THE EVOLVING VALUE ASSESSMENT OF CANCER THERAPIES:

Seven Principles from the Cancer Community

This consulting report was initiated, reviewed (for technical accuracy) and funded by AstraZeneca. BCG was commissioned by AstraZeneca to develop this report.
Authors

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Cancer Community Experts

The international expert group (hereafter “expert group”) brought expertise from around the healthcare ecosystem in cancer care. The experts contributed their time and expertise to the key themes described herein and the authors (above) have reviewed the report. They included patient advocates, payers, health economists, regulators, professional oncology societies and physicians, and represented perspectives from Australia, Canada, China, France, Germany, Italy, Japan, South Korea, Singapore, Spain, Sweden, the UK and US. The insights, ideas and key themes contributed are individual, and not of the organizations represented, past or present.

Sixteen experts participated as panelists across numerous fora over five months and are among the authors of this paper (See above): Keith Abrams, Susan Brown, Johannes Bruns, John Carpten, Russell Clark, Javier Cortes, Giuseppe Curigliano, Andrea Ferris, Louis P. Garrison, Gary Lyman, Luca Pani, Zack Pemberton-Whiteley, Bettina Ryll, Tomas Salmonson, Peter Sawicki and Richard Vines. An additional eight representatives were interviewed outside the panel group: Anne-Marie Baird, Y. K. Gupta, Ataru Igarashi, Ravindran Kanesvaran, Zhao Kun, Barry Stein, Dong-Churl Suh and Galina Velikova.

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The evolving value assessment of cancer therapies:

Seven Principles from the Cancer Community

Executive Summary

Cancer management today is moving toward earlier detection and more personalized treatment. The evolution of oncology science is delivering scientific advancements that can lead to more targeted and effective treatments for people with cancer. Together, early-stage diagnosis and therapeutic innovation can significantly improve clinical outcomes. Investigating and treating cancer earlier has been shown to improve outcomes and early cancer detection has improved in recent decades, owing to a combination of advanced diagnostic technologies and public health campaigns that emphasize the importance of screening and early diagnosis and treatment. As the cancer community looks to leverage scientific innovation to improve outcomes for people with cancer, the identification and utilization of additional oncology-relevant measures should be considered in terms of their role in accelerating the detection of even nascent cancers, speeding up drug development, better informing treatment pathways and value assessments.

People with cancer need access to effective treatment options for them and their particular tumor type in the early stages of their disease to have the optimal chance of transformative and sometimes curative outcomes. This, in turn, may provide direct and indirect long-term healthcare savings by reducing the amount of healthcare spending per patient, limiting the length of time that they are less able to contribute to the workforce and their communities, and easing the emotional stress and financial strain of employment-related issues for their caregivers. The COVID-19 pandemic experience showed how global health systems prioritized investment in healthcare for the benefit of patients, society and the economy. However, current medicine value assessments do not always consider the full economic and societal benefits of cancer therapies.

To achieve the common goal of all cancer community stakeholders—improved outcomes for people with cancer—sustained collaboration is needed to define the value of oncology medicines in terms of clinical and other value components, including economic benefit and value from the perspective of people with cancer. To that end, this international group of leading cancer community experts came together to develop a set of principles for defining and assessing value of cancer therapies (See Section II: Methodology). We considered: shifts in cancer care toward treating earlier stage disease; enhanced criteria on value principles for the assessment of new medicines, such as those articulated in the value flower from the International Society for Health Economics [Pharmacoeconomics] and Outcomes Research (ISPOR) and constrained resources across the healthcare ecosystem.

Discussions focused on two areas where we agreed that consensus could help shift how the value of medicines is assessed within healthcare systems and processes:

- **Oncology-Relevant Endpoints:** Which oncology-relevant endpoints should be used for the development and evaluation of treatments for early-stage disease, focusing on breast and lung cancer (two of the mostly commonly studied cancers). Endpoints may be either one or both of 1) predictors (or surrogates) of clinical benefit where correlation is needed to clinical outcomes and 2) with inherent value to people with cancer as an oncology-relevant measure because they will benefit even if it does not show correlation to established endpoints (See Table 1).

- **Value Components in Oncology:** Which value components are relevant to consider in appraising a medicine. (See Table 2).
<table>
<thead>
<tr>
<th>Table 1: Oncology-Relevant Endpoints (listed alphabetically)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Additional oncology-relevant endpoints</strong></td>
</tr>
<tr>
<td>Additional oncology-relevant endpoints (beyond OS) that are often used in early-stage cancer could include those listed below; the following are referenced in this paper: DFS, RFS, DoR EFS, pCR, ORR. They should be informed by the needs of all relevant stakeholders including payers, regulators, patients and oncologists.</td>
</tr>
</tbody>
</table>

| **Disease-Free Survival (DFS) / Relapse-Free Survival (RFS)** |
| Length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. Also called relapse-free survival. |

| **Duration of Response (DoR)** |
| Length of time from randomization to disease progression or death in patients who achieve complete or partial response; measures how long a patient will respond to treatment without tumor growth or metastasis. |

| **Event-Free Survival (EFS)** |
| Length of time after primary treatment for a cancer ends that the patient remains free of certain complications or events that the treatment was intended to prevent or delay. These events may include the return of the cancer or the onset of certain symptoms, such as bone pain from cancer that has spread to the bone. |

| **Liquid Biopsy (LB)-related measures** |
| LBs are a broad concept that encompasses the analysis of circulating nucleic acids, tumor cells or exosomes as a tool to molecularly profile tumors to guide clinical decision making. |

| **pathologic Complete Response (pCR)** |
| The lack of all signs of cancer in tissue samples removed during surgery or biopsy after treatment such as that with radiation or chemotherapy. |

| **Progression-Free Survival (PFS)** |
| Length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. |

| **Overall Response Rate (ORR)** |
| Percentage of people in a study or treatment group who have a partial or complete response to the treatment within a certain period of time. A partial response is a decrease in the size of a tumor or in the amount of cancer in the body, and a complete response is the disappearance of all signs of cancer in the body. |

| **Overall Survival (OS)** |
| The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. |

*Unless otherwise noted, definitions are from the National Cancer Institute (NCI) Dictionary of Cancer Terms."
Table 2: Value Components in Oncology* (listed alphabetically)

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equity of access</td>
<td>Promotes equal access for equal need.</td>
</tr>
<tr>
<td>Economic value</td>
<td>Considers value for money. Includes measurement of direct and indirect costs to the healthcare system, individuals and society.</td>
</tr>
<tr>
<td>Impact on caregivers</td>
<td>Impact on a caregiver such as on their time and QoL.</td>
</tr>
<tr>
<td>Impact on patients</td>
<td>Impact on a patient, for example, on patient function and QoL.</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>These may include loss of income and other expenses for working-age patients, and, on aggregate, the financial burden to society due to reduced or lost productivity across the workforce.</td>
</tr>
<tr>
<td>Insurance value</td>
<td>Value to healthy individuals of being protected from the physical and financial burden of illness due to the availability of a new medicine or technology.</td>
</tr>
<tr>
<td>Patient Reported Outcomes (PROs)</td>
<td>Report of the status of a patient’s health condition or QoL measures that come directly from the patient.</td>
</tr>
<tr>
<td>Quality-Adjusted Life Years (QALY)</td>
<td>A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life.</td>
</tr>
<tr>
<td>Quality of Life (QoL)</td>
<td>An individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Health-related quality of life is a combination of a person’s physical, mental and social well-being; not merely the absence of disease.</td>
</tr>
<tr>
<td>Real option value</td>
<td>Value of a therapy that helps maintain a person’s health status, enabling the possibility of benefitting from future medical treatments when they become available.</td>
</tr>
<tr>
<td>Safety</td>
<td>The safety of a medical product concerns the medical risk to the patient, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and hematology), vital signs, clinical adverse events (diseases, signs and symptoms) and other special safety tests.</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Represents the degree to which overt adverse effects can be tolerated by a patient.</td>
</tr>
<tr>
<td>Socio-economic impact</td>
<td>This includes the effect a treatment has on a patient or caregiver’s ability to engage in paid and voluntary work.</td>
</tr>
<tr>
<td>Value of choice</td>
<td>Gives weight to the importance of treatment options, and the more the better.</td>
</tr>
<tr>
<td>Value of hope</td>
<td>Differences in patients’ risk tolerance: some may value a treatment with high variability in outcomes, with the hope that they may be fortunate and respond very well.</td>
</tr>
</tbody>
</table>

*General definitions of terms shown as used for discussion by this expert group; definitions can vary within the literature.
The following seven consensus principles emerged from this expert group:

**Principles on oncology-relevant endpoints for consideration in value assessments, particularly for early-stage cancers**

**Principle 1: Consider oncology-relevant endpoints other than OS which have intrinsic value for decision-making.**
In early-stage cancer OS data takes time to mature or may not be possible to collect in the longer term in early-stage disease. Indication, intent of treatment and feasibility of measuring patient-relevant outcomes (e.g., EFS, DFS, RFS) within a reasonable timeframe should be evaluated when considering oncology-relevant endpoints as alternative to OS in value assessments.

**Principle 2: Continue to build evidence for endpoints that provide earlier indication of treatment efficacy.**
Emerging additional oncology-relevant endpoints that can detect treatment impact earlier, such as pCR, generally currently require confirmatory longitudinal outcome data. As evidence builds that pCR in specific disease settings and therapeutic classes correlates with other outcomes data (e.g., EFS, DFS and RFS), and/or people with cancer and oncologists confirm it reflects meaningful benefit, pCR may become established as a predictor and/or measure of clinical benefit.

**Principle 3: Develop evidence for the next generation of predictive measures that detect and monitor disease.**
Advances in disease monitoring, such as through circulating tumor DNA (ctDNA), may provide important early information about treatment response and tumor recurrence. Trials should collect ctDNA data to assess their value as predictors of clinical outcomes.

**Principle 4: Use Managed Entry Agreements (MEAs) supported by ongoing evidence collection to help address decision-maker evidence needs.** Carefully designed MEAs with planned confirmatory evidence collection can support timely patient access to new therapeutics and help to address evidence uncertainties associated with earlier access for decision makers.

**Principles on Value Components in Oncology (across all stages of cancer)**

**Principle 5: Routinely use PROs in value assessments.** Data collected from patients via PROs including QoL should be routinely and consistently incorporated into value assessments, along with the value components that are already used relating to safety and efficacy.

**Principle 6: Assess broad economic impact of new medicines.** The economic impact of medicines is an essential component of the value assessment and should consider the downstream effect a medicine can have on the amount and associated cost of healthcare resources a patient eventually needs, as well as the socio-economic impact (paid and voluntary work) for patients and those in a caregiving capacity.

**Principle 7: Consider other value aspects of relevance to patients and society.** Insurance value, the value of choice, scientific spillovers, equity of access and real option value (See Table 2) should be considered in value assessments, although they may not all be readily quantifiable and may instead require a more qualitative assessment.

This group’s collective interest is the well-being of the millions of people who are diagnosed with cancer every year worldwide. In 2020 an estimated 19.3 million people were diagnosed with cancer globally which included an estimated 4.5 million for breast and lung cancers alone. To benefit from advancements in early detection and treatment, people with cancer need timely access to medicines for early-stage disease when treatment can be most impactful.

A list of recommendations is included in Section V: Next Steps. Bringing together different voices is a powerful way to stimulate discussion and kick-start a cross-healthcare ecosystem effort that could generate the changes needed to benefit people with cancer, those in a caregiving capacity and society as a whole. Voices of people with cancer are essential to the development of value assessments in order to better, and more holistically, understand the impact of cancer and its treatment on people with cancer.
SECTION I: CONTEXT

A paradigm shift toward early-stage cancer diagnosis and treatment

Innovations in cancer research, combined with a fundamental shift toward earlier diagnoses and treatments, have improved outcomes for people with cancer around the world. From the mid-1970s, and 2011 through 2017, five-year survival rate across all cancers in the US increased from 49% and 68% overall, and since 1991 the risk of death from cancer has steadily decreased, leading to a 32% decline and about 3.5 million cancer deaths averted as of 2019 (versus that would have been expected if cancer death rates had remained at their highest levels). After reaching their highest (levels in the late 1980s, cancer mortality in Europe has also declined steadily, with reductions of 1.6% per year between 2002 and 2009 for men and 1% per year between 1993 and 2009 for women). In Canada, from 1984 to 2021, age-standardized mortality rates for all cancers combined decreased from 335.4 to an estimated 216.9 per 100,000 in males, and from 203.9 to an estimated 162.6 per 100,000 in females; rates peaked in 1988 and have since decreased 37% in males and 22% in females. In Australia, age-standardized mortality rate for all cancers, men and women combined, have decreased from 197.7 per 100,000 in 1972 to 145.3 per 100,000 in 2022 (26.5% decrease).

Improvements in mortality rates are bolstered by an expansion in early detection, supported by a combination of advanced diagnostic technologies and public health campaigns that emphasize the importance of screening and early diagnosis. Between 2004 and 2017, for example, the percentage of people with cancer diagnosed in the US at a localized stage for breast cancer increased from 60.5% to 65.1%, and for lung cancer, diagnosis at a localized stage rose by 10 percentage points, from 16.8% to 26.8%. A recent cross-sectional epidemiological US non-small cell lung cancer analysis concluded that earlier detection and availability of effective treatments may underlie increased overall non-small cell lung cancer prevalence, and higher than previously reported survival.

Research and development into early-stage cancer medicines (stages I and II) has likewise accelerated, as shown by the growth in Phase II/III clinical trials in these settings for breast and lung cancers between 2009-10 and 2019-20 (See Figure 1). Advances in the identification of biomarkers also enable targeting of treatment to specific oncogene drivers.

Figure 1 | Cancer research is increasing in earlier disease stages in lung and breast cancers based on number and percent of early-stage cancer clinical trials starting in 2009-10 vs 2019-20

The number and percentage of Phase II, II/III and III breast and lung trials recruiting early- and/or late-stage people with cancer in 2009-10 and 2019-20. Clinical trials were categorized by early stage (I and II) late stage (III and IV). Source: AdisInsights, trials between 2009-10 and 2019-20 (Accessed November 2022) using the following search terms: Phase II AND III AND II/III; indication: breast OR lung cancer (depending on search); start date: 01/01/2009-31/12/2010 OR 01/01/2019-31/12/2020 (depending on search); patient segment: early stage (I and II) OR late stage (III and IV) (depending on search).

The current treatment paradigm, however, does not fully benefit from these scientific advances. It generally aims for remission, then administers the next round of treatments on relapse (See Figure 2). However, as cancer care increasingly starts with earlier detection, when tumor burden is low or only detectable as circulating cells in the blood (e.g., ctDNA, discussed further below), a future paradigm features monitoring that could include assessments of tumor heterogeneity to inform more localized and targeted treatments, as appropriate for each person with cancer.
Value assessments within healthcare systems and processes

For people with cancer to benefit from advancements in early detection and treatment, they need access to innovative treatments. Clinical benefit, economic value (e.g., direct and indirect costs of treatment, value for money) and health outcomes for people with cancer are currently used to assess the value of medicines. In addition to these essential elements, there are other important value components (See Table 2) that affect people with cancer, those in a caregiving capacity and societies as a whole. (See Table 3 for general definitions of additional terms and concepts as used for discussion by the expert group; definitions can vary within the literature).

In many countries, after a medicine receives regulatory approval, its value is evaluated to inform reimbursement decisions by national public and private payers. To guide clinical assessment, reimbursement decisions and shared physician-patient decision-making around treatments, value frameworks or algorithms have been developed to consider clinical and economic benefits and value from the perspective of a person with cancer.

Examples include the ISPOR value flower, value frameworks from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), and the magnitude of clinical benefit scale (MCBS) guideline from the European Society for Medical Oncology (ESMO).

These value frameworks vary in the breadth of components considered. The ISPOR value flower includes such components as insurance value, the value of scientific spillovers, and real option value. While some of these components are difficult to quantify on the basis of clinical trials prior to regulatory approval, they are important to discuss and incorporate in reimbursement assessments. (See Box 1).
Table 3: Key Oncology Terminology* (terms listed alphabetically)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant therapies</td>
<td>Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy or biological therapy.</td>
</tr>
<tr>
<td>Administration</td>
<td>In medicine, the act of giving a treatment, such as a drug, to a patient. It can also refer to the way it is given, the dose or how often it is given.</td>
</tr>
<tr>
<td>Cancer staging</td>
<td>A system that is used to describe the extent of cancer in the body. Staging is usually based on the size of the tumor and whether the cancer has spread from where it started to nearby areas, lymph nodes or other parts of the body.</td>
</tr>
<tr>
<td>Cancer type</td>
<td>Cancer is not one disease but rather a cohort of related diseases. Solid and blood cancers require a range of treatments with different goals and outcomes, and therefore relevant trial endpoints also vary.</td>
</tr>
<tr>
<td>Clinical benefit</td>
<td>A positive effect of a therapeutic intervention, for example, slowing or curing disease, and improving QoL.</td>
</tr>
<tr>
<td>Context modulator</td>
<td>Additional considerations beyond clinical and economic benefit which may impact value assessment and can include unmet need, uncertainty, disease burden, prevalence, disease staging (I-IV) and dosing and administration.</td>
</tr>
<tr>
<td>Direct costs</td>
<td>Examples include resources used in treatment, hospitalization and rehabilitation.</td>
</tr>
<tr>
<td>Disease burden</td>
<td>Considers health, social, political, environmental and economic factors to determine the cost and impact that disease and disability exert upon the individual and society.</td>
</tr>
<tr>
<td>Dosing</td>
<td>The amount of medicine taken, or radiation given, at one time.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>In medicine, the ability of an intervention (for example, a drug or surgery) to produce the desired beneficial effect.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Process of evaluating the possibility of conducting a particular clinical trial based on geography, disease type and stage and type of data collected (e.g., tumor growth, QoL assessments, OS) with the overall objective of project completion in terms of timelines, targets and cost.</td>
</tr>
<tr>
<td>Healthcare system resources</td>
<td>Financial and human resources from the healthcare system.</td>
</tr>
<tr>
<td>Hormone receptor</td>
<td>Proteins in or on cells that can attach to a specific hormone.</td>
</tr>
<tr>
<td>Human epidermal growth factor receptor 2 (HER2)</td>
<td>A protein on the surface of some cells that helps control cell growth. Cancer cells that are HER2 negative may grow more slowly and are less likely to recur (come back) or spread to other parts of the body than cancer cells that have a large amount of HER2 on their surface.</td>
</tr>
<tr>
<td>Indication of a medicine</td>
<td>Use of a drug for treating a specific disease (such as a specific type of cancer at a specific stage).</td>
</tr>
<tr>
<td>Intent of treatment</td>
<td>Overarching goal of a treatment, e.g., curative or other, adjuvant or neoadjuvant.</td>
</tr>
<tr>
<td>Neoadjuvant therapies</td>
<td>Treatments that focus on shrinking a tumor prior to the main treatment.</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Uncertainty associated with the quality of evidence base early on in clinical trials for evaluating value across other measures.</td>
</tr>
</tbody>
</table>

*General definitions of terms shown as used for discussion by this expert group; definitions can vary within the literature.
Box 1: An introduction to value assessment and value frameworks

Before patients can receive a new treatment, regulators and payers evaluate the therapy for approval and reimbursement, respectively. Regulators are agencies such as the Food and Drug Administration (FDA) in the United States that ensure treatments meet the standards of safety, efficacy and quality. They focus on protecting public health and base their decisions largely on the added benefit of a new therapeutic compared to the current standard of care, weighed against the treatment’s uncertainties. Payers are agencies, such as insurance companies or government bodies, that decide whether to fund or reimburse healthcare services, including medicines. They often align their decisions with assessments made by health technology assessment (HTA) bodies. Payers focus on optimizing scarce resources on treatments that are most likely to generate positive patient outcomes in terms of mortality, morbidity and QoL. Both payers and regulators desire reliable, high-quality evidence for clinical benefit, as demonstrated in a clinical trial, either against the current standard of care or a placebo.

Value assessment frameworks help guide payer decisions in a standardized and transparent fashion, placing emphasis on important value dimensions (See Figure 3). Cancer organizations, including ASCO and ESMO, have developed frameworks for cancer treatments. Examples of national payer frameworks include the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany and the National Institute for Health and Care Excellence (NICE) in the UK. Value frameworks generally consider a combination of dimensions, each comprising different value components (See Table 2). The extent to which a given framework considers the full breadth of potential components reflects the various stakeholder groups at which they are aimed.

Figure 3 | Value components can be categorized in four value dimensions

<table>
<thead>
<tr>
<th>Context modulators can include</th>
<th>Value dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet need</td>
<td>1. Clinical benefit</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>2. Patient/caregiver benefit (inc. clinical &amp; economic value)</td>
</tr>
<tr>
<td>Disease burden</td>
<td>3. Healthcare system benefit (inc. economic value)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>4. Social &amp; macro benefit (inc. economic value)</td>
</tr>
<tr>
<td>Disease staging (I-IV)</td>
<td></td>
</tr>
<tr>
<td>Dosing &amp; administration</td>
<td></td>
</tr>
</tbody>
</table>

Illustration of four key value components and six context modulators that can influence treatment benefit. For example, a treatment for early-stage disease that delivers transformative or curative outcomes may provide direct and indirect long-term healthcare savings by reducing the amount of healthcare spending per patient, limiting the length of time that they are unable to fully contribute to the workforce and their communities, and easing the workload and financial strain for those in a caregiving capacity. Additionally, a medicine that targets a common cancer with greater prevalence (e.g., breast, lung, colorectal) would be seen to deliver overall greater clinical and economic value at a population level, because it benefits a greater number of people with cancer, compared to a therapy for a rare cancer.
Economic considerations within healthcare systems and processes

It is also essential to recognize that health systems have defined budgets in which to operate. Funding decisions would be more straightforward if the cost of a new therapy would offset other healthcare expenses. However, if the additional expenditure is not completely offset, a cost-effectiveness analysis must weigh the new therapy’s benefits against its additional costs. Net health benefits to society should increase, meaning the cost of a new therapy’s health benefit (e.g., QALY) should not exceed that of existing therapies that are removed from coverage. This is an important criterion for reimbursement decisions in countries such as the UK, Canada and Australia. Several countries’ payers restrict their assessment criteria to the cost impact on the healthcare system, and broader societal costs are only considered as additional qualitative information (most notably the UK). However, in others (e.g., the US), the Institute for Clinical and Economic Review (ICER) value framework includes quantitative analyses of both healthcare and broader societal impact.

In addition, a recent report in Australia quantified the societal net present value of prolonging and improving the quality of life of people with cancer as $48 billion AUD ($31 billion USD at the time of publication) over 5 years.

OS in many cases remains the current standard endpoint for payer decision-making of new medicines. OS is undeniably important to people with cancer; however, its use has consequences that are not always compatible with improving access to new medicines that could improve treatment results. In early-stage disease, OS may not always be possible to collect in the longer term and/or can take many years to mature and be confounded by subsequent therapies. Waiting longer for OS data (that may or not be feasible to collect depending on the cancer) to make access decisions can mean that people with cancer today don’t have the option of a treatment that could make them eligible for more future treatments (real option value), which collectively may contribute to longer survival.

Waiting longer for OS data (that may or not be feasible to collect depending on the cancer) to make access decisions can mean that people with cancer today don’t have the option of a treatment that could make them eligible for more future treatments.

Based on their distinct roles in the healthcare system, regulators and payers have varying acceptance of endpoints—beyond OS—in the assessment of clinical benefit. Our group determined that while both regulatory and reimbursement assessments focused value assessments on final outcomes (e.g., mortality, morbidity and QoL), regulators more readily accepted some additional oncology-relevant endpoints (e.g., PFS, DFS), despite some questions over statistical certainty of surrogate relationship to established endpoints like OS. Ultimately, it is important for people with cancer to receive a medicine where there is sufficient evidence of efficacy and details of its safety profile/tolerability, as early as is feasibly possible. Resolving evidence uncertainties around oncology-relevant endpoints other than OS would accelerate access to new medicines that meet the necessary safety, quality and efficacy thresholds (See Table 1).
A Delphi-based process to build consensus across the cancer community

This expert group represents a range of professionals in the cancer community: patient advocates, oncologists with different specializations, health economists, regulators, members of payer and HTA bodies and representatives from professional societies. The insights and ideas contributed are individual, and not of the organizations represented, past or present. Additionally, only those who had previously worked in regulatory agencies, payers and HTA bodies were involved to protect against any conflict of interest.

Discussions followed the Delphi approach to build consensus across a range of expertise and topics. Over five months, sixteen members of the expert group participated in numerous structured interactions, including a survey, two virtual plenary meetings (panels), one-on-one interviews and structured discussion on a secure social platform. Eight additional experts contributed their perspectives through individual interviews. The group (hereafter “we”) represented perspectives from Australia, Canada, China, France, Germany, Italy, Japan, South Korea, Singapore, Spain, Sweden, the UK and US.

We discussed two areas where consensus could help shift how the value of treatments is assessed: 1) which oncology-relevant endpoints to use for assessing the benefit of treatments for early-stage cancer in clinical trials, and access decisions for early-stage cancer treatments and 2) which additional value components are important and how they can be integrated in value assessments within the healthcare system and processes. We did not discuss pricing of medicines.

Our research and discussions were guided by the universal recognition that cancer care is moving to focus on treatment of early-stage disease and that accelerating development and regulatory approval for medicines in this setting has implications for the maturity of the evidence available for access and funding decision-making.

Seven consensus principles to assess cancer treatments in the setting of early-stage cancer

Together, we developed seven principles: Four outline oncology-relevant endpoints that could be used for assessing the clinical value of treatments for earlier-stage cancers, and three represent important value components that could be integrated into healthcare system assessments and processes (e.g., payer and regulator assessments).

Our overarching goal is to stimulate dialogue on appropriate value assessment, with a focus on oncology-relevant endpoints for early-stage disease. We wanted to develop principles that are easily understood and applicable to the whole cancer community, actionable and able to address areas that are not currently consistently considered.

The principles are presented as a resource to facilitate cross-stakeholder discussion and decision-making, and to support the evolution of existing value frameworks with the universally held goal of improving outcomes for people with cancer. In the final section of this report, we present a high-level summary of collaborative efforts that the entire cancer community can engage in, that together could help facilitate early access to cancer innovations for people with cancer (See Section V: Next Steps).
SECTION III: PRINCIPLES ON ONCOLOGY-RELEVANT ENDPOINTS

The following four consensus principles around oncology-relevant endpoints consider accelerating generation of early evidence of treatment effect, balanced with considerations over long-term effectiveness and safety. We propose these principles on oncology-relevant endpoints for consideration in value assessments, particularly for early-stage cancers.

**Principle 1: Consider oncology-relevant endpoints other than OS which have intrinsic value for decision-making.** In early-stage cancer OS data takes time to mature or may not be possible to collect in the longer term in early-stage disease. Indication, intent of treatment, and feasibility of measuring patient-relevant outcomes (e.g., EFS, DFS, RFS) within a reasonable timeframe should be evaluated when considering oncology-relevant endpoints as alternative to OS in value assessments.

Cancer is not one disease but rather a cohort of related diseases that requires a range of treatments with different goals and outcomes. Relevant trial endpoints therefore also vary according to cancer type (e.g., solid or blood cancers) and staging (I-IV), intent of treatment (e.g., neoadjuvant and adjuvant) and feasibility, which is the likelihood of capturing relevant endpoint data (e.g., tumor growth and spread, QoL assessments from people with cancer) within time and cost constraints.

To date, access and funding decisions are largely focused on OS data to determine the efficacy of a treatment\(^{34}\). Longitudinal studies designed to collect OS data can take years, especially for early-stage disease\(^{35-37}\), and participants in the clinical trial are likely to start other treatments during the follow-up period, confounding the OS data of the initial therapy\(^{38-40}\). People with cancer may not survive long enough, or may have disease that is too advanced, to benefit from access to new treatments while the OS data in a trial matures. Medical oncologists and patient advocates both emphasized the importance of not delaying access to cancer treatment options because mature OS data are not available.

Thankfully, payers and regulators within healthcare systems and processes used to evaluate medicines increasingly recognize additional oncology-relevant endpoints\(^{41}\) as proxies for OS or as oncology-relevant endpoints in their own right\(^{42}\). Payers in our group noted that they were more likely to accept endpoints for initial value assessment that were proven to correlate with long-term outcomes, but that they currently lacked sufficient and consistent evidence and consensus on which of the alternative to OS oncology-relevant endpoints in which settings meet these criteria (See Figure 4). They acknowledged the challenges of demonstrating statistically significant OS benefit in early-stage cancers.

The group discussed that endpoints such as PFS and DFS have in some instances been shown to be predictors of OS benefit (in some, though not all, contexts)\(^{43}\) and have shown to be relevant endpoints in their own right, both in terms of delaying disease progression and in expanding real option value for people with cancer to be able to access future treatments.

### Figure 4 | Expert indication of potentially acceptable oncology-relevant endpoints that can be used to demonstrate efficacy in value assessments

Percent of experts (n=9) who indicated via the Within3 platform discussion which alternative oncology-relevant endpoints in their opinion are most likely to provide meaningful data on their own in early-stage breast and lung cancers. The endpoints could either be as measures of efficacy or predictors of clinical outcomes depending on the type and stage of cancer. Experts could choose more than one. Source: External engagement on the Within3 platform among 9 expert respondents.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Percentage of experts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>56</td>
</tr>
<tr>
<td>pCR</td>
<td>44</td>
</tr>
<tr>
<td>DoR</td>
<td>33</td>
</tr>
<tr>
<td>DFS / RFS</td>
<td>33</td>
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<tr>
<td>EFS</td>
<td>33</td>
</tr>
<tr>
<td>ORR</td>
<td>22</td>
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The group discussed that endpoints such as PFS and DFS have in some instances been shown to be predictors of OS benefit (in some, though not all, contexts)\(^ {43}\) and have shown to be relevant endpoints in their own right, both in terms of delaying disease progression and in expanding real option value for people with cancer to be able to access future treatments.
Principle 2: Continue to build evidence for endpoints that provide earlier indication of treatment efficacy. Emerging additional oncology-relevant endpoints that can detect treatment impact earlier, such as pCR, generally currently require confirmatory longitudinal outcome data. As evidence builds that pCR in specific disease settings and therapeutic classes correlates with other outcomes data (e.g., EFS, DFS and RFS), and/or people with cancer and oncologists confirm it reflects meaningful benefit, pCR may become established as a predictor and/or measure of clinical benefit.

Given that the selection of the appropriate endpoint is very context-dependent, the expert group worked through a series of case studies (See Box 2) and discussed which other oncology-relevant endpoints may be appropriate on their own, with a focus on breast and lung cancer, which are both well-studied. Patient advocates and oncologists said choice is essential, as the overall intent of treatment for individuals with cancer varies significantly.

Payers and regulators preferred OS in the adjuvant setting but recognized inherent challenges with relying on mature OS, particularly in the curative-intent setting of early-stage breast cancer and OS can take years to mature. Patient advocates and oncologists, however, were more amenable to accepting oncology-relevant endpoints such as pCR as measures on their own without correlating OS, PFS, DFS, RFS data. Improved information sharing among cancer community stakeholders, in addition to further research, would accelerate evidence generation to support how pCR should be used across contexts (either as a predictor of longer-term outcomes and/or an oncology-relevant endpoint in itself).

We generally agreed that as endpoints, PFS, pCR, DoR, DFS, RFS and EFS, on their own or in combination, could provide meaningful efficacy data in early-stage cancers. We also agreed that perspectives of people with cancer, with regards to QoL and tolerability, also add value. Additionally, we welcomed studies looking at the correlation of other oncology-relevant endpoints such as pCR with clinical outcomes, e.g., EFS, and noted that as research develops, the prognostic value of these relevant endpoints may be confirmed.

Our findings are consistent with other consensus-building exercises. In 2018, the NCI convened a working group with a focus on metastatic breast cancer. The working group included breast medical oncologists, patient advocates, biostatisticians and FDA representatives and was charged to provide evidence-based consensus recommendations on oncology-relevant endpoints for clinical trials, with a focus on biologic subtype and line of therapy.

In the NCI group’s work, PFS as an oncology-relevant endpoint was applied alongside OS in a number of studies and hypothetical case simulations, and PFS was found to be valuable in many situations. The expert group also emphasized the difficulty in relying only on OS to assess the impact on one individual treatment given that OS, even in late-stage disease, is likely to be the result of the impact of multiple treatments a person with cancer has received, with their sequence also being important. It is also recognized that OS should be considered as a key endpoint when expected survival is short (e.g., 6-12 months).

With regard to pCR specifically, the use of pCR is increasing in clinical trials as an oncology-relevant endpoint and acceptance is growing among regulators. Our group explored its role in early-stage cancers in the neoadjuvant setting, as a potential interim oncology-relevant endpoint to support conditional reimbursement approval pending longer-term data. The published regulatory guidelines (excerpts below) show the emergent thinking:

- **EMA:** “Approval based on pCR may be acceptable for patients with aggressive (high-risk) early-stage breast cancer as add-on to an established (neo) adjuvant regimen, if there is a well-characterized mechanism of action and provided the results show major increase in pCR with only minor changes in toxicity. Such results may lead to an approval with agreed conditions for confirmatory study data in terms of DFS/OS.”

- **FDA:** “The FDA acknowledges that important regulatory questions persist regarding use of pCR to support accelerated approval in high-risk early-stage breast cancer. A trial-level relationship between improvement in pCR and improvement in long-term outcome has not been established. If such a relationship exists, it is unknown whether the necessary magnitude of improvement in pCR will differ according to breast cancer subtype or drug class. Hence, we [the FDA] recommend that sponsors pursuing a neoadjuvant indication meet early with the FDA to discuss their plans for designing a neoadjuvant trial in the context of a robust breast cancer drug development program. These discussions should include a justification for the proposed magnitude of improvement in pCR rate and long-term outcome, additional trials that would provide supporting evidence of clinical benefit in breast cancer, and the anticipated safety database to support the drug’s use in a curative intent setting.”
**Box 2: Expert discussion: Alternative oncology-relevant endpoints in three hypothetical case studies in breast and lung cancer**

To build on discussions with more specificity, this expert group worked through three hypothetical case studies in breast and lung cancer and provided their perspective on endpoints that may provide sufficient evidence in clinical efficacy for future trials (See Figure 5).

- **Case study 1:** Early-stage breast cancer in the neoadjuvant setting, a stage 2 hormone-positive, HER2-negative invasive ductal carcinoma. About 60% of the stakeholder group preferred PFS in this example and ~40% identified pCR as the second potentially relevant endpoint, but with preference to see it in conjunction with other longitudinal data; n=8. DFS/RFS was also a popular second choice.

- **Case study 2:** Early-stage breast cancer in the adjuvant setting, a stage 2 triple-negative breast cancer that has spread to lymph nodes. Again, the preferred first choice was PFS with ~60% of stakeholders selecting this oncology-relevant endpoint (n=8). Second preferred choices were EFS and DFS/RFS (a delta of 10% with a hazard ratio of 0.7 for EFS was also specified). There was no consensus on other potential oncology-relevant endpoints, but measuring the impact on QoL was highlighted as important.

- **Case study 3:** Early-stage lung cancer in the neoadjuvant setting, a stage 1B peripherally located non-small cell adenocarcinoma. EFS was preferred by almost 70% of this stakeholder group (n=6), and the importance of combining this data with QoL impact was again referenced. The second most popular choice in this indication was PFS.

Within these discussions, patient advocates emphasized the importance of assessing the impact on QoL and oncology-relevant outcomes, and advocates, oncologists and former regulators agreed on the need to collect QoL and tolerability data from people with cancer themselves, as clinicians have different perspectives. In subsequent follow up individual discussions, oncologists commented that PFS was not suitable as an early-stage endpoint, preferring instead DFS or EFS for early-stage disease. This difference of opinion showed the importance of ongoing efforts to harmonize across the cancer community which are the oncology-relevant endpoints for use in clinical trials and value assessments. It also reinforced the need for 1) evaluation of a range of oncology-relevant endpoints that demonstrate value to people with cancer beyond OS and 2) continued data collection to strengthen the evidence on benefit to people with cancer and the broader healthcare ecosystem of new medicines.

**Figure 5**  |  **Expert indication of potentially acceptable oncology-relevant endpoints that could be used to demonstrate efficacy for initial value assessment in specific cancers**

Percent of experts who selected oncology-relevant endpoints as most likely to provide meaningful data on their own. Source: Expert discussion around three hypothetical case studies: 1) a stage II hormone-positive, HER2-negative invasive ductal carcinoma in a neoadjuvant setting (n=8); 2) a stage II triple-negative breast cancer which has spread to lymph nodes in an adjuvant setting (n=8); and 3) a stage IB peripherally located non-small cell adenocarcinoma in the neoadjuvant setting (n=6). Experts could select more than one endpoint.
This expert group, in particular the oncologists, generally hoped that eventually pCR could be used as an oncology-relevant endpoint as more evidence is collected to show that it is able to measure benefit to people with cancer without demonstrated correlation to longer-term outcomes. The expert group indicated that pCR can provide early data on treatment response. However, the expert group also highlighted that currently pCR data still needs to be complemented with longitudinal data to inform both regulatory and payer decisions.

As more trials use pCR as a primary oncology-relevant endpoint and collect additional endpoints data, stronger evidence will emerge to inform its utility in decision-making and firstly as a predictor of longer-term outcomes.

Some recent studies underway in lung and breast cancer show an expansion of oncology-relevant endpoints to include pCR as a potential predictor of longer-term outcomes. Meta-analysis data in early-stage breast cancer showed that the association between pCR and long-term outcomes has been observed to be strongest in people with aggressive tumor subtypes (e.g., triple-negative and HER2-positive and hormone receptor-negative breast cancers) 47,51.

The data also suggested that the prognostic relevance of pCR may differ across breast cancer subtypes47,51. In slower-growing, early-stage breast cancer (e.g., HER2-negative and hormone receptor-positive disease), the most accepted surrogate markers for endocrine therapy-based trials include changes in the molecular target Ki67 and the preoperative endocrine prognostic index47.

Principle 3: Develop evidence for the next generation of predictive measures that detect and monitor disease. Advances in disease monitoring, such as through ctDNA, may provide important early information about treatment response and tumor recurrence. Trials should collect ctDNA data to assess their value as predictors of clinical outcomes.

Precision medicine and research into cancer biomarkers are providing additional information on cancer detection and/or progression that could transform the way cancer care is managed in the future. Assessed with a simple blood test (called liquid biopsy), ctDNA measures use a tumor’s specific genetic signature to detect disease at a very early stage when there are much lower levels of tumor burden, allowing for potential early intervention24. Some emerging data has shown correlation of ctDNA with PFS in metastatic breast cancer53,83 and ctDNA is being investigated as a measurement in lung cancer56,84. Research across oncology therapy areas remains ongoing. It is also showing potential as a therapeutic predictor in metastatic breast cancer22. Further studies are warranted to establish how to use ctDNA measures as a disease monitoring tool and/or predictor of clinical outcomes.

As an example, in the post-remission phase of treatment, ctDNA measures can also be used to monitor treatment for early signs of growth and appropriate interventions along the treatment pathway. Such non-invasive approaches also have the potential to improve the experience for people with cancer and lower healthcare spending, both by reducing the amount of healthcare used and restoring people’s productivity earlier on.

Consensus is starting to form in the cancer community around the need to assess the potential value of ctDNA analysis for people with early-stage solid tumors55. In draft guidance issued for consultation purposes in May 2022, the US FDA supported several uses of ctDNA in clinical trials, though not as an oncology-relevant endpoint46. In the EMA’s 2019 draft guidance on the evaluation of anticancer medicines (consultation closed February 2021, current draft under revision), the EMA stated that whilst some biomarkers are used as clinical trial endpoints, for acceptance as a surrogate endpoint to support benefit/risk assessment in a regulatory submission, their clinical validity should be comprehensively established regarding the relationship with a treatment effect in the clinical endpoint57. However, the EMA has not issued any specific guidance with regards to ctDNA which it considered as a surrogate for mutations present in tumor lesions. Our group agreed that ctDNA eventually had the potential to be used as an oncology-relevant measure for value assessment decisions.

Toward that goal, we recommend ctDNA data collection in clinical trials to continue, contributing to the growing evidence on how the data should be used to impact treatment choices. Patient advocates and oncologists indicated that in order to enable uptake of ctDNA monitoring in routine clinical practice, liquid biopsies would need to be more widely used. They also stressed that once validated, monitoring tools would need to be adequately funded and available to physicians to realize the benefits in clinical practice.

Principle 4: Use MEAs supported by ongoing evidence collection to help address decision-maker evidence needs. Carefully designed MEAs with planned confirmatory evidence collection can support timely patient access to new therapeutics and help to address evidence uncertainties associated with earlier access for decision makers.

The expert group highlighted that medicines with a positive value assessment on the basis of surrogate or predictor endpoints may need additional data collected to confirm long-term outcomes. Coverage with evidence agreements have been shown to provide answers about uncertainties in real-world effectiveness by using patient-relevant outcomes58, however several studies have shown that not all medicines approved on such endpoints eventually show correlation to OS,
contributing to skepticism\textsuperscript{56}. Progress in this arena is also challenged by limited flexibility to adjust data requirements to support therapeutic development\textsuperscript{58}, as well as evidence requirements that are out of sync between regulators and payers\textsuperscript{59}. Closer alignment of evidence-generation requirements between HTA bodies and regulators could mean that improved evidence development could feed into flexible pricing agreements\textsuperscript{59}.

In some countries, carefully designed MEAs can help address the uncertainty around efficacy endpoints other than OS. In France, for example, “accès précoce” is a program that enables early access to innovative therapies with the requirement to collect confirmatory real-world evidence on treatments\textsuperscript{60,61}. In the UK, the Cancer Drugs Fund (CDF) has the same intent. Medicines that are funded by the CDF undergo real-world data collection\textsuperscript{61,64} to enable further evaluation and confirmation of the benefit\textsuperscript{63}. Where benefit is not confirmed, the CDF ceases funding the medicine. This approach is complemented by the Medicines and Healthcare products Regulatory Agency (MHRA)’s increased surveillance and managed access at specialist centers as part of its Early Access to Medicines Scheme (EAMS)\textsuperscript{64}. This enables proactive management around uncertainty and fast action within clinical practice working in partnership with the pharmaceutical company to mitigate any emerging adverse events not detected during clinical trials.

There may also be product- or indication-specific agreements between manufacturer and payer where reimbursement is contingent upon pre-specified real-world outcomes. Adjustments to the type of agreement may be needed in countries where citizens pay the majority of medical costs out of pocket.
SECTION IV: PRINCIPLES ON VALUE COMPONENTS IN ONCOLOGY

We agreed that it is useful to consider broader elements of value that early-stage cancer treatments bring to people with cancer, society, and the healthcare system overall. To this end, three value-related principles are put forward.

**Principle 5: Routinely use PROs in value assessments.** Data collected from patients via PROs including QoL should be routinely and consistently incorporated into value assessments, along with the value components that are already used relating to safety and efficacy.

Patient advocates stressed, and regulators, payers and oncologists agreed, that in appropriate trials, standard measures of clinical benefit need to be complemented with PROs that assess impact on QoL for people with cancer including importantly, tolerability in terms of frequency, duration and severity (grades 1-4) of adverse events (AEs). Two actions would support expansion of this goal:

1. **Improved and more consistent use of QoL data in value assessments:** QoL data are routinely included in regulators’ assessments and in many HTA assessments. Germany’s IQWiG, the US Centers for Medicare & Medicaid Services (CMS)⁷⁵ and the UK’s NICE review QoL data as part of their value assessments. Other HTA bodies and payers, including Haute Autorité de Santé (HAS) in France, are considering QoL data more often. However, the expert group highlighted that others, such as private insurers in the US, focus less on QoL in their review, particularly in areas such as oncology. Consistency here is vital. While a number of QoL instruments exist, patient advocate groups often report that they are too complicated or not relevant. Simpler tools are needed.

2. **In appropriate trials, utilization of PROs to collect QoL data and support cumulative reporting over time of lower-grade adverse events.** Recalibrating value frameworks to include information on lower grade adverse events that could impact QoL tolerability measures (e.g., pain, frequent diarrhea) would further support informed decision-making for oncologists and people with cancer alike. Patient advocates also encouraged the collection of tolerability data directly from people with cancer via PROs and other mechanisms to get a true understanding of a treatment’s tolerability from an individual’s perspective.

Fortunately, efforts are underway to identify challenges in collecting, analyzing and applying PRO data to inform regulatory and treatment decision making. In Europe, the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium was formed to set recommendations for PRO analysis in cancer trials⁷⁶. In the US, the FDA and the Critical Path Institute’s PRO Consortium co-sponsored an international workshop to explore how the NCI’s PRO-informed Common Terminology Criteria for Adverse Events (PRO-CTCAE) can be integrated alongside the physician-reported CTCAE⁷⁷. A systematic review of the literature in 2022 also determined that incorporating PROs has led to improvements in caregiver-patient-physician communication, patient risk group identification, unmet problems and needs detection, disease course and treatment tracking, prognostic markers, cost-effectiveness measurement and comfort and support provision people with cancer and those in a caregiving capacity⁷⁸.

**Principle 6: Assess broad economic impact of new medicines.** The economic impact of medicines is an essential component of the value assessment and should consider the downstream effect a medicine can have on the amount and associated cost of healthcare resources a patient eventually needs, as well as the socio-economic impact (paid and voluntary work) for patients and those in a caregiving capacity.

Patient advocates stressed, and regulators, payers and oncologists agreed, that in appropriate trials, standard measures of clinical benefit need to be complemented with PROs that assess impact on QoL for people with cancer.

Some payers, such as in Canada, Australia or the UK⁷⁹, use incremental cost-effectiveness ratios that compare incremental cost to QALY gained. In the US, there is no mandate to use QALYS to contain healthcare costs; in fact, some federal agencies are banned from using measurement tools like QALY while some states and federal partnerships, such as state Medicaid programs, may do so⁸⁰. Formalized analyses are often limited to costs within the healthcare system and exclude broader societal impacts that are examined by the various HTA bodies⁸¹. Recent research in Australia quantified $2.13 billion (AUD) ($1.38 billion USD using exchange rates at the time of publication) of return on investment over 5 years in societal benefit of new technologies, therapies and services that extend the prognosis and quality of life of people with non-curable cancers. Societal benefits incorporated in the analyses included ability to care for children, continue to support family financially and avoidance of emotional stress in having to say goodbye to loved ones⁸².

The ISPOR framework suggests additional economic value components⁸³. In our discussions on economic value components, we considered two important factors: a treatment’s socio-economic impact—the effect it has on a person with cancer or those in a caregiving capacity ability to engage in paid and voluntary work—and its impact on healthcare resource utilization overall. Socio-economic value components are equally important for early- and late-stage cancer and can usually be measured by patient-reported outcomes such as utility values (e.g., the European Quality of Life (EuroQol)’s Five Dimension system (EQ-5D-5L)⁸⁴ and Work Productivity and Activity Impairment (WPAI) questionnaires.

Direct costs of medicines, and the amount of healthcare used, are the mainstay measurements used for assessing healthcare costs. The lens should be widened to include broader societal costs such as the socio-economic impact for people with cancer and those in a caregiving capacity, as well as healthcare expenses that are avoided due to effective earlier treatments. Ways to measure these metrics are detailed in the literature so our group, and in particular the health economists, agreed that implementing them seemed feasible⁸⁵. Although some questioned whether this was the role of payers, there currently is no other established process where these factors could be assessed.
Principle 7: Consider other value aspects of relevance to patients and society. Insurance value, the value of choice, scientific spillovers, equity of access and real option value should be considered in value assessment, although they may not all be readily quantifiable and may instead require a more qualitative assessment.

A special ISPOR task force\(^1\) considered 12 important components of value. Within our group, we highlighted five: insurance value, value of choice, scientific spillovers, equity of access and real option value. While there is no consensus on how to capture these components quantitatively, a qualitative assessment could be undertaken for a given cancer indication with input from people with cancer or patient advocates. The five components were:

1. **Insurance value** captures value to healthy individuals of being protected from the physical and financial burden of illness due to availability of a new medicine or technology. Research suggests that most insurance value metrics disproportionately underrate treatments for the most severe illnesses, where physical uncertainty is the costliest\(^2\). Patient advocates valued this component because it provided assurance to people that should they get sick, there are treatment options for them. Every person with cancer is unique and each will have their own personal goals, appetites around uncertainty and QoL priorities.

2. **Value of choice** was vital for patient advocates, with an emphasis on bringing people with cancer’s concerns and preferences to regulators and payers directly in order to inform their assessments. For example, patient advocates said that some people with cancer may prefer significantly better QoL status over some OS benefit.

3. Technological breakthroughs can potentially have **scientific spillovers** benefits that enable advances beyond the current product or indication. This should be rewarded to recognize the uncertainties involved in innovation and to provide incentive. This value component has not been detailed comprehensively in the literature, but ICER pointed out\(^69,77\) that some HTA bodies, such as in Australia\(^86\), are starting to consider it. Avenues for measuring these components have been discussed, but no consensus has been reached\(^72,76,79\). Related to this concept is the consideration that earlier access to treatments means more data can be collected in a real-world setting and subsequently inform new innovations in development.

4. **Equity of access** was an important topic for our group, particularly for oncologists and patient advocates, as the benefits are only seen if people with cancer are aware of options, able to access and stay on treatment as appropriate\(^83\). Data from the US found that in disadvantaged neighborhoods, a lack of physicians and healthcare resources, weak referral systems, poor social support networks, and barriers to travel for initial and ongoing care negatively impact outcomes for people with cancer\(^46\). Health inequities—whether related to access to quality care or to genetic variation\(^76\)—are challenging components to measure and incorporating this should be rewarded\(^76\). Equity impact and trade-off analyses have been proposed to address this\(^79,81\). ICER acknowledges the importance of this value component but due to the lack of reliable measurement tools, it does not usually take equity into account\(^86\). We propose having innovators rewarded for addressing inequities in both drug development and post-approval access designs. This would give oncologists essential information on dosing and point to ethnic differences in patient response to a given treatment. Insights on access designs would help inform strategies to eliminate barriers that some populations have encountered when trying to access medicines.

5. **Real option value** would also be valuable, and it was especially so for our patient advocates and oncologists. Real option value is generated when treatments extend the lives and wellbeing of people with cancer so they can benefit from future treatment options and subsequent lines of treatment after their current treatment. Payers already to some extent consider this; for example, HAS in France designed option-value rewards for therapeutics that extend the life of a person with cancer so they might benefit from future treatments.

Our group discussed many other value components, but found less consensus on their importance and how they could be taken into account as part of access and reimbursement decision-making. The value of hope—which is when a subset of people with cancer are expected to have a durable response with impact on survival and QoL—was considered as a component, as it can be neglected when only summary measures of benefit such as median or average improvements are considered. Some payers may restrict access and reimbursement to those sub-populations likely to gain the most benefit, and payers, regulators, and health economists expressed concerns that people with cancer may have false expectations when treatment outcomes are highly variable.
SECTION V: NEXT STEPS: ADVANCING KEY POINTS IN THE CONSENSUS PRINCIPLES

Cancer science has ushered in many new and improved diagnostic tools and therapies that enable increasingly specific and earlier diagnosis and treatment—with better outcomes for people with cancer. We hope that the results of our group’s discussions, summarized in the principles outlined in this paper, provide stimulus and reference points for the evolution of value frameworks used to inform regulatory and reimbursement decision-making, as well as key considerations for medicines development.

The seven consensus principles articulated in this report offer a perspective from a number of experts across the healthcare ecosystem, including current or former patient advocates, payers, health economists, regulators, professional oncology societies and physicians with expertise in Australia, Canada, China, France, Germany, Italy, Japan, South Korea, Singapore, Spain, Sweden, the UK and US. Perspectives from those outside the countries represented here are needed, as care resources, experiences and outcomes vary widely across the globe.

Throughout these actions, collaboration across the cancer community is essential to make further progress on how value is assessed for early-stage cancer treatments. Below are some specific actions the cancer community can take together toward the goal of improving access to new medicines for early-stage cancer.

Increase awareness and further empower people with cancer to participate in value assessments

- Use best practices from public health campaigns to enhance awareness of the evolution of cancer-relevant endpoints involved in advancing research and development. Make curing cancers, where possible, a policy priority across countries.
- Establish best practices in value assessments that put the perspectives of people with cancer and those in a caregiving capacity in the center of the healthcare system.
- Have clear mechanisms in place so that any information that people with cancer will access as part of medicine assessments is provided in layperson terms and multiple languages to enable people with cancer and their advocates to fully participate.

Add to the science of oncology-relevant endpoints and leverage PROs

- Continue to encourage the use of a broad set of oncology-relevant endpoints (e.g., EFS, DFS, RFS, pCR, ctDNA) in clinical trials to further validate their relevance as endpoints either as predictors of clinical outcomes or endpoints with intrinsic value.
- Advance the deployment of large-scale linked data, machine learning and AI across the healthcare ecosystem to uncover optimal short- and long-term oncology-relevant endpoints for people with cancer.
- Prioritize the development of, and systemic use of, easy-to-use tools to capture PROs including tolerability data and QoL assessments.

Evolve value assessments, manage uncertainties and assess overall impact

- Consider expanding value components in therapy assessments to include, for example, insurance value, the value of choice, scientific spillovers, equity of access and real option value.
- Structure MEAs to manage clinical uncertainty and balance budgets.
- Develop mechanisms to capture and measure the downstream benefits of cancer care as well as broader value components to support the evaluation of treatment options for people with cancer, including socio-economic effects to people with cancer, those in a caregiving role and society.

Keep the conversation going. There are many different roles and experts across the healthcare ecosystem, but the cancer community shares common goals: to increase health equity and access, improve the experience for people with cancer from diagnosis through treatment, increase survival rates, and ultimately deliver cures. Science is continually advancing to support these goals. This paper outlines key value principles for assessing and evaluating that innovation, with interests of people with cancer at the core.
Bibliography


6. Hiom SC. Diagnosing cancer earlier: Reviewing the evidence for improving cancer survival. Br J Cancer. 2015;112:S1-S5. doi:10.1038/bjc.2015.23


29. Rare Cancers Australia and Canteen. Counting the Cost. 2022


32. Center for Drug Evaluation Research. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. FDA. Published online September 2021. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-licensure


64. NHS. Apply for the early access to medicines scheme (EAMS). Published online 18 December 2014. https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams
