used in TPP development to date and assesses areas of commonality.
- **Annex C** presents a detailed cross-analysis of insights from six stakeholder workshops (Work Package 2), including points raised about the relevance of developing TPPs and the nature of TPP development processes. It also covers feature-related considerations workshop participants flagged as important in TPP development based on their experiences and factors to consider when deciding which use cases to develop TPPs for.
- **Annex D** presents a cross-analysis of the 13 interviews conducted with general practitioners and pathology laboratory experts (Work Package 3). The interviews explored their perspectives on cancer-diagnosis areas needing innovation and improvement, features to consider specifying in a TPP, cancer-specific

diagnostic TPP development processes and prioritisation considerations.

- **Annex E** presents our economic modelling tool (Work Package 4), specifying questions for a proposed diagnostic test's profile that TPP developers may want to consider regarding the key features expected to impact its potential cost-effectiveness. Annex E shows how the tool can be used to perform a simplified early economic evaluation to identify the TPP requirements expected to have the most significant impact on cost-effectiveness and indicate the test's potential cost-effectiveness (assuming 'perfect implementation').
- **Annex F** summarises insights from an expert workshop testing a draft TPP guide (Work Package 5), summarising the feedback on the TPP development process, features, prioritisation and economic modelling tool, focusing on the clarity of the content.
- **Annex G** provides further information about features included in demand signalling diagnostic TPPs to date. It builds on cross-project findings (Work Packages 1–5) to begin identifying insights relevant beyond the in-vitro diagnostic space, where the existing TPP landscape is primarily focused.
- **Annex H** provides more detailed information on different stakeholders' roles and what types of expertise are relevant in developing a TPP.

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1. Introduction

1.1. The context

1.1.1. Early and improved detection and diagnosis are critical to tackling cancer in the UK and globally

Cancer is a major global health burden. In 2020, 19.3 million new cancer cases were detected worldwide[2] and the disease was responsible for almost 10 million deaths, making it the leading cause of death globally.[3] In the UK, approximately 400,000 newly diagnosed cancers and 160,000 cancer-related deaths were recorded in 2019, and about half of people born in the UK since 1960 will be diagnosed with cancer in their lifetime.[4] In England, just over half of cancers are detected early, and this percentage varies across different cancers.[5] Given its disease burden, tackling cancer is a priority for health system decision-makers.[6-14]

Early detection and diagnosis (EDD) are central to most policy-related efforts to improve cancer outcomes, given that early diagnosis is associated with more timely access to treatments and better survival outcomes. For example, the WHO passed a resolution on global cancer control in 2017 urging governments to draft national strategies that emphasised improving early detection and diagnosis.[6] EDD is also prominent in England's 2019 NHS Long Term Plan,[7,8] which flags improved cancer survival as a key priority and aims to increase the proportion of cancers diagnosed early from approximately 50% to 75% by 2028.[9] Each of the UK's devolved nations also consider EDD as a policy priority.[10] Scotland's 2023–2033 Cancer Strategy aspires to improve areas such as early intervention,[11] and the Scottish Government's Detect Cancer Early Programme aims to invest almost £6m in cancer diagnostics.[12] Similarly, the Welsh Government and the Wales Cancer Network published a 2023–2026 Cancer Improvement Plan for NHS Wales, which sets out the issues, actions and timeframes for improving Welsh cancer services over the next three years, including focusing on EDD.[13] The 2022–2032 Northern Ireland Department of Health's Cancer Strategy also focuses on early detection.[14]

1.1.2. Innovators need to better understand the diverse requirements new and improved tests must meet

Developing and adopting innovative diagnostic tests can help improve EDD, but new tests must respond to areas of unmet need. There is growing recognition that innovators need clear information from potential users and consumers of diagnostic tests on the tests needed so that product developers can direct efforts accordingly. This imperative is reflected in national policy programmes and funding calls, highlighting the importance of giving clear demand signals. Examples include the NHS England Cancer Programme's work,[15] the Small Business Research Initiative's (SBRI's) funding calls[16] and the efforts of leading charities such as CRUK.

In 2020, CRUK developed a roadmap for cancer early detection and diagnosis (EDD)[5] that considers key themes and tools to support efforts towards early detection and diagnosis and establish them as routine practice. CRUK's roadmap identifies diagnostic Target Product Profiles (TPPs) as an important tool in this respect.[5] TPPs are documents intended to clearly and precisely specify and communicate the requirements new tests must meet to the innovators developing them. CRUK's roadmap sees TPPs as one way of supporting wider efforts towards clearer demand signalling and better alignment between new tests and unmet needs. Our project is a direct response to CRUK's EDD roadmap. It follows CRUK's broader focus on addressing the gaps in developing, translating and adopting innovations to improve cancer outcomes.

1.2. Diagnostic Target Product Profiles can guide innovation

TPPs are product specification documents intended to support the development and assessment of new medical technologies, focused on demonstrating how far a new product addresses specific unmet health needs within a target population.[1,17] There is growing interest in TPPs as demand-signalling specification documents to inform innovation needs and help guide innovators' research and development (R&D), an aim nested in broader ambitions to improve patient care. As specification documents, TPPs might also increase the chances of successful uptake of new products and technologies by ensuring innovators consider more than just technical performance criteria in their product

development, i.e. where, how and by whom the test will be used. The TPP facilitates a better understanding of how scientific performance characteristics (e.g. diagnostic sensitivity and specificity) must fit patient care pathways and align with the priorities of healthcare providers, regulatory organisations, Health Technology Assessments (HTAs), consumers and patients.[1]

Diagnostic TPPs can include information about the medical technology/product itself and its real-world use context.[1] As planning tools, diagnostic TPPs help innovators structure their R&D thinking and approach from the outset by providing upfront clarity on key specifications and unmet needs, thus identifying the types of diagnostic tests for which there is demand.[1] Thus, TPPs can help clarify the innovation's aim, connecting it to a real-world clinical or public health need and helping map the necessary steps in its development. While innovators already engage with customers to inform their product development, such conversations may not yield a clear understanding of the diverse requirements an innovation must address to maximise its chances of success. There are several possible reasons for this.[18] One is that innovators may not engage a sufficiently diverse sample of relevant stakeholders in conversations about unmet needs and required features to support the product's successful development and adoption.

Developers of diagnostic tests must also consider a health system's scientific, technological, economic, workforce, patient, infrastructure, regulatory, HTA and procurement realities and constraints. While developing a TPP may help identify cost types and economic considerations (alongside other context-related requirements) that can impact the chances of successful procurement, a TPP alone cannot guarantee procurement. Risks around shifting and evolving priorities for innovation can also affect a developed test's relevance.

Nonetheless, TPPs may provide greater clarity on the types of tests needed if teamed with broader efforts to increase a new test's chances of successful adoption in the NHS. This highlights the importance of considering how TPP development efforts can interface with broader health system initiatives to identify unmet needs, demand areas and willingness to pay, including their possible interface with funding initiatives supporting innovation in cancer and policy priorities. In this context, TPP development can also facilitate stakeholder communication and engagement, providing a framework for stakeholders to collaboratively optimise how far TPP-specified requirements can align with real-world adoption and procurement contexts for diagnostic tests for cancer and different stakeholders' priorities and needs.

While TPPs for diagnostics exist for some areas (most notably infectious diseases),[1,19-26] none have been developed for cancer (although there are some ongoing nascent efforts). Based on infectious disease methods, TPPs generally take the form of a report comprising long tables of desired features, specifications related to minimum (and sometimes optimum/preferred) feature requirements and decision justifications, sometimes with additional information on how the TPP was developed, who it involved and the methods used (see Annex A).[1]

The features for which TPPs provide specifications broadly fall into nine core categories, as summarised in Table 1 (see Section 4). Annex G provides comprehensive details on these categories' features.

2. Research aims and objectives

2.1. What the work set out to do

This project's overarching goal was to advance practical knowledge on possible approaches to developing diagnostic TPPs for cancer.

The project aimed to produce a 'general' (tumour-site agnostic or for cancer generally regardless of where it started in the body) guide for developing cancer TPPs as a tool and resource for developing future bespoke TPPs for specific cancers or test types, not to create a TPP for a specific cancer type or use case. The project's key objectives were to:

1. Identify the types of stakeholders to engage in developing a diagnostic TPP for cancer and critical considerations related to governing and overseeing TPP development.
2. Identify the most important feature types or categories to consider in TPP development.
3. Describe possible approaches and methods for developing a diagnostic TPP for cancer (and the associated trade-offs of using specific methods over others).
4. Create an economic modelling tool to help TPP developers consider test features that have clear economic implications and indicate their impact on cost-effectiveness. The tool may also prove useful given potential considerations relevant to the National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) decision-making, considering the evidence types, sources and levels that may help inform HTA-related features.

Some TPP requirements will likely be common across all cancer types, while others will be unique for TPPs developed for specific tumour sites, clinical use cases and test types. We intend the guide we develop from our research to be an overarching evidence-based tool that can assist with and adapt to future site-specific TPP development efforts.

The project was commissioned with a focus on the United Kingdom, acknowledging that some determinants of TPPs' capacity to incentivise industry will have global dimensions (see Section 4.5, 'Principles', for further discussion on this) and different jurisdictions will have specific characteristics.

2.2. Who this document is for

This document's primary audience comprises organisations and decision-makers in the UK's health and innovation system who might be involved in efforts to develop a diagnostic TPP for cancer. The impetus to develop a TPP and the institutions that might initiate and/or drive it could be diverse, including cancer research charities, innovation funding bodies, policy-level bodies or professional associations (Section 4.6.2).

The audience for any diagnostic TPP developed in the future based on the information shared in this document comprises those developing novel products and technologies (i.e. innovators in industry and academia, clinical entrepreneurs, and collaborative innovation efforts). However, stakeholders involved in TPP development (and thus likely to be interested in the information this document shares) encompass a much broader range of organisations and groups with key roles in sharing information on the requirements a novel test needs to meet. Section 4.2.1 elaborates on this further. An inclusive view of who can play a role in TPP development and who may have a stake in any outputs is important if a TPP is to be a tractable demand-signalling tool supporting the life course of innovation development, assessment, approval, procurement and use.

3. Methods

3.1. Overview of approach

We adopted a mixed-methods approach, beginning with preliminary scoping desk research and interviews to understand TPPs and gather insights on their development process from existing work on the topic (Work Package 1). This process identified issues for further exploration via stakeholder engagement, conducted via workshops (Work Package 2) and interviews (Work Package 3) with diverse stakeholder communities to examine various perspectives on how to approach TPP development and the types of feature-related considerations that matter for developing a TPP for cancer. To complement the stakeholder engagement, we developed an early economic modelling tool (Work Package 4) to inform decisions about key feature specifications influencing the cost-effectiveness of any diagnostic test developed in response to a TPP. We conducted the project between March 2023 and January 2024.

Based on the insights gathered from each work package, we developed and tested a draft TPP guide (Work Package 5) to support stakeholders in developing TPPs for specific cancer sites, test types, use cases and use settings in the future. Figure 1 (below) overviews the aims and approaches used, and Sections 3.1–3.6 detail each core work package's approach.

We analysed the insights from individual data-collection work packages (Work Packages 1–5) thematically (see Annexes A–D and F for further detail). We cross-analysed and synthesised findings by triangulating insights across data sources and methods to arrive at our final output (Work Package 6).

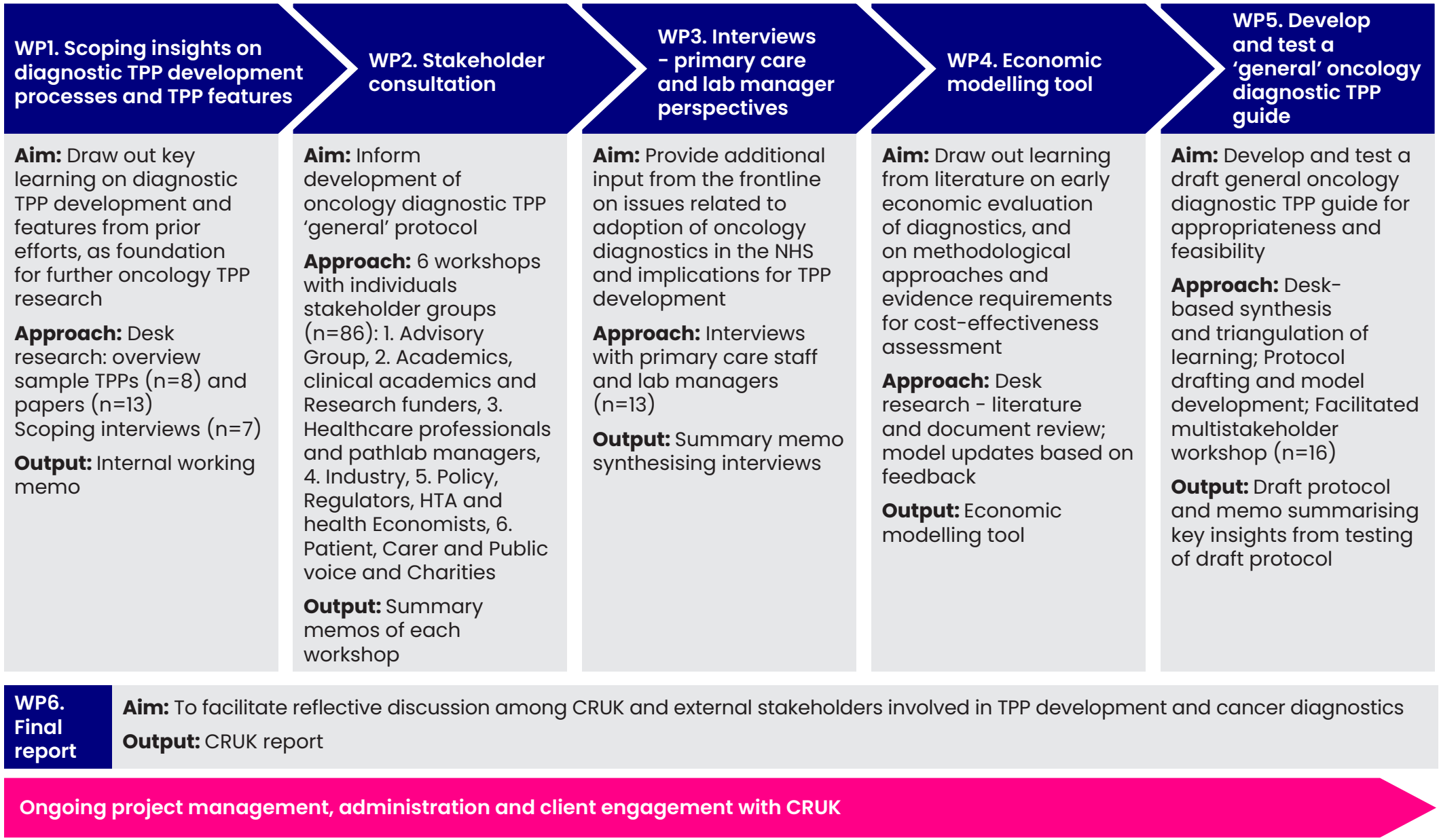
Over 100 individuals (n=129)[ii] contributed knowledge, lived experiences and expertise to this process from diverse stakeholder communities, including academia and research, research funders, healthcare professionals, industry, policymakers, regulators, HTA experts, health economics, and patient, carer and public voice perspectives. We engaged with these diverse stakeholders to obtain a rounded picture of the key issues needing consideration when developing diagnostic TPPs for cancer regarding the pertinent issues when identifying the features to specify and the TPP development process itself, i.e. which approaches and methods to use.

3.2. Work Package 1: Exploring the TPP landscape (initial desk research and interviews)

We designed our scoping work package as a foundation for broader stakeholder consultation on approaching a TPP for a diagnostic cancer test. We reviewed the critical existing evidence and insights on TPP development processes, desired features and enablers/barriers to TPP development for diagnostic tests. Our scoping review comprised three elements: (a) rapid scoping desk research by RAND Europe and the Office of Health Economics (OHE) on key related literature and examples of existing demand-signalling diagnostic TPPs (predominantly related to infectious diseases), (b) key evidence on using early economic modelling in TPP development, and (c) initial stakeholder consultation (seven interviews between May and June 2023) focused on the experiences of those involved in prior or ongoing TPP development efforts in the diagnostic space. Annexes A and B detail the resulting evidence and learning acquired as the project evolved.

ii Although there were 129 contibutions in total, there were only 103 unique individuals across all work packages. This is because many advisory group members and individuals from stakeholder groups engaged in more than one research activity. For example, an advisory group member would have attended their group workshop *and* their stakeholder-specific one. Similarly, a frontline interviewee may also have contributed to the workshop testing the draft TPP guide.

Figure 1. Project workflow



3.3. Work Package 2: Stakeholder consultation workshops

We conducted stakeholder workshops to explore the experiences and perspectives of representatives from diverse stakeholder groups, covering a range of issues relevant to developing a diagnostic TPP for cancer for UK use and the features it would need to consider. We held six online workshops facilitated by the project team between 22 May and 13 July 2023. Alongside participants from the project team and CRUK (the latter as observers), the workshops gathered insights from a total of 86 individuals,[iii] including project advisory group members (n=12) and external participants (n=74) identified through a combination of desk research, research team networks and project advisors' suggestions. The participants reflected diverse perspectives across academia, research, healthcare, industry, policymaking and regulations, the HTA, health economics, patients, carers and the general public. Annex C provides a detailed cross-analysis of evidence and insights from the stakeholder workshops.

3.4. Work Package 3: Stakeholder consultation interviews

To complement findings from the stakeholder workshops, we interviewed primary care practitioners (n=9) and diagnostic lab experts (n=4, including four pathology lab experts and one genomics lab expert) between 14 June and 14 July 2023. Annex D details the findings from these interviews.

3.5. Work Package 4: Establishing an early economic modelling tool to inform future TPP development

We also developed an early economic modelling tool to help integrate health economic input into the TPP development process. Economic evaluation involves identifying, measuring and valuing the inputs and outcomes of two alternative activities. Healthcare uses economic evaluation to understand the impact of introducing a new health technology on costs and health benefits compared to standard practice. This comparison usually involves modelling cost and health outcomes along a patient pathway. Early economic evaluation (and economic modelling) refers to applying these concepts before finalising the evidence – perhaps even before the technology exists. Our workshop and literature findings suggested that the perspectives of those assessing health technologies for adoption in the NHS (e.g. NICE) are essential for TPP development but rarely considered. Our early economic modelling tool aimed to draw out the main value elements of the proposed diagnostic test, quantify these parameters and perform a simplified early economic evaluation using an Excel-based tool. The results can indicate a diagnostic test's potential cost-effectiveness (if developed as hoped) and the features expected to impact its cost-effectiveness significantly. Annex E details the economic modelling tool designed by OHE.

iii The total number of contributions across the workshops (n=92) is higher than the number of individuals (86) because many advisory group members also engaged in stakeholder specific workshops relevant to their experience and expertise.

3.6. Work Package 5: Establishing and testing a TPP development guide

We drew on insights from all data collection and analysis conducted in Work Packages 1–4 to develop a draft guide for developing diagnostic TPPs for cancer in the UK. The draft guide considered options for approaches and methods to build a diagnostic TPP for cancer (and associated trade-offs), the stakeholder types to engage in different stages and key governance and oversight considerations related to the TPP development process. It also provided insights on the types or categories of features that will likely be important in TPP development and included the draft economic modelling tool established in Work Package 4.

We used the draft guide to facilitate workshop discussion and 'test' the draft content, sharing it in advance with invited participants. We facilitated an online workshop to explore the experiences and perspectives of the project's advisory group and stakeholder representatives. The workshop explored various issues to refine the proposed draft for developing TPPs for diagnostic cancer tests, focusing discussions on suggestions and feedback on the TPP guide's framing, format and content, including TPP features and priority areas. We held the workshop on 16 November 2023. Annex F details the findings that informed the guide's final iteration.

3.7. Work Package 6: Cross-analysis, synthesis and final reporting

To consolidate findings from Work Packages 1–5, we discussed all findings and reflected on feedback from the guide-testing workshop. We revisited the individual work-package contents in our team discussions to consolidate these findings into a final report via desk-based triangulation and synthesis by the research team, consultation with CRUK, quality assurance, design and copy editing. We designed the output's reporting skeleton, structure and format per CRUK's style guidelines.

3.8. Ethics

All participants gave informed consent before contributing to the study. Advice from the Health Research Authority (HRA) did not deem this project to require HRA approval or review by an NHS Research Ethics Committee (REC) due to the nature of its participants and recruitment channels.

4. Results: A guide for developing diagnostic TPPs for cancer

This section presents our key research findings. We begin by sharing findings on the feature types to specify in a diagnostic TPP for cancer (Subsection 4.1) before discussing which stakeholders to engage and why (Subsection 4.2). We then summarise the prioritisation criteria for deciding which TPPs to develop (Subsection 4.3) and present the results of the economic modelling tool for helping specify features relevant to a TPP (Subsection 4.4).

The guide then presents findings about the constituent phases, activities and methods for developing a diagnostic TPP. We present these in subsections 4.5–4.9, beginning with a brief overview of the process and the fundamental principles that should guide it (Subsection 4.5) before focusing on each stage in TPP development, including inception (Subsection 4.6), scoping (Subsection 4.7), drafting (Subsection 4.8) and consensus building (Subsection 4.9).

4.1. Feature-related considerations in TPP development

TPPs must provide specifications for a diverse range of features, i.e. a test's desired characteristics. These include a resulting test's scientific and technical performance (e.g. its ability to detect and diagnose cancer accurately), its fit within the operational context in which it will be deployed (e.g. existing health system facilities, equipment and patient care pathways), how well it aligns with the user context (e.g. health workforce skills and capacity and patient acceptability), and its accordance with regulatory, HTA and procurement realities (e.g. meeting safety, efficacy and cost-effectiveness requirements).

Based on a systematic review by Cocco et al. (2020)[1] and refined through our research to test and validate their typology, we found that features used in diagnostic TPPs typically fall into nine conceptual categories, summarised with brief 'working explanations' in Table 1 below. Our research also flagged historically neglected considerations within these categories, italicised in Table 1.

Since diagnostic TPPs for cancer do not yet exist in the public domain, this conceptualisation of TPP feature categories derives from areas other than cancer. However, our research and the expertise of diverse stakeholders suggest that the categories and their features will be equally relevant in an oncological context, although specifications for individual features will be unique to particular tests, cancer types and TPPs. Since current insights primarily draw on research in the in-vitro diagnostics space, future research should build knowledge and understanding of how relevant features relate to different diagnostic test *types* given scientific and technological advances in diagnostics, extending beyond in vitro diagnostics.

Our evidence-based analysis suggests some common features across different types of diagnostic tests. For instance, many features presented in the systematic review by Cocco et al. (2020)[1] appeared in half or more of the TPPs analysed (see Annex G for further detail). Examples include features reflecting the *nature of unmet need* (e.g. intended use and the target care level, population and user) and *analytical performance* (e.g. sample type, specimen preparation and time to result), *clinical validity* (e.g. diagnostic/testing sensitivity and diagnostic/testing specificity), *human factors* (e.g. training and education), *infrastructure requirements* (e.g. storage conditions, shelf life, temperature, humidity and power requirements, stability during transport, waste disposal) and *economic considerations* (e.g. price/cost per test).

Expanding on the overview in Table 1, the narrative in Sections 4.1.1–4.1.10 elaborates on the considerations TPPs should address and their relationship to each conceptual category of features introduced in Table 1. We aim to illustrate the diversity of issues that need consideration and can influence a resulting diagnostic test's suitability. However, we do not imply that all issues will be relevant to every TPP context. Instead, this will depend on the test's type, cancer site, use case and setting. Prioritising which features matter most to a diagnostic TPP's overall value proposition (i.e. core improvement prospects) and which features should and can be specified must be considered on a case-by-case basis (as discussed in Section 4.5 of this report).

Table 1. Conceptual categories of features used in demand signalling TPPs*

Conceptual categories of diagnostic test features in TPPs	Explanations
 **Unmet need**	Features related to the unmet need a diagnostic test responds to and its application scope, including information on its test concept, intended use, role in medical decision-making, medical justification, fit with clinical workflows and its target healthcare level, population and user. (Information on how a test might interact with or affect other needs/tests or decisions about patient care is often missing).**
 **Analytical performance**	Features related to a test's ability to accurately detect and measure a disease analyte/marker, i.e. whether the test accurately quantifies what needs to be measured. This includes 'output' features on analytical performance and those supporting appropriate analytical performance. (Information on how the real-world conditions in which the test will be used might differ from experimental laboratory conditions is often missing, not recognising that a test must consider real-world performance needs, not just those in lab settings).
 **Clinical validity**	Features that describe what the test measures and how this correlates appropriately with a physiological condition, pathological process or state, i.e. information to ensure the test measures an appropriate disease marker in a specific population.
 **Clinical utility**	Features describing how a test must influence downstream care outcomes, e.g. features showing associations with survival, quality of life and patient experience (directly or indirectly). (Proxy measures of clinical utility are often missing, an area needing further research in the context of cancer diagnostic TPPs).
 **Human factors**	Features describing how individuals should interact with the test and how it must align with user skills and abilities relevant to healthcare professionals and patients (e.g. administering it to a patient, handling/preparing it for use, capturing and interpreting its results, and any training needs therein). (Considerations around patient acceptability, accessibility and experience, including how the test should mitigate inequalities, are often missing. Examples include requirements related to invasiveness, cultural acceptability for specific target groups, and ease of access).

Conceptual categories of diagnostic test features in TPPs	Explanations
Infrastructure	Features describing infrastructure requirements (e.g. facilities, equipment, supplies and IT systems) or other operating conditions that must be established and maintained for the test's effective transport, storage, operation/use and/or disposal.
Costs/economic considerations	Features describing requirements concerning economic and other commercial considerations (e.g. a test's acceptable price, affordability considerations, information on alternative tests and the competitive pricing landscape). (Consideration of cost-effectiveness rather than price, i.e. 'value for money,' is often missing, an area early economic modelling can help clarify).
Regulation	Features related to a test's safety, quality and efficacy under regulatory requirements. (It is also essential to specify features related to data governance, ethics and informed consent).
Environmental impact	Features related to requirements concerning the test's impact on the environment.

**Adapted from analysis and framing in Cocco et al. (2020)[1]*

Our research also revealed a lack of clarity and consistency in the terms used to describe the same or similar features across diverse diagnostic TPPs. Annex G provides 'working explanations' for diverse features in each conceptual category (as informed by desk research and consultation with advisors).[27] However, those explanations are by no means formal definitions. Future research needs to address this gap in the knowledge base and establish a consistent terminology. Annex G also discusses insights on feature-related considerations for different test types beyond in-vitro diagnostics (e.g. multianalyte platforms, multicomponent tests and digitally enabled diagnosis).

The section below highlights insights from across-the-desk research and stakeholder consultations in this project about key considerations when specifying features in diagnostic TPPs for cancer in each conceptual feature category introduced in Table 1.

TPP developers must be mindful of scope 'creep' when deciding which features to include. In addition, a TPP can flag critical features for an innovator to provide information on, even if the TPP itself does not specify a concrete value or range. In other words, the TPP can signal the importance of an innovator providing information and evidence about a feature, even if the actual specification might be at the innovator's discretion.

4.1.1. Unmet-need features

This category tends to cover features describing the nature of the unmet need that a diagnostic test must address. Examples include *why the test is needed* (e.g. the nature and scale of unmet need), *what it will be used for*, i.e. its medical purpose and the medical decisions it will affect (e.g. screening for and diagnosing cancer, identifying its stage, and determining the most appropriate care); *the target population* (i.e. who it will test); *the target user* (e.g. who would administer it); *the setting in which the test will be used in* (e.g. primary care), and information on the range of technological approaches available to accomplish the test's aims, i.e. *the*

concept behind the test, given clear needs and opportunities presented by science and technology developments (e.g. the type of analysis needed).

When considering unmet needs, it is also critical to consider how a test under development will need to *align with existing clinical workflows and patient care pathways*, e.g. how it will interact with other tests a patient might undertake and further care decisions (e.g. referrals, prioritisation for additional testing and treatment decisions). Such considerations are sometimes omitted from TPPs but can influence how fit for purpose a new test is and the likelihood of its uptake.

Developers should also consider requirements concerning the potential to *address inequalities* in test access, eligibility and accuracy for specific population subgroups. If a test might introduce inequalities, this should be made transparent by developers responding to the specifications outlined in a TPP. While a TPP cannot solve the challenges of healthcare inequalities, it should clarify how such challenges were considered and how they informed the specifications. Considerations about potential inequalities may be relevant to different types of features, i.e. they are a cross-cutting theme. For example, unmet needs can relate to disparities in access, experience, affordability, and test performance in specific population subgroups and outcomes.

4.1.2. Analytical-performance features

Features in the analytical performance category cover specifications about a test's ability to correctly detect and measure a disease analyte/marker. Some such TPP features relate directly to the test's desired performance, while others concern operational requirements the test must meet to achieve the desired analytical performance.

Though outside the cancer field, examples of relevant features in prior diagnostic TPPs include information on the *type of diagnostic test* (e.g. molecular, serologic or antigen detection), *the target molecule* detected, analytical performance measures of *the test's ability to detect the intended substance accurately* and *information about the smallest amount of substance needed for accurate detection* (e.g. analytical specificity, analytical sensitivity and the detection limit), the *time to test result*, and measures of *a test's stability under changing conditions* (e.g. robustness, device failure, invalid or indeterminate result rates, duration of a valid result and result/analytical stability).

Information on the operational and analytic requirements a test must meet to achieve the desired analytical performance can also vary. While TPPs often specify features related to the sample *type, required sample/specimen volume* and *preparation process*, other operational and analytical requirements may be relevant to consider. Examples include features related to *throughput requirements* (e.g. how many tests are possible in a specific time frame), *analysis type* (e.g. qualitative, quantitative, chemical or genomic), *quality control*, and *setting up the test correctly* (e.g. calibration).

4.1.3. Clinical-validity features

The clinical validity category includes features and associated specifications that help ensure a test measures an appropriate disease marker in a specific population. It includes considerations about the *test's ability to accurately identify individuals with the disease* (i.e. diagnostic sensitivity) and *accurately identify those without the disease* (i.e. diagnostic specificity). It can also include other indicators of clinical validity, such as *the probability of a confirmed diagnosis among those with a positive result* (i.e. positive predictive value) and *precision/concordance* (how much the test results agree with other tests applied to the same sample/individual). Information about the *performance of the test in specific disease subgroups and population subgroups* is also vital to consider, as is the risk of inaccurate test results (e.g. due to human error, sample issues or operational conditions).

When considering clinical validity, it is helpful to identify how the conditions in which the test will be applied in the real world might differ from those in an experimental laboratory (which also relates to the analytical performance/validity domain). Providing information on a novel test's *real-world performance requirements* can help innovators consider performance under different environmental conditions (e.g. temperature, dust, humidity), human-related variables (e.g. operator fatigue) and capacity-related variables such as volume of use/required throughput capacity as an explicit part of a test's development process. These details can also determine

the evidence innovators should collect before submitting a new test for regulatory approval and HTA assessment.

4.1.4. Clinical-utility features

This category covers features specifying how a test must influence downstream care outcomes.

It can be challenging to establish direct associations between a diagnostic test and its intended patient outcomes, e.g. improved survival or quality of life. Indirect impacts – such as earlier diagnosis, improved triage processes or more timely access to treatment (e.g. by minimising the need for further tests, offering quicker results) – merit consideration. However, future research should explore which proxy measures can be meaningfully specified in a cancer-related TPP, as there is a lack of consensus. Some studies are investigating these issues, e.g. stage shift as an endpoint in cancer screening,[28] and making a case for surrogate markers of cancer screening's effect on patient outcomes.[29] These developments address the challenges in linking timely diagnosis to changes in mortality, including the need for large, expensive and time-demanding trials.[30] However, surrogate markers also come with challenges, as some can be misleading.[29] A recent review cautions against using surrogate endpoints to replace longer-term analyses of mortality-related impacts but also sees their value as early indicators.[31]

4.1.5. Human-factor features

This category covers features specifying how individuals should engage with the test and how it must align with user needs, skills and abilities. The focus (per the rest of this report) is on tests requiring professional healthcare engagement rather than self-tests for at-home patient use without professional healthcare involvement.

This category's specifications include clarity about how a healthcare professional must *handle and prepare the test, administer it to a patient* and *label it*; the *time needed to conduct the test; the data to be captured, exported and inputted into a platform, and how*; and *the interpretation of test results* (e.g. features related to the ease of test interpretation and associated error rate). It can also include specifications related to the *test's complexity, e.g. operators' skill requirements and training needs*. This category may also include additional specifications, such as requirements concerning a *test's size and portability, patient identification capability, safety precautions and potential for misuse*.

Alongside healthcare professionals' engagement with a test, TPP development must also consider *patients' interactions with it*, i.e. end users. This area needs attention as patient-related factors have not featured prominently in the TPP landscape. Relevant considerations span features related to *diverse populations' access to a test* (to understand and identify inequalities and necessary access routes and inform eligibility criteria that do not exclude patients needing screening and testing who risk falling under the radar, e.g. due to age), *acceptability* (to understand invasiveness from a patient perspective and across diverse population groups), *speed and efficiency* (e.g. processing and result turnaround times that can *impact on patient anxiety and experience* and influence timely access to treatment), accuracy (patient perspectives related to improvement needs regarding trust and confidence in existing tests' performance) and *patient-clinician communication requirements* that must accompany test administration or result display (to ensure patient understanding of the testing process), e.g. specifications on the test-related information a clinician should communicate to a patient, such as potential side effects, time to results and how the result will be communicated).

Data governance and ethics considerations are also related to human factors (such as individual trust in data security and privacy and informed consent). We discuss these in the 'Regulation features' section (see Section 4.1.8 below).

4.1.6. Infrastructure features

A TPP must also provide specifications regarding the health system infrastructure in which a test will operate. If the test's deployment requirements do not align well with health service organisations and diagnostic laboratories' existing infrastructure, its uptake is less likely. The infrastructure category in a TPP thus includes requirements related to *facilities, equipment, supplies, IT and data systems or other operating conditions* that must be established and maintained to ensure a test's effective operation. Examples include temperature and/or humidity specifications and other storage requirements, e.g. biosafety,

assay packaging, reagent kits, other necessary supplies, transportability, operational power needs and waste disposal.

4.1.7. Economic features

This category covers features describing requirements related to *economic considerations* reflecting test affordability (e.g. cost per test, per diagnosis, per instrument and compared to competitors' market costs) and other *commercial considerations* (e.g. potential market size and nature, routes to market and reimbursement pathways).

Considerations about *cost-effectiveness* as an indicator of value for money (as opposed to just price) are often missing from TPPs. Economic modelling can help inform specifications for cost-effectiveness, as discussed in Section 4.4.

Though not always straightforward, this category of features is essential to consider in TPP development, given that a TPP's traction and impact will depend on the likelihood of a procurement channel and viable market.

4.1.8. Regulation features

This category covers features related to a test's *safety, quality, efficacy and/or effectiveness requirements* under regulatory stipulations and can provide information on the product registration pathway.

A TPP may not provide detailed specifications on these aspects (and regulations in fields with fast scientific and technological development can be prone to change). However, a TPP can signpost information sources and guidance from relevant regulatory agencies.

TPP developers must consider whether the TPP's focus is local or spans regulatory jurisdictions (see Section 4.5, which discusses issues related to a TPP's geographical scope).

While data governance and ethics considerations are not always prominent in TPPs, they are important for ensuring a test's safe and appropriate use, including informed, safe and secure data handling, storage, transfer and sharing. With developments in the digital and multicomponent diagnostics space, features relevant to data governance and management in TPPs are gradually evolving. Examples from recent TPPs include considerations about data types (e.g. diagnostic information, patient data/personal data, contextual data), entry methods, validation, handling and storage, export, reporting, recovery, access controls, connectivity methods and requirements, exchange standards, provenance (origins), flow-process requirements, and ownership, privacy and security.[32-34]

4.1.9. Environmental-impact features

The environmental impact category covers features related to *any environmental impacts of test production, use and disposal*. There is increasing attention to these matters in the health innovation system, and TPPS must clarify expectations related to sustainable innovation and environmental footprints. The NHS net-zero criteria for procurement requirements and other environmental impacts[35] will be important to consider (separate from regulatory requirements).

Finally, TPPs are often intended as 'living' guidance documents (see Box 1 below), containing specifications for features that can be updated as new information becomes available (see Annex A).

Box 1. Tip on ensuring a TPP is relevant long enough to incentivise innovators to action

A TPP's relevance will be influenced by how dynamic and responsive it is. However, there needs to be a balance between keeping a TPP up to date and ensuring that it is a stable demand signal that allows innovators to develop a diagnostic test in response and capture value from their investment and innovation efforts. Changing specifications too often can disincentivise innovators, given the risk that a product's market and demand have changed by the time a diagnostic test is developed. From the outset of TPP development, it is vital to consider its short and long-term relevance, the features that may be more stable or prone to changing specifications, and how that might impact its relevance and impact.

4.2. Who to involve in TPP development: Stakeholder considerations

As outlined earlier, diagnostic TPPs aim to support those developing innovative diagnostics to consider diverse criteria in their product development efforts. These criteria include technical performance criteria and criteria that can help maximise the chances of any resulting diagnostic test being a good fit with the broader health system care pathways, its users and the infrastructure, regulatory and HTA requirements with which it will operate.

Diverse stakeholders have a role in TPP development, as demonstrated in existing TPPs outside the cancer space. As part of our project, we explored the relevance of diverse perspectives (see Annexes A–D) by drawing on learning from TPP development efforts outside of cancer and the expertise and experiences of those developing, using, regulating or otherwise engaging with cancer detection and diagnosis. These insights highlighted the importance of involving expertise spanning academic, clinical academic and research communities; healthcare professional and diagnostic laboratory expertise; industry; patient, carer and public perspectives; research and innovation funders in the public sector and charities; and regulators, HTA and policymaker perspectives. Table 2 summarises the importance of involving these groups in TPP development. For more detailed insights on different stakeholders' roles and which expertise types are relevant, please see Annex H.

Table 2. Stakeholder groups and why they matter

Stakeholder group	Their importance in TPP development
Academic/ research expertise	Different clinical, natural and social science research expertise may have a role in specifying technical performance requirements for a novel diagnostic test. For economic considerations and criteria for ensuring a good fit of a diagnostic test with health services organisation, implementation science experts may also play a role.
Healthcare professional and diagnostic laboratory expertise	Healthcare professionals can provide insights on areas of unmet need regarding existing tests' 'technical' performance (e.g. diagnostic sensitivity and specificity) and their usability and fit within the health service's clinical and care pathways. Diagnostic laboratory expertise can help identify requirements for ensuring a diagnostic test's alignment with existing laboratory workflows and infrastructure.
Industry expertise	An industry perspective is vital for ensuring the specifications are feasible to implement, especially regarding a test's technical performance criteria, associated infrastructure, equipment and supply requirements and commercial considerations (i.e. payer and price). Industry will also be aware of other products on the market and can input that knowledge into early TPP development efforts to confirm that there is an unmet need.
Patient and carer representation	Patient experiences are key for understanding the needs and inequalities a novel test might meet, mitigate or inadvertently exacerbate. Patient voices can provide crucial insights into unmet needs related to a test's accessibility, acceptability, speed, testing efficiency and real/perceived accuracy.

Stakeholder group	Their importance in TPP development
Expertise from research and innovation funders in the public and charity sectors	Funding organisations have a broad understanding of unmet needs, ranging from the need for diagnostic tests' improved technical performance to broader health-system issues, such as diagnosis in primary care settings, accessibility, invasiveness and cultural acceptability issues.
Broader decision-maker expertise: regulators, HTA and policymaker perspectives	The perspectives of those influencing diagnostic tests' purchasing and adoption/uptake matter as they can shed light on where there is a viable value proposition within existing tests' improvement needs and cost-effectiveness considerations. Policymakers and HTA agencies will likely have some insight into purchasing realities.

The exact nature of the expertise required, i.e. the individuals and organisations that should be involved, will largely depend on the test type, cancer site, use setting and use case for which a TPP is being developed and must be considered on a case-by-case basis. However, some types of expertise may apply to multiple TPP development efforts, regardless of test type (see Box 2 below).

As an inherently complex and collaborative process, TPP development requires precise and transparent governance arrangements, i.e. clarity about who formally hosts the process and which organisation is best placed to take ownership of steering and coordinating the TPP development effort (alongside implementation support from the core working group). According to our research insights, there is broad consensus that hosting TPP development efforts should be more of a stewardship relationship than strict 'ownership', given the collaborative nature of TPP development and the need for buy-in from diverse organisations.

Diverse sources and organisations that host and steer TPP development can initiate decisions to embark on it; these groups must be trustworthy, reputable, influential and seen as independent. Any hosting organisation needs both convening power and the capacity and coordination ability to effectively oversee the effort's delivery. While our research identified many potential options (e.g. charities, arm's length bodies such as NHS England and their equivalents in the devolved nations, and cancer networks such as cancer alliances, professional associations or societies),

Box 2. Tip on balancing bespoke expertise with broader skills and knowledge applicable to multiple TPP development efforts via a national supporting body

Decision-makers in the health system may want to consider establishing an overarching national body that can provide input into multiple TPP development efforts. This organisation would include core members who can contribute expertise across all use cases and rotating members with expertise bespoke to specific use cases, cancer sites, use settings and test types. For instance, expertise from regulatory/HTA, health economics and clinical academic groups (e.g. cancer-centre leads spanning research on multiple cancer types) may be relevant to diverse diagnostic TPP development efforts in cancer. Other expertise needed for demand signalling TPP development will be specific to the cancer type, test type, use case and setting (e.g. specific academic, clinical or patient-voice expertise).

If a TPP that is primarily focused on use in a UK market also considers international markets and regulatory, HTA, reimbursement, and care pathway differences, then international expertise may be necessary within the rotating membership.

there was no firm consensus on any one body. In addition, our research highlighted possible trade-offs as factors worth considering in this choice (e.g. influencing power and ability to mobilise buy-in from wider stakeholders versus complete independence from political influence).

4.3.Deciding to develop a diagnostic TPP for cancer: Prioritising where TPPs can add the most value

The need for early detection and diagnosis spans diverse cancer types, use cases, settings and test types. Therefore, there are many areas where a TPP could help respond to unmet needs. Although we could not investigate whether any particular use case is more important than another within this project's scope, we used stakeholder consultation to examine criteria that could help inform prioritisation-related decisions about which cancer-related diagnostic TPPs to develop in the future.

The key considerations fall into five interrelated categories, as summarised in Table 3. These include those related to *epidemiology, early diagnosis, existing test performance, health services organisation and capacity, and prevention potential*. These considerations could help determine which use cases to design a TPP for.

Although we could not focus on it in depth as part of this project, it is also essential to consider how to make robust prioritisation decisions and the methods that can support it. For example, learning from the work of James Lind Alliance Priority Setting Partnerships (PSPs)[36] and insights from the literature on rapid prioritisation may be applicable.[37]

Table 3. Factors to consider when prioritising what to develop a TPP for

Overarching consideration	Specific factors to consider
Epidemiology: cancer incidence and prevalence	• Cancers with high incidence and prevalence (but poor early diagnosis rates) • Rare and neglected cancers • Cancers with pronounced inequalities in diagnosis, treatment and outcomes (remembering that inequalities can vary geographically).
Cancers with poor early-diagnosis rates (due to low presentation to health services or poor test performance) where new tests could generate stage shift	• Cancers with low screening rates • Cancers for which *early* diagnosis and detection are poor • Cancers with low survival rates associated with poor diagnosis and access to timely treatment • Cancers for which timely diagnosis of recurrence is an issue, alongside early diagnosis of the first occurrence.
Cancers where the performance of existing tests is inadequate on technical, accessibility or acceptability fronts	• Existing tests' poor accuracy in early diagnosis • Existing tests' accessibility issues • Existing tests' invasiveness issues • Existing tests' broader patient acceptability issues.

Overarching consideration	Specific factors to consider
Cancers where health services organisation and capacity issues align poorly with existing tests	• Where existing tests do not fit well with workforce and infrastructure capacity constraints • Where existing tests provide poor economic value for health services • Where there is scope for novel tests to inform better, more efficient triage decisions • Where there is scope for novel tests to minimise the need for multiple tests to confirm or rule out cancer • Where novel tests could minimise over-intervention risks (e.g. better exclusion).
Preventable cancers	• Where testing could assist prevention, e.g. Human Papillomavirus Infection (HPV) diagnosis.

4.4. Early economic modelling

A simple case exists for integrating early economic modelling within the TPP development process. Utilising the perspective of those undertaking the HTA and the value-for-money considerations can help determine the qualities necessary for a diagnostic test to be evaluated favourably by payers, i.e. its perceived cost-effectiveness.

Not all diagnostics in the UK undergo HTA. Purchasing decisions are made by commissioners such as NHS England or other regional and local-level payers. In England and Northern Ireland, diagnostics scheduled for health technology assessment (HTA) undergo cost-effectiveness evaluations conducted by the HTA body NICE (with separate bodies for Scotland and Wales). NICE assesses the cost-effectiveness of health technologies by considering their overall impact on health and healthcare costs (including health service resource use), using this to determine whether the health technology offers good value for money. This process is important because it recognises that healthcare resources are constrained and spending has an opportunity cost: if the technology does not offer good value for money, its adoption will displace more health gains than it generates: resources diverted to new technology are no longer available for other, more cost-effective, activities.

4.4.1. Insights from the early economic modelling scoping review

Our literature scoping review identified several key findings and considerations about how early economic evaluation (EEE) may fit into the TPP development process. Annex A provides a more detailed summary of the findings.

Diagnostic technologies are distinct from other technologies because their patient-impact route is often via the treatment decision they inform. Therefore, the test's impact on clinical decision-making helps determine its cost-effectiveness, often more than its accuracy.[38,39] This difference should be considered in a new test's value proposition when drafting a TPP.

The **clinical care pathway** describes the interactions a patient with a particular medical condition experiences as they move through the health system.[40] Establishing the clinical care pathway is crucial, given that novel diagnostics generate their value indirectly. However, there can be difficulty benchmarking if no pathway previously existed, resulting in uncertainty in demonstrating value.

Cocco et al. (2020 and 2021) identified areas in the development phase of TPPs where EEE could play a role.[1,41] **Care-pathway analysis** has been highlighted as particularly important in the scoping phase.[41,1]

Deterministic sensitivity analysis and **scenario analysis** could be performed in the drafting phase.[41] Where there is uncertainty, this would identify which variables have

the most significant potential impact on cost-effectiveness and enable alternative scenarios to be tested. In addition, threshold and headroom analysis could be undertaken using a willingness-to-pay threshold for a QALY (in contrast to the considerably lower NHS opportunity cost threshold) to back-calculate the maximum costs and minimum specifications for the test to be cost-effective in those terms.[41,42]

The early economic model must have a flexible design to incorporate evidence as it evolves.[41] Further sensitivity analyses could be undertaken, and an information analysis value could be achieved if the model is probabilistic.

4.4.2. Insights from the 'HTA, Health Economics, Policy and Regulation' workshop on EEE

This workshop aimed to elicit views on the benefits and challenges of using EEE in TPP development, the best information sources to populate a model, and which features of a TPP should be considered within its scope. This section summarises the main insights relevant to EEE, while Annex F provides a more detailed summary of the relevant workshops.

Findings from the workshops suggested that EEE can help:

- Distinguish between features that do and do not significantly impact cost-effectiveness and rank these by their potential relative impact.
- **Eliminate tests that are unlikely to be cost-effective** where the model suggests highly cost-ineffective results. However, having confidence in borderline results is inadvisable due to EEE's high degree of uncertainty.
- **Bridge the disconnect between the development and reimbursement process**. Participants highlighted that there is often a disconnect between the diagnostic development and reimbursement processes, yielding innovations that do not meet the required standard for reimbursement. Using EEE in TPP development may enable a better understanding of and alignment with the reimbursement process, which is essential to a product's success.

However, EEE is subject to important limitations that warrant recognition. Using EEE for an early assessment of potential cost-effectiveness is challenging, as its uncertainty limits confidence in borderline results. For this reason, developing high-quality evidence is essential; it can then be iteratively incorporated into the model, increasing confidence in the results.

A more general limitation of cancer diagnostics is the difficulty in **demonstrating an earlier diagnosis's clinical and economic value**. While earlier diagnosis can often generate a stage shift in cancer identification, this doesn't necessarily improve survival and health outcomes, particularly where there is no appropriate treatment or care pathway change to alter the disease course.

Furthermore, there is a risk of overdiagnosis, i.e. detecting non-progressive (or very slow-growing) cancers that will not cause medical harm, meaning a patient experiences cancer treatment, its side effects and the associated distress unnecessarily. Considering these factors when undertaking EEE is essential since they are potential barriers to demonstrating a diagnostic cancer test's value.

4.4.3. An economic modelling tool for TPP development

Assimilating findings from our scoping work and workshops, we developed an economic modelling tool to help integrate EEE into TPP development. We intend the tool as a resource to elicit the main value proposition a proposed test would need to meet the requirements specified in a TPP, which are expected to affect its economic health value directly.

The tool comprises an Excel-based model and a Word document in a 'guide-style' format (Annex E provides full details). Together, they can be used to perform a simplified early economic evaluation, with the primary objective of identifying the TPP requirements expected to have the most significant impact on cost-effectiveness and indicate the test's potential cost-effectiveness, assuming 'perfect implementation'.

Bespoke modelling efforts will be needed to derive more precise estimates, particularly given the heterogeneity in how diagnostics may derive value and affect the care pathway. Several aspects of the evolving diagnostic and

treatment landscape are difficult to predict and incorporate into an early economic model. Therefore, the value generated by the economic modelling tool is indicative only; it should be considered just one of the many pieces of information needed to develop the complete TPP.

The first stage in undertaking EEE is establishing the diagnostic's value proposition and identifying features that will likely impact its cost-effectiveness. Table 4 provides a series of questions/steps to draw out key information related to the diagnostic technology's potential cost-effectiveness.

Answers may concern the diagnostic's analytical performance, whether it impacts the care pathway or whether it will lead to cost savings for the health service. Furthermore, outlining where there may be future changes to the policy landscape or treatment options is essential. Any change to the broader context will likely impact the test's cost-effectiveness, particularly if a new treatment is on the horizon. Therefore, the broader context should be monitored and considered while the TPP is under review.

Table 4. TPP features relating to cost-effectiveness

Categories:	Questions:	Link to TPP features
Description of the test: provide a value proposition for the proposed test	What is the use case? What is the primary unmet need? What are the expectations for analytical performance (sensitivity and specificity) at this stage?	• Unmet need • Analytical performance
Comparator: usual clinical practice (not best practice) is the appropriate comparator	What is the current care pathway? Will the test replace or be used in addition to an existing test?	• Clinical utility • Human factors • Downstream impacts on care pathways and processes
Population	Who will likely be eligible to receive the test? How many people are expected to be tested? Are there any subgroups for sensitivity analysis?	• Inequalities and health equity • Clinical utility • Cost/economic considerations
Health service impact: This only applies to changes in service delivery costs to the NHS (and personal social services)	Will the test replace current practice (i.e. lead to disinvestment)? Might it yield savings in staff time, hospital bed days, GP visits (etc.)? Will the test require additional training or investments in infrastructure?	• Human factors • Cost/economic considerations • Downstream effects on care pathways and processes • Infrastructure
Patient/health impact: how the test may lead to improved health-related quality of life	How might the new test's introduction change the clinical care pathway? Could the test lead to an earlier/more timely diagnosis and potentially positive stage shift?	• Clinical utility • Downstream impacts on care pathways and care processes • Patient acceptability and experience

Categories:	Questions:	Link to TPP features
Key uncertainties and research questions	Are there any new treatments on the horizon? Are you aware of any significant policy changes? (e.g. NHS major conditions strategy) If you expect there to be multiple use cases, outline these.	(All that apply, depending on the uncertainties and research questions)

After articulating the cost-effectiveness drivers, their respective input parameter values must be estimated to compare the new test's potential costs and health-related quality-of-life impacts against the current care pathway. This comparison will facilitate estimates to give an initial sense of whether the new TPP-compliant test could offer good value for money.

The analysis involves an incremental cost-effectiveness assessment, generating the Incremental Cost-Effectiveness Ratio (ICER) as its primary output, which equals the new test's Cost per Quality-Adjusted Life Year (QALY). In England, NICE sets the threshold at which it deems technologies to offer value for money, generally £20,000–30,000 per QALY.[43]

The EEE inputs comprise population-level data, QALY impact and costing data. The population-level data include the population size likely to be eligible for the test, the average age of patients diagnosed, and the cancer's prevalence.

NICE considers QALYs as the primary health outcome, calculated as patients' estimated survival combined with their health-related quality of life (between 1–0) in their life span. One QALY equals one year in perfect health, equivalent to two years with a health-related quality of life of 0.5 or four years with a health-related quality of life of 0.25.

Finally, the relevant costs from the NICE reference case are from the perspective of NHS and Personal Social Services (PSS), not broader societal costs such as lost patient productivity due to treatment, illness or death.[44]

These values can be entered before or during the early economic model's population. We designed our economic modelling 'guide' (see Annex E) to accompany the modelling tool, providing resources supporting parameterisation. Once the evidence is synthesised and modelled, early estimations of the test's potential economic value can be calculated.

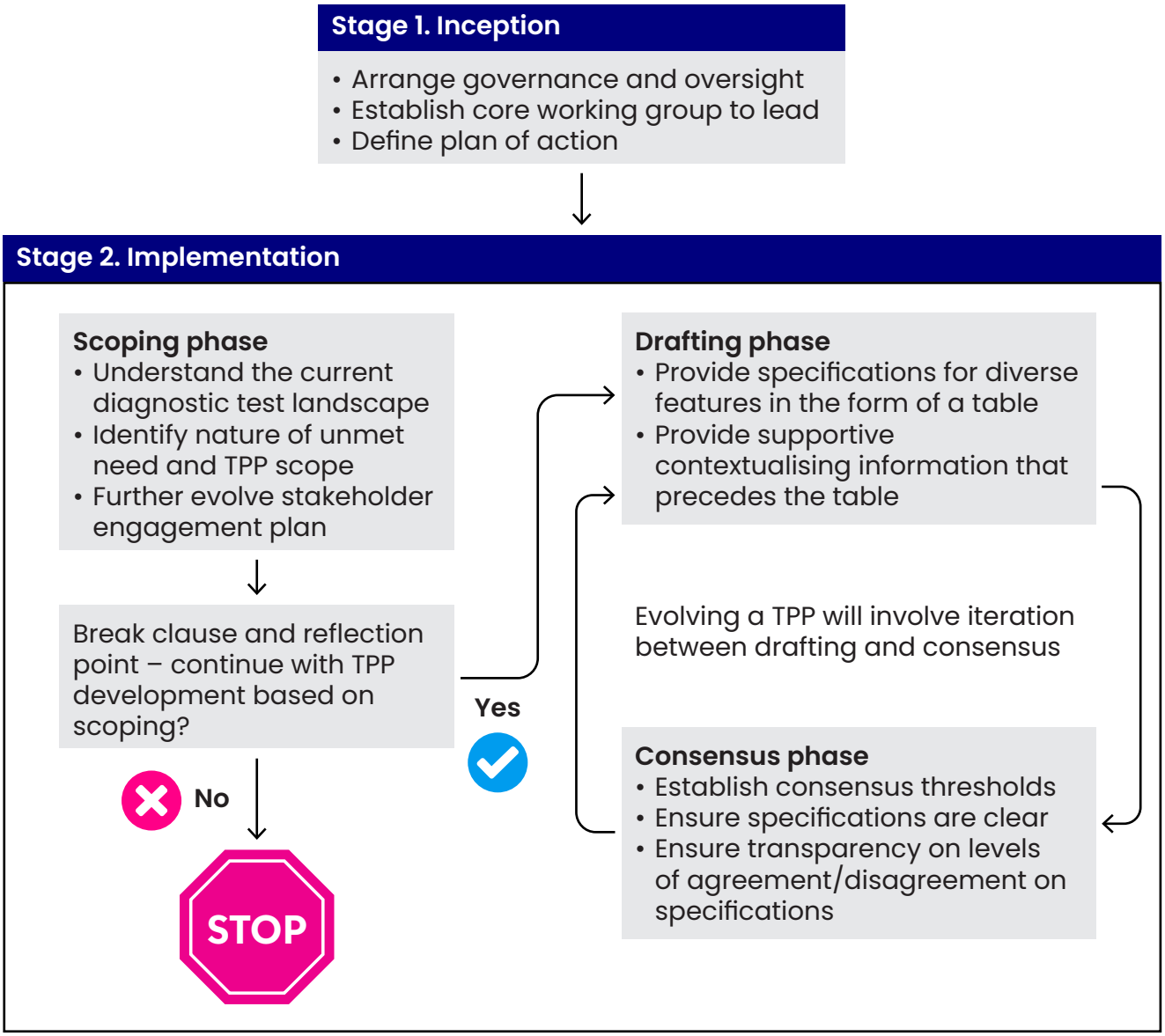
4.5. The TPP development process: Brief overview and guiding principles

TPP development typically occurs in two key stages. The first is the *inception stage*, which establishes a core working group, governance and coordination arrangements and an action plan. The second is the *implementation of the TPP development* stage. Building on insights from a recent systematic review by Cocco et al. (2020), this can be conceptualised as three phases [15]:[1]

- **Scope** the unmet needs potentially addressed by the proposed test and its key requirements.
- **Draft the TPP to explain its development's 'why?', 'how?', and 'who by?'**, list its relevant features and, where applicable, their specifications.
- **Build consensus** on a final draft TPP.

These phases are not necessarily linear. For example, the drafting and consensus-building phases often happen iteratively, as outlined below. Figure 2 provides an overview of the key phases and stages in TPP development.

Figure 2. Overview of the TPP development process and each stage's aims



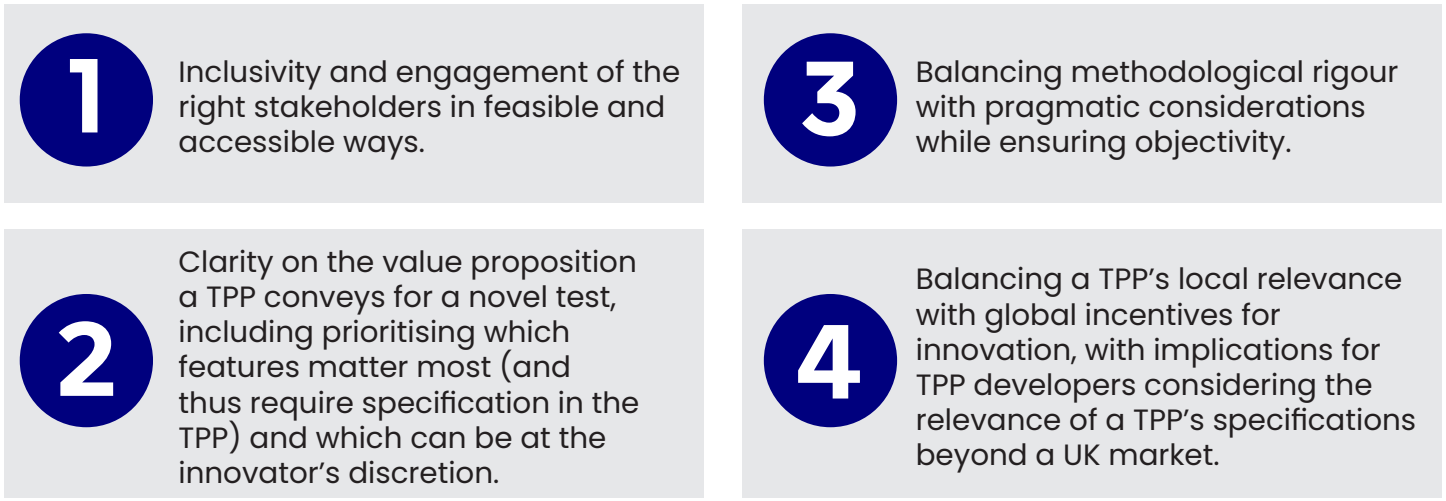
Based on stakeholder consultations throughout this project about what matters, we inferred **four overarching principles** that apply to all phases of TPP development and should be used to guide the process (see Figure 3).

Principle 1: Inclusivity and engagement of the right stakeholders in feasible and accessible ways

It is important that diverse stakeholder voices are reflected in TPP development, given the variety and multiplicity of features that matter for a diagnostic TPP for cancer. However, *who* engages in the process and *how* they do so must be considered in the context of feasibility. This includes considering the TPP's completion timeframe, including the time different individuals can devote to the process, their skills, capabilities and experiences (determining which aspects they can best contribute to), and *how* they can best contribute (e.g. through individual versus collective means, written versus verbal inputs, or informing initial specifications versus commenting and 'stress-testing' suggested specifications in drafts). Some individuals and stakeholder groups will input across all phases of TPP development (either by being on a core working group or having technical and professional skills relevant to different process phases and features). Others may be asked to provide specific inputs in distinct phases or for particular features.

The language and format of documents used

Figure 3. TPP development principles



to engage stakeholders must be accessible and clear to all involved. When engaging with patient and public voice representatives, it is imperative to try and avoid and/or explain technical jargon.

Principle 2: Clarity on the value proposition a TPP conveys

It is essential to identify features at the core to the value proposition of a test that is to be developed in response to a TPP, and their specifications early on. This process involves determining the key features and specifications in combination, not in isolation. Since the unmet needs a TPP seeks to address may comprise multiple dimensions, it is critical to understand which feature types matter most and the trade-offs associated with meeting each specification (e.g. trade-offs between technical features such as high diagnostic sensitivity or specificity and those related to test accessibility). Although identifying and specifying trade-offs can be challenging, it is important to optimise the value proposition of the test for which a TPP is being developed. Early economic modelling can help estimate the health economic value of different combinations of specifications and features. If a TPP tries to achieve too much, it may risk diluting focus away from things that matter most, and the development process could become unwieldy. It is essential to consider where TPPs should directly specify a novel test's required features and where they can signpost additional supportive information, resources and guidance (such as help with regulatory and HTA requirements, possible reimbursement pathways and accessing clinical samples).

Therefore, a TPP should not necessarily try to detail specifications for *all* the features a test developer will need to consider when bringing a product to market, as that is likely to be overly cumbersome and prescriptive. Prioritising which features need specification, given the core value proposition, will likely be necessary. In addition, it is vital to clarify what is *unwanted* in a novel test, i.e. undesirable features and specifications. Similarly, it is important to consider where minimal and preferred specifications are necessary, where only minimal suffice, and where no specification is required (even if innovators need to develop 'bottom-up specifications' for the latter as part of product development). A demand-signalling diagnostic TPP for cancer also needs to balance precise specifications for a desired test's primary features with some flexibility for innovators to devise 'bottom-up' solutions for features.

A demand-signalling TPP cannot be 'everything' to 'everyone': focusing efforts and balancing resources and time investments are important. A TPP can help ensure innovators consider diverse features, helping towards the successful uptake of any test developed in response. However, without wider policy levers, a TPP cannot solve broader challenges to incentivising innovation and its adoption in the NHS alone (e.g. challenges to workforce capacity and health service organisation or funding for novel tests). Therefore, TPPs are useful tools only as part of broader efforts to help align the supply of novel cancer tests with demand.

Principle 3: Balancing methodological rigour with pragmatic considerations while ensuring objectivity

As Sections 4.7–4.9 will discuss, TPP development can use several methods to arrive at desired specifications for different features. Methodological choices must consider trade-offs between comprehensiveness and rapidity, e.g. systematic reviews versus rapid evidence reviews to establish critical features and the nature of unmet needs, and formal Delphi surveys for consensus exploration on feature specifications versus lighter-touch Delphi-inspired workshops). Ultimately, 'fit for purpose' choices must balance optimal methods with real-world pragmatism while ensuring sufficient rigour and objectivity (i.e. independence from the vested interests of any single contributing group). Various factors can impact the time available to develop a TPP and the methods and rigour of its development. Examples include the (a) urgency for a new test (e.g. lack of existing solutions or new therapies on the horizon), (b) policy impetus, (c) financial resources available for TPP development, (d) possibility of stakeholder engagement within a desired timeframe, (e) strength of the pre-existing evidence base on feature specifications versus the need to gather new evidence and accommodate adaptability needs (i.e. the number of likely consensus rounds needed to arrive at final specifications).

Principle 4: Balancing a TPP's local relevance against global incentives for innovation

Global trends in diagnostics are crucial in incentivising industry innovation, even within the UK. At the same time, international tests may be unaffordable for the NHS, explicitly creating a need for improved diagnostics for the UK market. Whether a TPP could help incentivise innovation for a UK market only will depend on the value of that market and should be scoped out and assessed before embarking on a TPP development effort to that end. Similarly, a single test type may not meet all patient groups' needs, and developers will need to consider diverse user groups (even within a UK market) given the drive to curb inequalities and be explicit and transparent about who the test *is and is not* suitable for.

Adopting an international perspective to developing a cancer diagnostic TPP does introduce additional layers of complexity when planning who to involve in the TPP development process, which methods to use to inform it, how to resource it and the overall timeline. If a TPP's primary focus is on a specific market/geographical jurisdiction, its developers should still consider how international differences may affect the influence of international care pathway, payer/market, regulatory and HTA specificities on the key features driving a test's value proposition.

A demand-signalling TPP for cancer diagnostics developed for use in a UK context may have a priority focus on UK-specific health service and patient needs. However, there is a tension between specifying features for UK-specific needs (which may be distinctive) and specifying for relevance in major global markets such as the United States (which may maximise the viability of development for innovators). For example, if a TPP considers signposting information on regulatory requirements, these might differ in the UK compared to other jurisdictions. Since clinical pathways and routes to reimbursement will also differ, a TPP that considers the international dimension would need to recognise and flag such differences in the requirements specified.

The principles outlined above can help those developing TPPs to pursue effective diagnostic TPP development from inception through scoping, drafting and consensus phases, each discussed below.

Sections 4.6–4.9 draw on insights from a recent systematic review by Cocco et al. (2020) conceptualising key TPP development phases,[1] building on this work to provide novel, detailed understandings of each phase's aim and integral elements by triangulating insights from this study's desk research and stakeholder consultation.

4.6. Inception phase

4.6.1. Aims

The inception phase involves:

- **Establishing and confirming governance arrangements for overseeing TPP development.**
- **Creating a core working group to lead the implementation of TPP development and help ensure appropriate expertise inputs into each stage.**
- **Formulating an overall approach/plan of action for TPP development.**

4.6.2. Putting it into practice

4.6.2.1. Establishing governance arrangements for TPP development

A clear governance structure should be established to ensure effective and efficient decision-making, accountability and oversight of TPP development. By governance, we mean issues related to who formally hosts the TPP development process (i.e. which type of institution or network), assuming overall 'ownership' of steering it, and how. An example is establishing an overall steering committee and involving the lead(s) and/or coordinators from the hosting institution, funding organisation (if not the same), and core working group established to lead the implementation of TPP development. A chairperson who can effectively and efficiently steer the process and is respected as an independent expert with no conflicts of interest could facilitate the core working group.

Governance arrangements should clearly outline the overall terms and conditions of engagement with TPP development, covering key elements including:

- *Leadership roles within the governance structure* (e.g. chairperson, key coordinator, other key members and observers) and relationships between the chairperson/coordinator and other members.
- *Terms and conditions for the overall TPP development process*, such as those relating to the respective roles and responsibilities of key organisations and individuals involved (e.g. steering committee, host institution, core working group and stakeholders consulted as part of the TPP development process but not in the governance structure).
- *The decision-making process and approach* (e.g. whether decisions will be reached by consensus, voting or another method) and how conflicts of interest and disagreements between governance members will be declared and managed.
- *The purpose, nature and key terms for guiding the core working group* leading the implementation of TPP development (as elaborated on below).

4.6.2.2. Creating a core working group

Establishing a core working group to lead and oversee TPP development and develop an action plan is crucial. This group typically comprises experts from diverse backgrounds relevant to the TPP diagnostic test type, target cancer site, use case or use setting. Given a TPP's scope, intentions and role, the core working group needs to reflect expertise across the research, innovation and care pathway to ensure a range of perspectives (e.g. from R&D to approval, clinical uptake and access). Different stakeholder groups' contributions must also be feasible and commensurate with the value distinct perspectives can add. Experts in a core working group may come from academia and research, healthcare and clinical backgrounds, regulatory and health technology authorities, health economics, policymaking, payers and commissioning bodies and/or patient and public involvement and engagement (PPIE) groups. See Box 3 for a tip on establishing a core working group. While the importance of consulting with industry in the TPP development process is widely recognised, engaging an industry representative in a core working group can be challenging. Those involved in the overall governance of TPP development alongside core working group leads will need to decide whether to engage industry representation in the core working group. Some experts consulted in our study felt that there is a high risk of commercial interests influencing a TPP too strongly if the core working group includes industry representation.

The core working group's composition should reflect the specific nature of the cancer diagnostic test for which the TPP is being developed and be manageably sized.

These parameters may be context-specific depending on the expertise types and diversity required. A small number of individual leads can be appointed within the core working group (e.g. as a secretariat) and be responsible for overseeing and coordinating the group.

The core working group should establish its terms of reference (ToR) as a collective roadmap, ensuring everyone understands and aligns on their roles and responsibilities. Keeping in mind the overall governance arrangements mentioned earlier (under 'Governance of TPP Development'), the core working group's ToR should include the following key components:

- *The group's overarching aims and objectives*
- Its interactions with the host institution's governance structure (e.g. the steering committee's chair/coordinator).
- *The scope of its member involvement*, i.e. individual roles and responsibilities (given the expertise and skills required) and the distribution of tasks and duties within the group. This element should specify any potential 'leads' in the core working group (e.g. a secretariat) and others who may join as needed. It should also cover potential conflict of interest declarations.
- *The group's decision-making process* (i.e. through consensus, voting, or an alternative method). This element should also specify a process for when/if there is no group consensus.
- *The group's meetings and reporting arrangements*, e.g. meeting frequency, format, and reporting requirements. Regular communication and updates are essential to track progress and ensure accountability.

Box 3. Tip on establishing a core working group to lead TPP development

While consideration of diverse stakeholder groups' views matters, not every stakeholder group must be represented in the core working group leading a TPP development effort. Core working group members can include boundary spanners who, given their roles, may have good insights into diverse stakeholders' developments and priorities. Moreover, certain expertise types are not necessarily confined to any one stakeholder group (e.g. a clinical academic may also be a researcher and clinician and sit on national groups well-connected with policymaking bodies and policy priorities; a health economist might help understand a novel test's value proposition and have good insights into regulatory and HTA requirements; and expertise on product development can come from industry, consultancy and academic research groups).

A core working group needs to be of a manageable size, although there is currently no conclusive evidence on what this should be (e.g. our stakeholder consultation suggests that past efforts ranged between 15 to 40 individuals). The appropriate size is likely to be context-specific, depending on the diversity of expertise needed. Whatever the size, it is worth establishing a smaller sub-group (e.g. a secretariat) responsible for coordinating efforts and tapping into the group's broader expertise for specific tasks.

Box 4. Tip on managing flexibility and adaptation

Along with content-related needs, financial resources, and the urgency of determining the approach to TPP development, it is critical to build flexibility and adaptiveness to accommodate potential changes in the most feasible ways diverse stakeholders can contribute. Similarly, it is important to consider how to manage potential uncertainties when developing an action plan. For example, it is often difficult to foresee how many rounds of consensus-building may be needed to arrive at a final TPP. You may want to consider capping the number of rounds but still allowing for some flexibility (e.g. in alternative ways to explore consensus – see Section 4.9 for tips on managing timelines and resources). The need for adaptation may also arise due to differences or limitations in desired individuals/ organisations' capacity to input. Consider some contingency in your timeframe and the scope for offering different ways to incorporate individuals' views (e.g. scheduling an interview if a key contributor cannot make a workshop). You may also need to consider engaging individuals other than those envisaged initially to reflect a specific stakeholder group or organisation's views as a backup.

4.6.2.3. Establishing an action plan

An action plan for TPP development should be developed early, outlining how the TPP development process will proceed. At a minimum, it should cover the following key steps:

- *Defining and outlining the desired outputs of the TPP development process (i.e. the draft TPP documents, final report*, and any annexes/ supplementary materials).
- *Detailing the stakeholder engagement approach*. This includes outlining which stakeholders (organisations and individuals) should contribute, which issues they should contribute to and how. It is important to do this in a way that identifies external expertise and experience beyond the core working group alone. It also involves deciding on the methods and approaches to be used in TPP development and developing a strategy for collecting relevant data, which will often span desk research, consultation with relevant stakeholders and modelling (as discussed in later sections). An upfront drive to establish an action plan should help support an efficient decision-making process and ensure the TPP reflects real-world requirements and opportunities. See Box 4 below for a tip on how to be flexible and adaptive to stakeholder engagement over time.
- *Specifying the anticipated timeline and resource allocations*. This step involves identifying the process's likely duration and phasing, detailing the resources available (e.g. funding).

4.7. The scoping phase

4.7.1. Aims

The scoping phase's core aim is to assess the nature of the need for a novel test and identify its key requirements. This phase also aims to confirm whether there is an unmet need and, if not, to have a break clause in efforts (see Box 5 below for a tip on considering a reflection point). The core working group driving the overall TPP development effort typically leads the scoping effort, with engagement from other stakeholders at various points in the process.

Based on this overarching aim, the scoping phases' key objectives are to:

- **Understand the current diagnostic test landscape and determine whether the tests available are fit for purpose**. This step involves examining the existing tests available in a given market (e.g. the NHS) and their performance and fit within a desired use context.
- **Determining the nature of the unmet need, i.e. developing the rationale for the TPP**. After understanding the existing

landscape and its unmet needs, this step involves identifying the *nature* of the unmet need to clarify the novel test's desired features. Detailing the TPP's scope – i.e. the key features that will need to be specified and included and that will drive the primary value proposition and potentially achievable benefits – is key to this, as is distinguishing between *essential* features driving the value proposition and *desirable* features, accounting for feature combinations and where the greatest potential added value lies.

- **Further scoping work to identify key organisations and stakeholder groups that should be involved in further TPP development phases** (building on the inception phase and honing information on relevant individuals and routes for engaging them), e.g. drafting and consensus-building, as discussed in Sections 4.8 and 4.9.

Since the scoping phase is essential to confirm the need for a demand signalling TPP for novel tests, it must be pursued with rigour.

Box 5. Tip on including a reflection point and break clause

While those embarking on demand-signalling TPP development efforts may already have a good sense of the unmet need, the scoping phase's findings may ultimately negate the necessity for the TPP. As such, it is worth including a break clause or reflection point at the end of scoping to pause the process if the results suggest that developing a TPP would not add value. For instance, once the existing test landscape is mapped (or technologies in development have been horizon-scanned), the core working group developing a TPP may conclude that existing R&D progress renders a novel TPP unnecessary.

4.7.2. Putting it into practice

The scoping phase often focuses on activities that can inform a needs assessment (i.e. gap analysis) to support the aims above. This assessment helps to understand the unmet need and the case for developing a TPP, including the funding/sponsoring organisations' goals and TPP development oversight. Arriving at a gap analysis, i.e. identifying unmet needs, involves three core activities: (a) a diagnostic landscape review, (b) an unmet-needs assessment to identify key features and specifications driving a novel test's core value, and (c) an extension of the inception phase detailing who to involve in TPP development.

While the core working group leads the scoping phase, individual tasks are sometimes split between members (see Box 6 below for a tip on managing the core working group roles). For example, some members might lead on scoping the landscape of existing tests and their limitations; others might lead on detailing the unmet need and key novel test characteristics/specifications. These subgroups can come together.

Box 6. Tip on distinguishing between core working group decisions and those requiring external consultation in the scoping phase

Some TPP efforts seek external views (and even consensus) on which features to include in a TPP, not just on specifications for features. The decision to formally seek views from external participants may partly be influenced by how aligned the core working group's views are, how much certainty results from external consultations during the scoping phase and resources and timeline considerations.

4.7.2.1. Diagnostic landscape review

Identifying the test types already available as part of the diagnostic test landscape review involves mining national or international diagnostic test databases (public or commercial data sources, regulatory databases and repositories on existing tests) and horizon-scanning products that may soon enter the market (e.g. by reviewing relevant literature and patent databases). See Box 7 below for a tip on deciding whether scoping should be nationally or internationally focused.

Box 7. Tip on whether to scope the diagnostic test landscape available nationally or internationally

Remember to decide whether to scope tests only available in the UK or to look internationally, which will influence the scoping process (e.g. where you horizon scan or search). Such discussions should consider whether tests exist and whether they are suitable for use in a UK cancer-related context. Some policy efforts or national programmes to improve diagnosis may have already undertaken some form of horizon scanning in an area of interest, and existing databases may be relevant to horizon scanning. Examples include the NIHR Innovation Observatory's methods and data[45] or technology landscape analysis from MHRA's PARD[46] and the EU's Medical Devices EUDAMED.[47] However, further research is needed to assess these databases' cover of cancer diagnostics and how up-to-date they are.

4.7.2.2. Unmet needs assessment: Specifying a TPP's scope and identifying key features driving the value proposition

A range of methods (and combinations thereof) can help refine understanding of the nature of the unmet need and begin identifying and clarifying key features and specifications in a demand-signalling TPP that will drive a novel test's core value proposition. Such methods include:

- *Initial core working group expertise and perspectives* on the need for a novel test and its key requirements. This method includes *desk-based reviews of academic literature* complemented by grey literature analysis (e.g. policy documents, cancer diagnosis guidelines and technical reports).
- *Scoping consultations, interviews, or workshops with key experts* from diverse stakeholder groups to clarify and characterise the existing landscape (including its gaps and unmet needs) and gather initial perspectives on the key features and specifications necessary for a novel test.
- *Early economic modelling to understand which combinations of features and specifications in a potential novel test offer the greatest value* (see Box 8 below for a tip on how early economic modelling could help prioritisation). Although economic cost-effectiveness modelling is crucial in helping tackle areas of uncertainty, it must complement rather than substitute other scoping phase methods. Other modelling activities may also be useful for identifying key test requirements, including care pathway and capacity modelling. Early economic modelling will likely provide appropriate ranges to inform scoping and drafting discussions on possible ranges of key features. Early economic modelling can also inform acceptable trade-off limits for a TPP's specifications (e.g. accepting a sensitivity reduction of up to 'X', but only if the specificity increases by 'Y').
- *Reviewing HTA assessments of relevant diagnostic tests to identify what did and did not work.*

Box 8. Tip on managing scope-creep: Prioritising key features, focusing specifications and utilising the potential of early economic modelling

It is important to consider which features may be relevant for a TPP early so that the importance of different features (and combinations) can be weighted. There may be trade-offs between different features' requirements, e.g., technical performance versus accessibility. Early economic modelling can help complement literature-review and stakeholder-consultation insights by assessing feature combinations and associated trade-offs in different specification scenarios. It is also essential to clarify which features are non-negotiable, i.e. a specification that cannot be changed just to enable better overall cost-effectiveness. Such modelling is possible in scoping and drafting phases once certain specifications have been subject to wider consultation and are firmer, or it is clear where the evidence base is weak and likely to benefit most from modelling. Thus, early economic modelling can help reduce the risks of overly aspirational rather than realistic TPPs by creating a more robust scientific basis for prioritising test features (see Annex E for further information).

Combining initial core working group expertise, desk research and stakeholder consultation with early economic modelling can help consolidate diverse aspects of the unmet need, such as the intended test's use, clinical need, target population(s), health-system level(s) and users, with critical technical performance criteria (e.g. diagnostic sensitivity or specificity), broader health system and care-pathway-related features (e.g. accessibility, economic considerations, clinical utility, diagnostic infrastructure and laboratory capacity), and patient-related factors (e.g. acceptability, invasiveness and time to result).

During the scoping phase, stakeholders working on the TPP can decide which features need specifying in the TPP and which specifications are desirable but not essential, i.e. 'nice to have' but not critical to the core value proposition. As we discuss in Section 4.8, core features must be carefully specified according to minimal and preferred requirements. At the same time, desirable features may benefit from specifying *some* minimal requirements if possible but may also be left to the innovator's discretion. In addition, specifications must be realistic and feasible. However, it may not be possible to specify *all* features with full confidence, even when desired. For example, not all implementation challenges are foreseeable before test development. However, multiple stakeholder involvement can help ensure a better-informed process and discussion and greater foresight on possible and achievable specification types).

As introduced above, the scoping phase can utilise diverse methods. However, methodological choices must balance rigour with pragmatic considerations determined by urgency, stakeholder engagement, existing evidence/uncertainty about the novel test's requirements, and the resources/timeframes possible. Methodological decisions must evaluate different evidence types and their validity and reliability, not overly rely on expert opinion.

4.7.2.3. Detailing the organisations and individuals who should be involved in later TPP development phases

In early TPP development, the core working group and those hosting, governing and overseeing the process will have identified the key stakeholder groups to involve. During the scoping phase, more thought needs to be given to stakeholder involvement, particularly in identifying the diversity of individuals and organisations whose views are necessary and desirable for later TPP development phases. See Box 9 below for a tip on planning for stakeholder engagement.

Box 9. Tip on planning for stakeholder engagement to support TPP development

Consider which individuals and organisations you want to engage with and on what aspects given their expertise (i.e. do not ask everyone about everything but be cautious not to pre-judge entirely what different organisations and individuals can relate to). Prioritise the key issues you would like specific stakeholder views on and, time permitting, additional aspects you may want to explore with them.

Following diagnostic-landscape mapping and further scoping work on the unmet need, developing a stakeholder engagement strategy and plan is essential. Such a plan should consider:

- Which organisations and individuals to involve in drafting and consensus-building.
- Which issues to explore with them (i.e. considerations of the types of issues, conceptual-feature categories and the features different individuals/organisations can best input on).
- How (see Section 4.8 on 'Drafting' and Section 4.9 on 'Consensus building').

To achieve this, the core working group can lead on creating a database of relevant individuals and organisations to engage from the following categories: academic, clinical academic and research professionals; healthcare and diagnostic laboratory expertise; industry; patient, carer and public perspectives; research and innovation funders in the public sector and charities; and regulators, HTA expertise and policymaker perspectives.

This database can be complemented with information on conceptual feature categories to consult them on, specific issues and areas of uncertainty to explore to help determine TPP specifications, engagement methods (e.g. commentary on a TPP draft, interviews, workshops and surveys) and an engagement timeline (see Box 10 below for a tip on rightsizing scoping methods).

Box 10. Tip on rightsizing scoping methods

The scoping process must be rigorous to ensure that (a) there is a real unmet need, (b) accessible tests do not already respond to this need, and (c) the key requirements for a novel test are specifiable. Overall, using a mixture of appropriate methods and expertise helps ensure the necessary rigour and robustness. However, there is a need to 'rightsize' methods to ensure feasibility without compromising rigour. For example, decisions about conducting systematic literature reviews or rapid evidence assessments to specify the nature of the unmet need and the novel test's requirements must be carefully considered. If recent systematic reviews exist and stakeholder views on the nature of the unmet need are closely aligned, then a rapid evidence assessment of the scholarly and grey literature that has emerged since the last systematic review may suffice. Suppose there is clear evidence of requirements related to a test's technical performance (e.g. diagnostic sensitivity and specificity and sample requirements) but less on wider system-related factors (e.g. workforce acceptability, patient acceptability and accessibility). In that case, the scoping phase may need to dig deeper into the latter. If there are gaps in research evidence (as indicated by the literature and expert opinion) on the types of unmet needs and the key test requirements, then modelling may help shed light on the gaps.

4.8. The drafting phase

4.8.1. Aims

The drafting phase of TPP development aims to produce an initial TPP draft by consolidating findings from the scoping stage. The initial draft is then refined based on feedback and engagement with relevant stakeholders by gathering views that confirm or challenge the initial draft specifications and/or provide additional information on areas needing refinement. Economic modelling can also help during the drafting phase to help determine desired feature specifications that are challenging to specify based on desk research and stakeholder consultation alone. This stage involves iteratively developing an initial draft into more mature ones via stakeholder consultation, commonly between two and four drafts (the fourth being the final TPP).

Building on these overarching aims, a draft TPP's objectives are to:

- **Provide specifications for diverse features in a table format**, grouping features by conceptual category (as introduced earlier: see Table 1 and Annex G).
- **Provide contextual information that precedes the table**.

4.8.2. Putting it into practice

4.8.2.1. Providing specifications for diverse features in a table: initial draft and subsequent iterations

As an initial step, it is essential to ensure what a feature is about and clearly explain its specifications, as any ambiguity will compromise the quality of stakeholder engagement. As such, a draft must be reviewed by *at least* the core working group members. There must be clarity for patient and public representatives and professional expert stakeholders, for which a glossary of features and terms/measures used in the specifications can help.

For features for which a demand-signalling TPP provides upfront specifications, those involved must consider whether these specifications cover minimal requirements only or include optimal/preferred ones, too. What stakeholders consider 'optimal' or 'preferred' can also vary. In this case, the TPP must be transparent about any differences in opinion between stakeholder groups (even when developing an initial draft). While the TPP may fully specify some features and leave others to the innovator's discretion, it is still important to list the latter to help sensitise the innovator to the issue, regardless of whether they establish a specification.

Clarifying the reasons for a particular specification supports clarity and transparency, referencing the underlying evidence to demonstrate the specification is evidence-based and carefully considered. Information on the quality of the evidence base supporting a TPP's specifications is also important to contextualise the justification and reasoning for those consulted as the TPP's development evolves. It is equally important to clarify what cannot be specified (i.e. due to lack of evidence) or where specifications derive from modelling rather than real-world data and evidence.

A TPP should also clarify what is *unwanted* in a novel test. For this reason, the TPP document should detail how each specification was arrived at, the evidence supporting it, and any surrounding uncertainties (see Box 11 below for a tip on acceptable evidence levels).

The drafting phase can also explore acceptable evidence types/levels that innovators responding to a TPP must provide information on as part of product development, i.e. demonstrating that a novel test meets TPP requirements. However, views on whether TPPs should or should not engage with this aspect differ since it may be beyond a TPP's remit, especially as regulatory and HTA guidance often fulfils this role.

Box 11. Tip on deciding whether a TPP should specify acceptable evidence levels

Sometimes, a TPP may also signal the evidence types that innovators should provide to support their post-development product claims about specific features (and in response to a TPP's specifications). For example, a TPP may indicate whether evidence supporting such product claims should come from a randomised controlled trial or a quasi-experimental design and whether a specific sample size and/or sample diversity is required. An innovator may also refer to existing standards to support some product features. Unlike the licensing-based pharmaceutical approach, the primary regulatory route for medical devices is standardisation pathways, affecting what evidence is required and from whom. This can affect product development choices. For example, whether a TPP should specify required evidence levels may depend on a planned TPP's use case, the strength of existing evidence on specific feature requirements, the device type and the risks it presents, and the feasibility of achieving specific evidence levels. It will also depend on how far regulatory /HTA agency documents specify evidence levels. Those developing a TPP may want to point innovators to information on regulatory and HTA requirements for acceptable evidence types for product submissions, where available, rather than seeking to detail them in the TPP.

Table 5 presents an example template to guide drafting (adaptable to specific cases) using one feature category – analytical performance – to illustrate the principles.

Table 5. Example template for drafting a TPP illustrated through one feature category (analytical performance of a Target Product Profile); Use Case: Ovarian Cancer Diagnostic Test in Primary Care to Improve on CA-12548

Feature category: Analytical performance	Minimal requirements	Preferred (or optimal) requirements	Undesirable characteristic	Rationale for specifications provided
Stability of samples	<8hrs room temperature; <24hrs 2-8°		Requires immediate refrigeration	Primary care settings are burdened. Extra steps not in the course of usual practice are highlighted.
Stability of reagents	Minimum 14 days	Up to one month (30 days)	14 days	The expectation of making a diagnosis in primary care after sampling is two weeks; however, longer delays occur because of low capacity.

Feature category: Analytical performance		Minimal requirements		Preferred (or optimal) requirements	Undesirable characteristic	Rationale for specifications provided
Sample volume		Between 50 mL and a maximum of 200mL		Ideally 50 mL		This is fairly standard for most blood-based tests.
Need to repeat the test	Need for repeat sample collection should be minimal (<5%)	Need for repeat sample collection should be rare (<1%)	Test repetition highly undesirable in the primary care setting	Primary care settings are burdened. Extra steps not in the course of usual practice are highlighted.		
Internal quality control		Two levels tested daily; results within acceptable control range as determined by an appropriate internal laboratory quality control scheme				
Precision		Coefficient of Variation (CV) <10% across the measurable range		CV <4%		This level of precision is desirable clinically and would be as good or better than CA125[49] (the commonly used blood test that might indicate ovarian cancer).
Sample preparation		At innovator discretion		At innovator discretion		A variety of tests and platforms may be developed; being prescriptive may be a disincentive for innovators.

Feature category: Analytical performance	Minimal requirements	Preferred (or optimal) requirements	Undesirable characteristic	Rationale for specifications provided
Analytical Specificity	Cross-reactivity studies are performed to demonstrate that the test does not react with related pathogens, high-prevalence disease agents, and normal or pathogenic flora that are reasonably likely to be encountered in a clinical sample			It is appropriate to conduct an in-silico analysis of published genome sequences using the assay's primers and probes.[50]
Analytical Sensitivity	The capability of the method to distinguish between two close concentrations of the target marker/analyte			
Calibration	Calibration traceable to a recognised standard			Not meeting national or international standards is unacceptable.
Linearity	Linearity on dilution for samples with high analyte concentrations above the upper limit of the measuring range. The ability to provide measured quantity values directly proportional to the value of the measurand in the sample.[51]			
External controls[52]	Must meet UK Conformity Assessed (UKCA) Marking requirements.	Meets UKCA, EU, and USFDA requirements.	NA	Not meeting national or international standards is unacceptable.[53]

After the initial draft, those driving a TPP's development (i.e. the core working group) usually elicit stakeholder feedback and consultation. While there is no gold standard for evolving TPP drafts through consultation, the process can include one or more of the following:

- Sharing drafts for free text comments on feature specifications.

- Inviting further written comments from stakeholders on areas of uncertainty where feature specification has proven challenging in the scoping and early drafting phases.
- Eliciting feedback through interviews and workshops.
- Posting drafts on a website for wider public consultation.
- Using Delphi-inspired consensus surveys (a method that uses several rounds of questionnaires so that a group of experts can work towards a consensus by discussing the previous round's answers before moving on to the next).[54]

While pragmatic stakeholder-engagement methods should be pursued, it should not be at the expense of sufficient methodological rigour. This is also relevant to the consensus phase (see the next section) since drafting and consensus iterate (see Box 12 a tip for advice on deciding who to engage during drafting). It is essential to consult stakeholders for feedback at each drafting phase to evolve them. Ideally, the more comprehensive, engaging and systematic the method, the more rigorous the feedback, e.g. in-person workshops instead of online comments on a document posted on a website. However, some stakeholders may be unable to contribute to more systematic (and time-consuming) engagement types, so flexibility is needed.

Since representatives from different stakeholder groups contributing to TPP development will have limited time and capacity, it is essential to consider the best way to engage specific individuals/groups to elicit the insights and information required in practical ways. In addition, the financial resources available for TPP development, the envisaged urgency/acceptable timeframe, and the nature of the preexisting evidence base will also influence decisions about the most appropriate stakeholder engagement methods. For example, even if a workshop with many healthcare professionals may be ideal for discussing a draft TPP and collecting feedback on specifications, busy healthcare and diagnostic laboratory schedules may mean that options for one-on-one interviews/consultations or comments on written drafts may be more practicable. Furthermore, there may be differences in the mechanisms through which different stakeholders prefer to engage, e.g. face-to-face versus virtual.

Box 12. Tip on deciding who to engage on what issues during the drafting stage

The most suitable stakeholders to involve will vary depending on the use case/TPP effort (see Section 4.2). The core working group will likely all be involved in developing the first draft, but targeted outreach to other experts in various stakeholder groups can provide feedback on specific features and feature categories. Examples include pathology lab managers, academic experts and industry providing feedback on technical performance-related specifications, clinicians providing feedback on features related to target users in a health setting and on requirements for the test to fit with clinical workflows, and patient/public voice representatives to provide feedback on specifications related to patient experience and acceptability. The core working group should decide who needs to be consulted on different aspects of the draft and ensure widescale input to minimise the risk of bias.

Those leading a TPP's development must establish clear boundaries of acceptable rigour when choosing consultation methods during drafting. For instance, while bringing different companies together to elicit industry views on the specifications may be most practical, competitive and commercial sensitivities could compromise how much they are willing to share. See Box 13 below for a tip on planning for balancing consultation needs with feasibility.

Box 13. Tip on planning for uncertainty during the drafting phase

At the inception stage, the core working group leading TPP development must factor in the possibility of uncertainties (emerging needs). Depending on the quality and clarity of the evidence base for specifications and how aligned stakeholder views are (or are not) at the drafting stage, one or more consultation rounds may be necessary, and it is prudent to set a cap. Agreement on who will ultimately decide on a draft is also needed.

4.8.2.2. Providing supportive contextualising information to draft a TPP table

It is helpful to provide contextual information in the features and specifications table to ensure that TPPs are clear and transparent. Figure 4 shows the minimum set of considerations that a TPP document should cover.

It may also be helpful to summarise information detailed in the table of features and association specifications in the text preceding the table, focusing on the key features and information about them central to the value proposition. Such background can help set the scene for the more detailed information that follows.

It is also worth considering whether the TPP audience would benefit from information on the care pathways the test is designed to work within (and improve) and a summary of the existing tests' limitations the TPP seeks to address.

Figure 4: Core elements of a TPP report

Title page

Acknowledgements

Contextual information:

- Why the TPP was developed- its purpose
- Who the target audience for the TPP is
- A glossary of terms to ensure accessibility (e.g. explaining concepts, features, qualitative specifications and quantitative measures used in the TPP)
- Who was involved in developing the TPP
- The approach and methods used to arrive at the desired feature specifications (where applicable)
- Limitations in the approach and in the resulting TP

TPP tables with feature and specification related information

A discussion section with information providing full transparency on the reasons behind chosen specifications

References

Supportive materials

4.9. The consensus exploration phase

4.9.1. Aims

The main objective of the consensus-exploration phase of TPP development is to arrive at a final TPP whose feature specifications are agreed on by stakeholders, providing a clear demand signal to innovators. It is important to reiterate that drafting and consensus-building are not sequential or delineated phases. Instead, their boundaries are fluid, involving cross-iterations to refine the drafts. Those developing TPPs often seek consensus between drafts to help evolve them, i.e. strengthen each TPP draft's refinement process. The following key objectives relate to this:

- **Establish desired consensus thresholds/ agreement** levels and evaluate whether they have been achieved as the process evolves (either overall, within or between specific stakeholder groups).
- **Measure consensus and provide transparency on agreement/ disagreement levels regarding specifications for TPP features**.

Putting it into practice

4.9.2.1. Establishing desired consensus thresholds/ agreement levels before pursuing consensus-building activities

There is no golden rule on what constitutes consensus, which varies across consensus exploration studies (e.g. studies using Delphi, a method frequently employed to explore consensus).[19-26,55] However, consensus commonly refers to 'the percentage of agreement based on a predefined cut-off, central tendency, or a combination of both' (Nasa and Juneja 2021, p. 120).[56]

Although this topic needs further research, an exploratory analysis of six diagnostic TPPs using Delphi methods[19,20,22-25] suggests that 50% or 75% agreement are relatively common thresholds, with consensus sometimes lower in earlier drafting phases than in the latter. According to a systematic review of a random sample of 100 Delphi studies (not TPP-specific), the median threshold is 75% with a range of 50–97%, showing the diversity in thresholds.[55] Whatever thresholds are used in a consensus effort must be clearly defined in any final TPP (see Box 14 below for a tip on arriving at consensus thresholds).

Box 14. Tip on arriving at consensus thresholds

We recommend that the core working group agrees (and/or confirms) the threshold that will constitute consensus (if not already decided upon at the inception phase of TPP development) and the action to be taken if no consensus is reached through external consultation. This may include deciding whether only the core working group will make final decisions on specifications in such cases through a 'majority' voting approach or whether specifications will be left as they are based on the most recent consensus exploration round, with full transparency about where consensus was lacking.

When considering thresholds, limiting the number of consensus rounds in TPP development is also essential. Based on the TPP sample we analysed to explore consensus thresholds in previous TPP development efforts, the desired consensus thresholds tend to be higher if consensus is only sought once, usually before the final TPP is drafted (e.g. 70–75%). If consensus is sought for multiple drafts of the same TPP, the first consensus threshold is often lower (e.g. only above 50%) and focused on the nature of the characteristics under consideration. In contrast, later drafts typically seek higher consensus thresholds (e.g. above 70%) and revolve around more specific criteria regarding minimal and optimal specifications.

4.9.2.2. Exploring consensus and ensuring transparency on agreement/disagreement levels for TPP feature specifications

After establishing a consensus threshold, exploring consensus levels on TPP feature specifications is appropriate.

Some of the different ways of exploring consensus include:

- Systematic surveys using Delphi methodology (which typically uses Likert scale survey responses to gather insights on agreement levels with a specific statement/ feature/ specification).

Box 15. Tip on maximising consensus-building through flexible engagement approaches

Tailoring consensus-building to specific stakeholder communities can support the feasibility and quality of stakeholder engagement. It is vital to ensure contributors clearly understand the features and their specifications. This may necessitate different versions of TPP drafts for different stakeholder groups, e.g. a draft with more technical terminology for academic experts and one with lay explanations for patient and public contributors, supporting meaningful engagement and accessibility for all involved. An alternative option is one draft with additional tailored information and terminology/content clarifications for different contributors. Those participating in the consensus phase must understand how feature specifications were decided (i.e. the evidence base behind certain specifications and how this translated into the chosen specifications).

Although views differ on whether to include industry in the consensus stage, there is agreement on the importance of consulting industry as a critical stakeholder in the overall scoping and drafting phases.

- Interviews with experts to help refine specifications.
- Guided consensus-exploration workshops.
- A more general request for comments on drafts (via free text).

The methods to pursue should be decided on based on how different stakeholder groups can best engage, rigour and pragmatic time/resource considerations. See Box 15 above for a tip on how to ensure appropriate engagement methods at the consensus-building stage.

Regarding how the process evolves, consensus can be sought internally in the core working group before consulting a broader set of stakeholders to evolve later drafts. Consensus rounds can be conducted for every draft, some drafts, or one draft only, usually the final TPP draft (see Box 16 below for a tip on deciding how many consensus rounds to pursue). It is common to have between two and four drafts, the fourth being the final TPP (see Annex A).

Box 16. Tip on determining how many rounds of consensus to pursue and what to seek consensus on: Balancing planning, pragmatism and uncertainty management

Early in TPP development, consider how many consensus rounds will likely be feasible given limiting factors and pragmatic considerations, e.g. the time and resources available for TPP development. Build some flexibility for dealing with uncertainty in case of more uncertainty/disagreement about specifications as the process evolves than initially anticipated. For example, there may be sustained disagreement over multiple consensus rounds during the consensus-building process, potentially affecting how disagreement levels change. Pragmatic considerations can also play a role in methodological decisions for exploring consensus (e.g. formal surveys versus more practical workshops or interview-based versus questionnaire-based consultation). Decide also how to target specific stakeholders to explore consensus around aspects within their expertise area (e.g. a patient-voice representative is unlikely to be well suited to highly technical specifications on a test's operating conditions). However, be careful not to pre-judge who can contribute to what too prescriptively; it may be desirable for some feature categories to explore consensus with diverse stakeholder groups involved with TPP development, while consultation with a subset of stakeholders may suit others better. The core working group will need to decide on this before implementing consensus exploration.

As introduced earlier, Delphi surveys are a standard, robust method used in the consensus phase. Delphi surveys typically use Likert scale responses, occasionally including free-text options (i.e. qualitative, narrative data) for when stakeholders disagree on a feature specification included in a TPP and scope at the end for stakeholders to comment if they feel something important was not covered in the Delphi survey (see Box 17 below for a tip on using both quantitative and qualitative insights in consensus building and final decision-making). The consensus exploration must be based on clear specifications, and providing consultees with opportunities to give feedback on the clarity can be helpful in this regard.

Although Delphi survey processes are often considered the gold standard, implementing them in full can be expensive. Hence, Delphi-inspired or 'Delphi-light' approaches adopt Delphi principles but may not involve full Delphi surveys (e.g. consensus workshops) are also used. The resulting TPPs flag information relevant to consensus or uncertainty issues. Moreover, survey-based approaches do not necessarily work for all stakeholder groups. Some stakeholders may prefer consultation via interviews or workshops, for example. Since survey-based approaches also depend on a sufficient sample size, they may not be optimal for all stakeholder groups, particularly smaller ones (e.g. from a small number of regulatory, HTA or policy decision-makers).

Box 17. Tip on utilising quantitative *and* qualitative consensus-building approaches

Consider qualitative *and* quantitative methods when conducting and interpreting consensus-building efforts. It is important to understand views of the different stakeholder groups consulted and the reasons behind those views. Those developing a TPP may have more representation from some groups than others and engaging with quantitative data is informative in terms of understanding the proportional weight alongside the strength of opinion. Conversely, it is important to understand the meaning of a numerical value (e.g. rating) through more qualitative means such as free-text comments.

The above section discussed various methods and approaches for exploring and seeking to reach a consensus. Based on the insights gained through stakeholder consultation, the best options to pursue in a TPP development effort will depend on the following:

- How many consensus rounds can be accommodated (i.e. more consensus rounds will likely be more time-intensive, necessitating lighter-touch methods for some rounds).
- What the agreement threshold is (or should be) for defining consensus. For example, requiring higher consensus figures may necessitate fewer consensus rounds or consensus across particular groups of stakeholders.
- Which stakeholders participate in the consensus phase and their engagement preferences.
- The time and resources available.
- Consensus fatigue (i.e. the maximum number of consensus rounds stakeholders are willing to participate in).

4.9.2.3. Finalising the TPP

The core working group leading the TPP development effort can be tasked with final decision-making, including those related to specifications where consensus levels proved lower than hoped. Where there is no consensus for particularly challenging or controversial specifications after the maximum number of consensus rounds, the core working group may want to pursue additional, targeted consensus engagement with relevant topic experts. Final consensus meetings are another way to invite relevant field experts to discuss and decide on inclusion/exclusion where desired consensus thresholds were not previously achieved. In this case, inclusion is decided based on votes within the specific field expertise group for a given characteristic.

If consensus cannot be reached on all desired specifications, this must be made clear in the final TPP (see Box 18 below for a tip on finalising a TPP with clarity and transparency). Consensus should be sought but not forced. All consensus-building outcomes, as well as their processes, should be transparently

documented in any final TPP. Therefore, a final TPP should explicitly clarify the following:

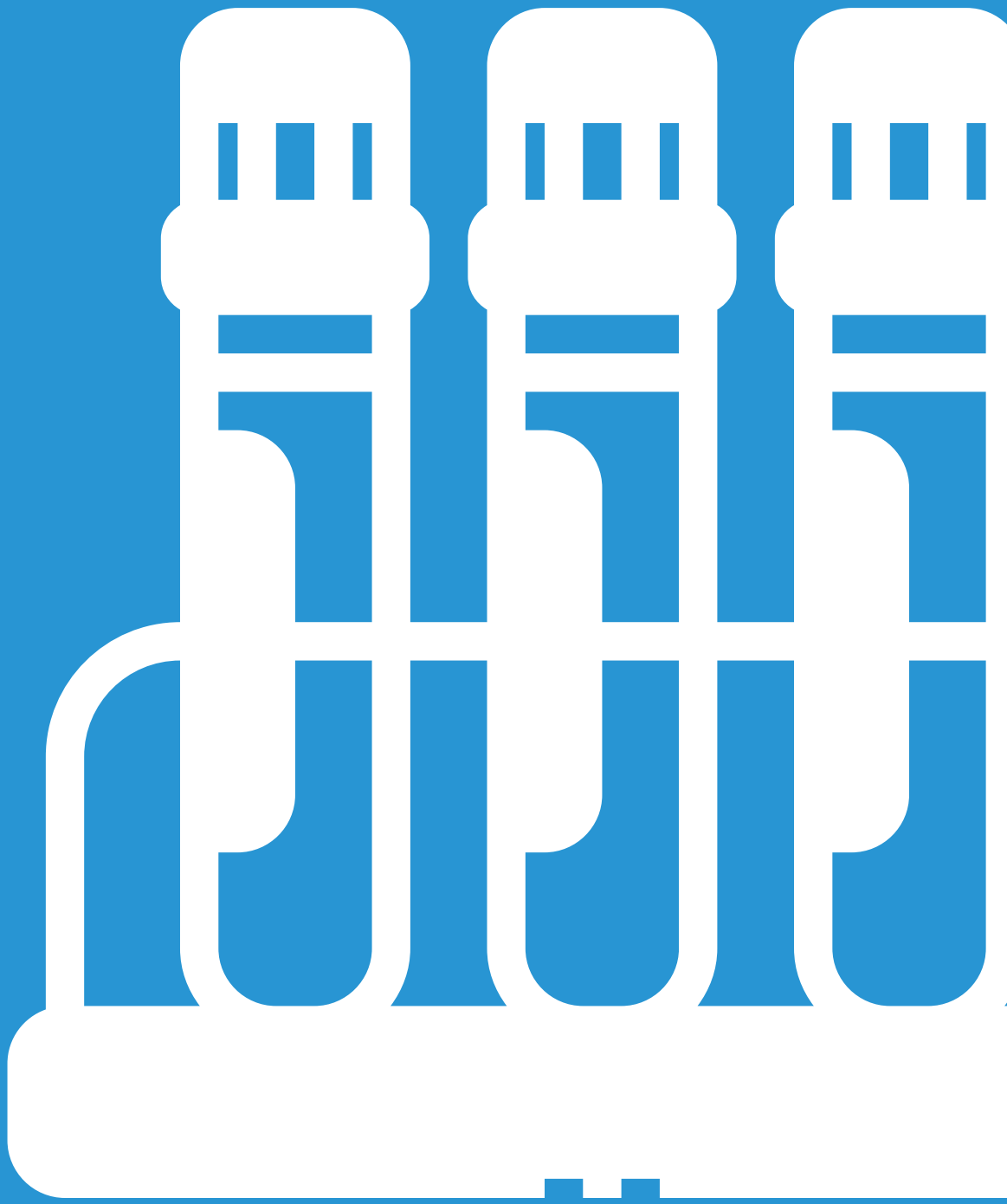
- The consensus levels used and the reasoning/rationale for them.
- Whether consensus was sought between or within groups, and why.
- Any minority opinions and the rationales behind them (which may provide helpful nuance if TPPs evolve due to new evidence or technological developments).
- Justifications for why and how specifications for which consensus was not reached were included in a TPP. Even where consensus is not achieved, the core working group must still finalise the process.

Box 18. Tip on finalising the TPP with clarity and transparency

The core working group will likely be tasked with making ultimate and final decisions on specifications and presenting and explaining them. The consensus phase may not yield the chosen consensus threshold for all desired features. This possibility must be considered when choosing a robust but pragmatic approach to specifying minimal and/or optimal/preferred features. Transparency in final reporting is key, especially on how consensus was sought (via which methods and with which types of contributors), whether it was reached or not for various features, and whether there were higher levels of uncertainty in specifications for some features than others. If there are areas where consensus is not reached or where consensus is seen as less important by a core working group, this must be made clear alongside associated reasons. Consensus may matter for some core features more than others, where flexible specifications may be possible, and a lack of consensus can even inform flexible final specifications.

Even if the core group makes final decisions and provides specifications when a consensus threshold is not reached, the TPP must communicate this transparently. As part of this process, consider whether different stakeholder groups' inputs to the same specifications will be 'equally weighted' and whether to seek consensus across *and* within groups. In some cases, capturing consensus within specific groups or panels may be just as important as overall consensus. Be transparent in cases where different groups' views are or are not aligned.

5. In reflection



5.1. This project's key contributions to the knowledge base

This study is unique in exploring diagnostic TPPs in the cancer field, where they have not yet (to the best of our knowledge) been used to signal demand for innovation. It considers a novel approach to help align supply and demand. It is a robust and timely analysis combining different research methods, including harnessing the expertise of numerous individuals across diverse stakeholder communities. It will interest various organisations and individuals who have a stake in improved cancer diagnosis and better patient outcomes.

This work has focused on advancing knowledge on the potential of diagnostic TPPs for cancer to serve as demand-signalling documents to innovators and inform future innovation efforts. The insights gained through the generous sharing of perspectives, expertise and experiences by the 103 individuals who contributed to the project and from the literature consulted have surfaced multifaceted considerations related to the important features to consider in efforts to develop diagnostic TPPs. The research has also contributed to practical and actionable insights on the best approaches and methods to employ in future stakeholder-inclusive TPP development.

Regarding a novel test's features, our research flags the importance of a balanced approach that considers the diversity of influences on developing successful innovations and their adoption while also highlighting the need to prioritise which features (within different categories) are core to a TPP's and any resulting test's value proposition. The economic modelling tool we developed is intended to help those developing TPPs arrive at specifications that can optimise a novel test's value.

The insights gained also reveal the importance of TPP development processes' adaptivity to specific contexts. To this effect, the research team established a guide detailing an overarching approach to diagnostic TPP development and presenting a range of possible activities and methods that can help support the process (see Figure 5 below for a summary, reflecting the different phases described in Sections 4.6–4.9).

This project's findings also bring inclusiveness, rigour and feasibility concerns to the forefront, as reflected in our recommended TPP development principles, process, and associated advice. Our research highlights the importance of ensuring feasible and accessible ways to mobilise expertise and experience across diverse communities in academia, research, healthcare, laboratories, industry, regulation, health technology, health economics, policymaking (including experts who understand the payer perspective), patients and the public. The TPP development process must pursue rigour within pragmatic considerations, clarifying where there is flexibility in approaches that do not compromise rigour but ensure a realistic process and where such compromises are impossible. Engaging all desired stakeholders can be challenging due to practical issues and perceived risks (e.g. perceptions that engaging in a TPP process commits them to decisions outside that process).

Our research acknowledges that a TPP cannot achieve everything in efforts to align the development and supply of innovative diagnostics with demand and willingness to pay. As specification documents, TPPs are only a resource – albeit an important one – in wider health-system innovation efforts in the cancer space. Therefore, those embarking on developing diagnostic TPPs for cancer need to consider how to maximise the traction and impact of any TPP to be developed, including considering how the TPP complements and aligns with broader health system efforts to improve early cancer detection and diagnosis. An example is how a TPP will relate to NHS cancer innovation programmes and funding streams (e.g. the NHS England cancer innovation programme and SBRI Healthcare funding calls for cancer diagnostic innovation), the work of cancer alliances and Academic Health Science Networks (AHSNs), the research conducted in cancer research institutes across the country, public and not for profit research funding programmes including CRUK's wider strategy and manifesto, and MHRA and NICE refinements in regulation and HTA assessment over time.

Finally, this report has highlighted that innovators often see global markets as an incentive; therefore, TPPs focused entirely on a UK market may risk limited traction. If a TPP primarily focuses on a UK market, those developing it should still consider how key international differences may affect how far the feature specifications 'hold up' against specificities within international care pathways, payer/markets, and regulatory and HTA requirements.

5.2. Limitations

Despite this research's significant strengths, it is important to consider the following caveats when interpreting the findings.

First, the desk research builds on insights from diagnostic-test applications other than cancer, given that (to the best of our knowledge and as indicated via consultation) there are no publicly available, demand-signalling TPPs for cancer applications. Stakeholder consultation confirmed that many features considered within infectious disease applications (where diagnostic TPPs have primarily been used) would also be relevant for cancer. That said, there are likely to be some additional features that need consideration in a cancer-use context, especially given that many (although not all) TPPs in other areas have referred to in vitro diagnostics and that other types of tests (including multi-component platforms, imaging tests and Artificial Intelligence [AI] and digital-technology-informed diagnostics) have a role to play in cancer. As far as possible within this work's scope, we sought to explore the unique considerations involved, which we share in Annex G as a foundation for future work in this area.

Second, this work aimed to develop a 'tumour-site agnostic' guide focused primarily on considerations and options for developing a diagnostic TPP for cancer. While this is important in advancing and informing future bespoke efforts, future initiatives to develop bespoke TPPs for specific cancer sites, test types and use cases will likely reveal additional pertinent considerations, building on and evolving this work's insights.

Third, while we engaged with a diverse range of stakeholders through the project, future efforts to develop bespoke diagnostic TPPs will benefit from involving additional expertise on specific cancers and test types. For example, although we gained insights from individuals experienced in payment/procurement realities in the NHS, including via roles in policymaking bodies and regional health networks such as cancer alliances, we did not hold separate consultations with diverse payers such as trust-level (i.e. a unit within the NHS that serves a particular geographical area or has a specialised function like an ambulance service)[54] financial directors or integrated care system budget holders, due to resource and time limitations associated with our work's scope.

Related to this, our work focused on applicability in the UK context. As innovation incentives span geographical boundaries, we cannot claim to have developed a guide that reflects all potentially relevant influences on TPP development aimed at signalling the demand for tests relevant to markets outside the UK.

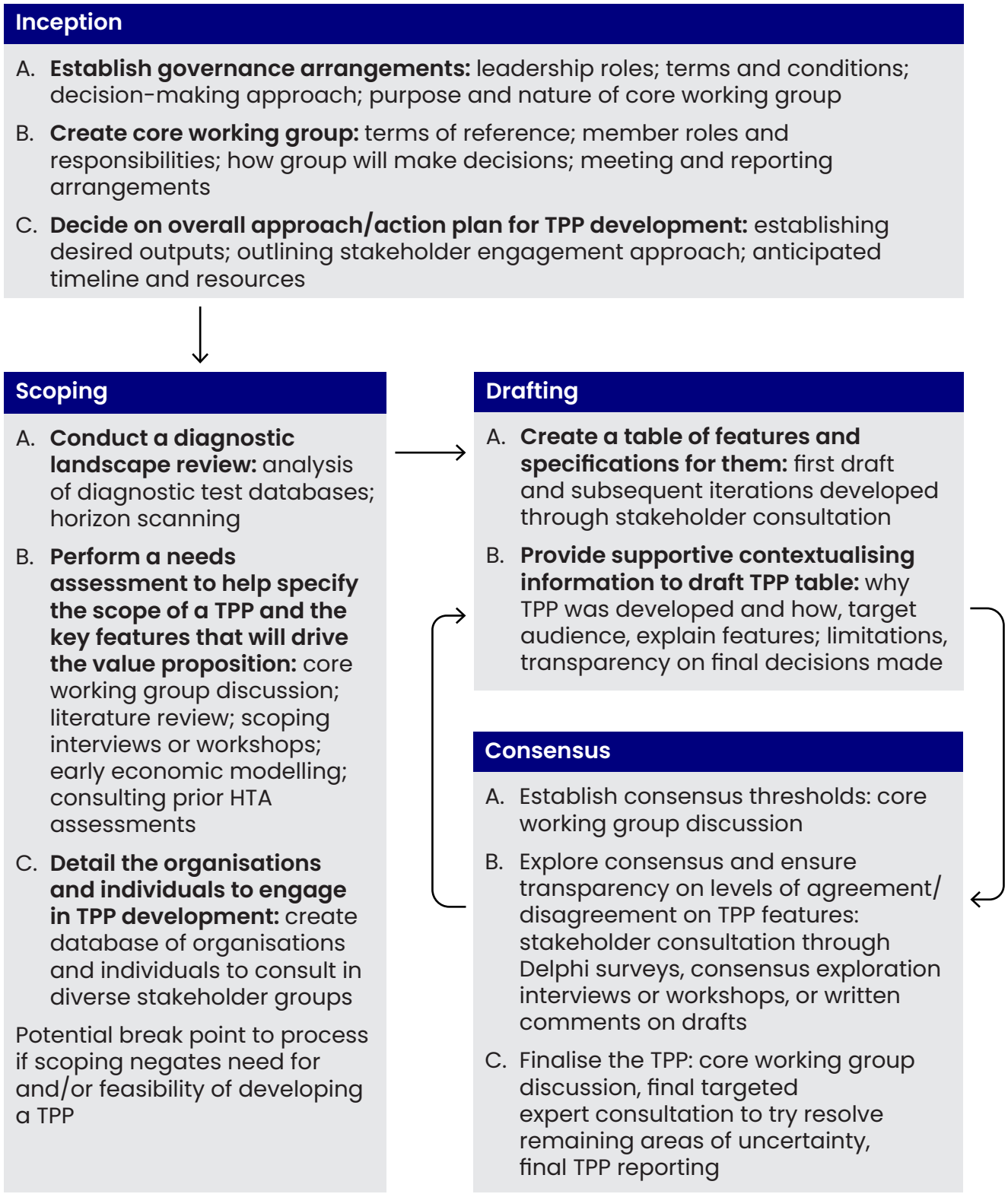
Finally, this work is based on a combination of desk research and stakeholder consultation. Given the project's scope, the desk research was exploratory but targeted. It covered a combination of research on diagnostic TPPs and analysis of a sample of diverse TPPs. Coupled with the breadth and depth of our stakeholder consultation, we are confident we have arrived at robust, well-rounded and unique insights. However, we cannot claim to have analysed all documented evidence on the topic.

Despite these limitations, we hope that the balance of breadth and depth of issues explored in this research provides a helpful resource and a practical guide for decision-makers and broader stakeholders who may be involved in leading future TPP development efforts.

5.3. Towards a future research agenda

Future TPP development efforts will no doubt have value in refining the insights developed through this work and help continue building a body of evidence on the nature of TPPs best

Figure 5. An overview of activities integral to TPP development



suited to UK cancer diagnostic development efforts. Important considerations for a future research agenda identified through the research for this project include:

- **Which TPP use cases to prioritise**: We highlighted a series of criteria to consider when prioritising where TPPs for cancer might add the most value and which use cases to develop cancer diagnostic TPPs for. There is a need to build on these insights and consider the types of prioritisation processes and methods to adopt in decision-making, perhaps in consideration of established principles and practices, such as those of the James Lind Alliance Priority Setting Partnerships[57] that inform research prioritisation, and adapting the principles to a TPP prioritisation context. Other methodologies, such as multicriteria decision-making and consensus exploration, can also help inform prioritisation.
- **Clarifying the terminology used to describe diagnostic features**: We identified a need to develop the terminology used to describe different diagnostic test features relevant to TPPs to achieve greater consistency and harmonisation across diverse efforts and to prevent inconsistent interpretation. This process can also help reflect on the robustness of different types of features that can speak to similar characteristics (e.g. analytical sensitivity versus positive predictive value).
- **The role of EEE in TPP development**: Future work should focus on applying the framework to a real TPP. It would be helpful to test how useful, understandable and usable the tool is to different stakeholder groups. We anticipate that its application in practice will require the input of individuals with health economic expertise, as we recognise that each value proposition will be unique and may require an adapted set of considerations for the early modelling exercise. Furthermore, the tool has been developed with a UK NHS focus in mind, using NICE decision-making criteria. While we explain the guiding principles, consideration of and adaptation to other local country contexts will be necessary for TPP development for other countries; this is an important avenue for future research, given the international remit of diagnostic developers.
- **Advancing understandings of features relevant for diverse diagnostic technology types**: Future research is also needed to advance insights on the feature types that may be relevant across a broad range of tests. As discussed earlier in the report, most insights into TPP features come from the in-vitro diagnostics space. With science and technology advances unfolding rapidly, further work is needed on additional features specific to multianalyte platforms, imaging, multicomponent tests, and digitally enabled diagnosis.
- Research on relevant but less-studied features to specify in a TPP: Further research is also needed to consider how features that have been comparatively neglected in past TPP efforts can best feed into future initiatives to develop diagnostic TPPs for cancer and beyond. Examples include considerations about how a test might fit with other tests in a care pathway; conditions in real-world rather than lab settings that can affect performance; appropriate proxy measures for clinical utility; explicit attention to features that matter for patient acceptability, accessibility and experience, including in terms of how the test needs to perform to mitigate inequalities; and considerations of routes to market and cost-effectiveness as opposed to only price.
- **Understanding evidence needs to ensure confident and robust feature specifications in an evolving regulatory landscape**: In the UK (and Europe), the primary regulatory route for diagnostics operates through standardisation and conformity assessment, with differential requirements according to the risk category of the medical device in question.[58,59] This can impact the evidence required on test performance (and by whom) and affect product development choices, such as limiting device functionality to remain in a lower-risk category or otherwise reducing potential evidence requirements. Keeping informed about the evolving regulatory landscape will matter for future TPP development efforts, and research has a role in generating evidence related to appropriate regulation.

- **Evolving insights on optimal governance and management of TPP development efforts**: Our research has identified limited evidence on the governance of TPP development, and further work is needed to understand the benefits and limitations of different governance and management model choices (e.g. in terms of the nature of hosting institutions, the sizes of core working groups, and financial governance for potentially ceasing TPP development if scoping reveals an absence of need).

5.4. In conclusion

The ultimate aim of any TPP is to develop better diagnostic tests that reach the health service and benefit patients by enabling earlier and/or better diagnosis and improving chances of timely treatment and improved patient outcomes. The ultimate end goal must be kept in mind from the outset of any decision to embark on a TPP effort. Stakeholders deciding on whether to develop a TPP and which TPPs to prioritise must go beyond clinical-need considerations for a novel test TPP to address the viability of demand and willingness to pay. Key decision-makers in a health system must be engaged in early discussions to help prioritise which TPPs should be developed, given policy and NHS priorities in the cancer diagnosis space and funding programmes for purchasing tests. This also calls for evaluating and learning from TPP development efforts to help understand what works, why and how across diverse diagnostic contexts.

This project addresses the scarcity of evidence on tools that can help inform the development of fit-for-purpose, innovative cancer tests. Our guide is intended to inform future practical efforts to develop bespoke diagnostic TPPs for specific cancer sites, diagnostic test types, use cases and settings. In doing so, we hope to support broader health system efforts focused on early and improved cancer detection and diagnosis, ultimately improving patient prognosis and outcomes.

Although the core focus of our work was on cancer, many of the insights gained, especially those related to developing a robust TPP and the possible approaches and methods, may apply to other clinical areas and contexts. We hope this report is useful for both the cancer community and wider diagnostics stakeholders across diverse clinical areas.

References

1 Cocco, P., Ayaz-Shah, A., Messenger, M. P., West, R. M. & Shinkins, B. 2020. 'Target Product Profiles for medical tests: a systematic review of current methods'. *BMC medicine* **18**, 1-12.

2 Sung, H. *et al.* 2021. 'Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries'. *CA Cancer J Clin* **71**, 209-249. As of 22 March 2024: https://doi.org/10.3322/caac.21660

3 World Health Organization. 2022. *Cancer (who.int)*. As of 22 March 2024: https://www.who.int/health-topics/cancer#tab=tab_1

4 Ahmad, A. S., Ormiston-Smith, N. & Sasieni, P. D. 2015. 'Trends n the lifetime risk of developing cancer in Great Britain: comparison of risk for those born from 1930 to 1960'. *Br J Cancer* **112**, 943-947. As of 22 March 2024: https://doi.org/10.1038/bjc.2014.606

5 Cancer Research UK. 2023. *Early Detection and Diagnosis of Cancer Roadmap*. As of 22 March 2024: https://www.cancerresearchuk.org/funding-for-researchers/research-opportunities-in-early-detection-and-diagnosis/early-detection-and-diagnosis-roadmap

6 World Health Organization. 2017. *Cancer prevention and control in the context of an integrated approach*.

7 Alderwick, H. & Dixon, J. 2019. 'The NHS long term plan'. *BMJ* **364**, l84 (2019). As of 22 March 2024: https://doi.org/10.1136/bmj.l84

8 Department of Health and Social Care. 2022. *10-Year Cancer Plan: Call for Evidence*, GOV.UK. As of 22 March 2024: https://www.gov.uk/government/calls-for-evidence/10-year-cancer-plan-call-for-evidence/10-year-cancer-plan-call-for-evidence

9 NHS England. 2023. *Faster Diagnosis Framework and the Faster Diagnostic Standard*. As of 22 March 2024: https://www.england.nhs.uk/cancer/faster-diagnosis/

10 Cancer Research UK. 2018. *Our policy on national cancer plans*. As of 22 March 2023: https://www.cancerresearchuk.org/about-us/we-develop-policy/our-policy-on-cancer-services/our-policy-on-national-cancer-plans

11 Cabinet Secretary for NHS Recovery, Health and Social Care. 2023. *Cancer strategy 2023 to 2033*. As of 22 March 2024: https://www.gov.scot/publications/cancer-strategy-scotland-2023-2033/pages/4/

12 Cabinet Secretary for NHS Recovery, Health and Social Care. *Recovery and redesign: cancer services - action plan*. As of 22 March 2024: https://www.gov.scot/publications/recovery-redesign-action-plan-cancer-services/pages/7/

13 Wales Cancer Network. *A Cancer Improvement Plan for NHS Wales 2023-2026*. As of 03 April 2024: executive.nhs.wales/functions/networks-and-planning/cancer/cancer-improvement-plan-docs/full-plan/

14 Department of Health Northern Ireland. 2022. *A Cancer Strategy for Northern Ireland 2022-2032.*

15 NHS England. *Cancer*. As of 22 March 2024: https://www.england.nhs.uk/cancer/

16 SBRI Healthcare. 2023. *NHS Cancer Programme awards £12.1 million to accelerate new front-line innovations that detect and diagnose cancer earlier*. As of 22 March 2023: https://sbrihealthcare.co.uk/news/nhs-cancer-programme-awards-12-1-million-to-accelerate-new-front-line-innovations-that-detect-and-diagnosis-cancer-earlier

17 Medicines and Healthcare products Regulatory Agency. 2022. *Target Product Profile: In Vitro Diagnostic (IVD) self-tests for the detection of SARS-CoV-2 in people without symptoms*. GOV.UK. As of 22 March 2024: https://www.gov.uk/government/publications/how-tests-and-testing-kits-for-coronavirus-covid-19-work/target-product-profile-in-vitro-diagnostic-ivd-self-tests-for-the-detection-of-sars-cov-2-in-people-without-symptoms

18 Greenhalgh, T., Fahy, N. & Shaw, S. 2018. The Bright Elusive Butterfly of Value in Health Technology Development Comment on "Providing Value to New Health Technology: The Early Contribution of Entrepreneurs, Investors, and Regulatory Agencies". *Int J Health Policy Manag* **7**, 81-85. As of 22 March 2024: https://doi.org/10.15171/ijhpm.2017.65

19 Dailey, P. J. *et al.* 2019. 'Defining System Requirements for Simplified Blood Culture to Enable Widespread Use in Resource-Limited Settings'. *Diagnostics* **9**, 10.

20 Vetter, B. *et al.* 2021. 'Development of a target product profile for a point-of-care cardiometabolic device'. *BMC Cardiovasc Disord* **21**, 486 (2021). As of 22 March 2024: https://doi.org/10.1186/s12872-021-02298-7

21 Program for Appropriate Technology in Health. 2018. Diagnostics Instrument–Target Product Profile. Diagnostic Instrument: Hemoglobinometer. Seattle, WA, USA.

22 Pellé, K. G. *et al.* 2020. 'Electronic clinical decision support algorithms incorporating point-of-care diagnostic tests in low-resource settings: a target product profile'. *BMJ Global Health* **5**, e002067 (2020). As of 22 March 2024: https://doi.org/10.1136/bmjgh-2019-002067

23 World Health Organization, FIND and Medecins sans frontieres. 2020. A Multiplex multi-analyte diagnostic platform. As of 22 March 2024: https://www.who.int/publications/m/item/TPP_20180327

24 Mather, R. G., Hopkins, H., Parry, C. M. & Dittrich, S. 2019. 'Redefining typhoid diagnosis: what would an improved test need to look like?' *BMJ Global Health* **4**, e001831.

25 Kadam, R. *et al.* 2020. 'Target Product Profile for a mobile app to read rapid diagnostic tests to strengthen infectious disease surveillance'. *PLoS One* **15**, e0228311.

26 World Health Organization. *Target product profiles for antibacterial resistance diagnostics*. World Health Organization Antimicrobial Resistance Division (AMR), Global Coordination and Partnership (GCP). As of 22 March 2024: https://www.who.int/publications/i/item/10665331054

27 The Clinical and Laboratory Standards Institute (CLSI). *Harmonized terminology database*. 2023. As of 22 March 2024: https://htd.clsi.org/

28 Owens, L., Gulati, R. & Etzioni, R. 2022. 'Stage Shift as an Endpoint in Cancer Screening Trials: Implications for Evaluating Multicancer Early Detection Tests'. *Cancer Epidem Biomar* **31**, 1298-1304. As of 22 March 2024: https://doi.org/10.1158/1055-9965.Epi-22-0024

29 Woo, K. M., Gönen, M., Schnorr, G., Silvestri, G. A. & Bach, P. B. 2018. 'Surrogate Markers and the Association of Low-Dose CT Lung Cancer Screening With Mortality'. *Jama Oncol* **4**, 1006-1008 (2018). As of 22 March 2024: https://doi.org/10.1001/jamaoncol.2018.1263

30 Callister, M. E. J., Crosbie, E. J., Crosbie, P. A. J. & Robbins, H. A. 2023. 'Evaluating multi-cancer early detection tests: an argument for the outcome of recurrence-updated stage'. *British Journal of Cancer* **129**, 1209-1211. As of 22 March 2024: https://doi.org/10.1038/s41416-023-02434-4

31 Cuzick, J., Cafferty, F. H., Edwards, R., Moller, H. & Duffy, S. W. 2007. 'Surrogate endpoints for cancer screening trials: general principles and an illustration using the UK Flexible Sigmoidoscopy Screening Trial'. *J Med Screen* **14**, 178-185. As of 22 March 2024: https://doi.org/10.1258/096914107782912059

32 World Health Organization. 2023. *Target product profile for readers of rapid diagnostic tests*. As of 22 March 2024: https://www.who.int/publications/i/item/9789240067172

33 Rigveda Kadam , W. W., Nicholas Banks, Zachary Katz, Sabine Dittrich, Cassandra Kelly-Cirino. 2020. 'Target Product Profile for a mobile app to read rapid diagnostic tests to strengthen infectious disease surveillance'. As of 22 March 2024: https://doi.org/10.1371%2Fjournal.pone.0228311

34 Karell G Pellé, C. R.-A., Valérie D'Acremont, Gretchen Moran, Rangarajan Sampath, Zachary Katz, Francis G Moussy, Livingston Mehl, Sabine Dittrich. 2020. 'Electronic clinical decision support algorithms incorporating point-of-care diagnostic tests in low-resource settings: a target product profile'. *BMJ Global Health*. As of 22 March 2024: https://doi.org/10.1136/bmjgh-2019-002067

35 NHS England. 2023. *Carbon reduction plan and net zero commitment requirements for the procurement of NHS goods, services and works*.

36 Staley, K., Crowe, S., Crocker, J. C., Madden, M. & Greenhalgh, T. 2020. 'What happens after James Lind Alliance Priority Setting Partnerships? A qualitative study of contexts, processes and impacts'. *Res Involv Engagem* **6**, 41. As of 22 March 2024: https://doi.org/10.1186/s40900-020-00210-9

37 Cowan, K. *et al.* 2021. 'Rapid prioritisation of topics for rapid evaluation: the case of innovations in adult social care and social work'. *Health Res Policy Syst* **19**, 34. As of 22 March 2024: https://doi.org/10.1186/s12961-021-00693-2

38 Ferrante di Ruffano, L., Hyde, C. J., McCaffery, K. J., Bossuyt, P. M. & Deeks, J. J. 2012. 'Assessing the value of diagnostic tests: a framework for designing and evaluating trials'. *BMJ* **344**, e686. As of 22 March 2024: https://doi.org/10.1136/bmj.e686

39 Soares, M. O., Walker, S., Palmer, S. J. & Sculpher, M. J. 2018. 'Establishing the Value of Diagnostic and Prognostic Tests in Health Technology Assessment'. *Med Decis Making* **38**, 495-508. As of 22 March 2024: https://doi.org/10.1177/0272989X17749829

40 NIHR Newcastle In Vitro Diagnostics Co-operative. 2023. *Care pathway analysis to identify the value proposition*. As of 22 March 2024: https://newcastle.mic.nihr.ac.uk/expertise/evaluation-themes/early-stage-evidence/care-pathway-analysis/

41 Cocco, P., Messenger, M. P., Smith, A. F., West, R. M. & Shinkins, B. 2021. 'Integrating Early Economic Evaluation into Target Product Profile development for medical tests: advantages and potential applications'. *Int J Technol Assess* **37**. As of 22 March 2024: https://doi.org/10.1017/s0266462321000374

42 Girling, A., Lilford, R., Cole, A. & Young, T. 2015. 'Headroom Approach to Device Development: Current and Future Directions'. *Int J Technol Assess Health Care* **31**, 331-338. As of 22 March 2024: https://doi.org/10.1017/S0266462315000501

43 National Institute for Health and Care Excellence. 2024. *Diagnostics Assessment Programme*. National Institute for Health and Care Excellence. As of 22 March 2024: https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-diagnostics-guidance

44 National Institute for Health and Care Excellence. 2024. *NICE health technology evaluations: the manual*. National Institute for Health and Care Excellence. As of 22 March 2024: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

45 National Institute for Health Research (Homepage). *Innovation Observatory*. As of 22 March 2024: https://www.io.nihr.ac.uk/

46 Medicines and Healthcare Products Regulatory Agency. 2023. *Public Access Registration Database (PARD)*. As of 22 March 2024: https://pard.mhra.gov.uk/

47 European Commission. 2023. *Medical Devices - EUDAMED*. Public Health. As of 22 March 2024: https://health.ec.europa.eu/medical-devices-eudamed_en

48 Kessler, L. 2022. *Target Product Profile - New Hypothetical Diagnostic Tests for Ovarian Cancer*. 1-37. US-UK Fulbright Commission, London, UK.

49 Burnett, T. 2022. *CA 125 test: A screening test for ovarian cancer?* As of 03 April 2024: https://www.mayoclinic.org/diseases-conditions/ovarian-cancer/expert-answers/ca-125/faq-20058528

50 Center for Devices and Radiological Health. 1998. *Guidance for Submission of Immunohistochemistry Applications to the FDA*. As of 03 April 2024: https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/guidance-submission-immunohistochemistry-applications-food-and-drug-administration-final-guidance

51 International Organization for Standardization. 2022. *Information supplied by the manufacturer (labelling)*. As of 03 April 2024: https://www.iso.org/standard/67943.html

52 Parvin, C. A. 2016. *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions*. 4 edn. As of 03 April 2024: https://clsi.org/standards/products/clinical-chemistry-and-toxicology/documents/c24/

53 Drake, L. 2024. 'The Necessity of External Controls.' *Microbiologics BLOG*, Vol. 2024. As of 03 April 2024: https://blog.microbiologics.com/clinical-qc-external-controls/

54 RAND Corporation. *Delphi Method*. Santa Monica, Calif.: RAND Corporation. As of 22 March 2024: https://www.rand.org/topics/delphi-method.html

55 Diamond, I. R. *et al.* 2014. 'Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies'. *J Clin Epidemiol* **67**, 401-409. As of 22 March 2024: https://doi.org/10.1016/j.jclinepi.2013.12.002

56 Nasa P, J. R., Juneja D. 2021. 'Delphi methodology in healthcare research: How to decide its appropriateness'. *World J Methodol*. **11**, 116-129. As of 22 March 2024: https://doi.org/10.5662%2Fwjm.v11.i4.116

57 James Lind Alliance. 2023. *About Priority Setting Partnerships*. As of 22 March 2024: https://www.jla.nihr.ac.uk/about-the-james-lind-alliance/about-psps.htm

58 Maak, T. G. & Wylie, J. D. 2016. 'Medical Device Regulation: A Comparison of the United States and the European Union'. *J Am Acad Orthop Surg* **24**, 537-543. As of 22 March 2024: https://doi.org/10.5435/JAAOS-D-15-00403

59 Medicines and Healthcare Products Regulatory Agency. 2024. *Guidance: Regulating medical devices in the UK--Medicines and Healthcare products Regulatory Agency*. As of 22 March 2024: https://www.gov.uk/guidance/regulating-medical-devices-in-the-uk