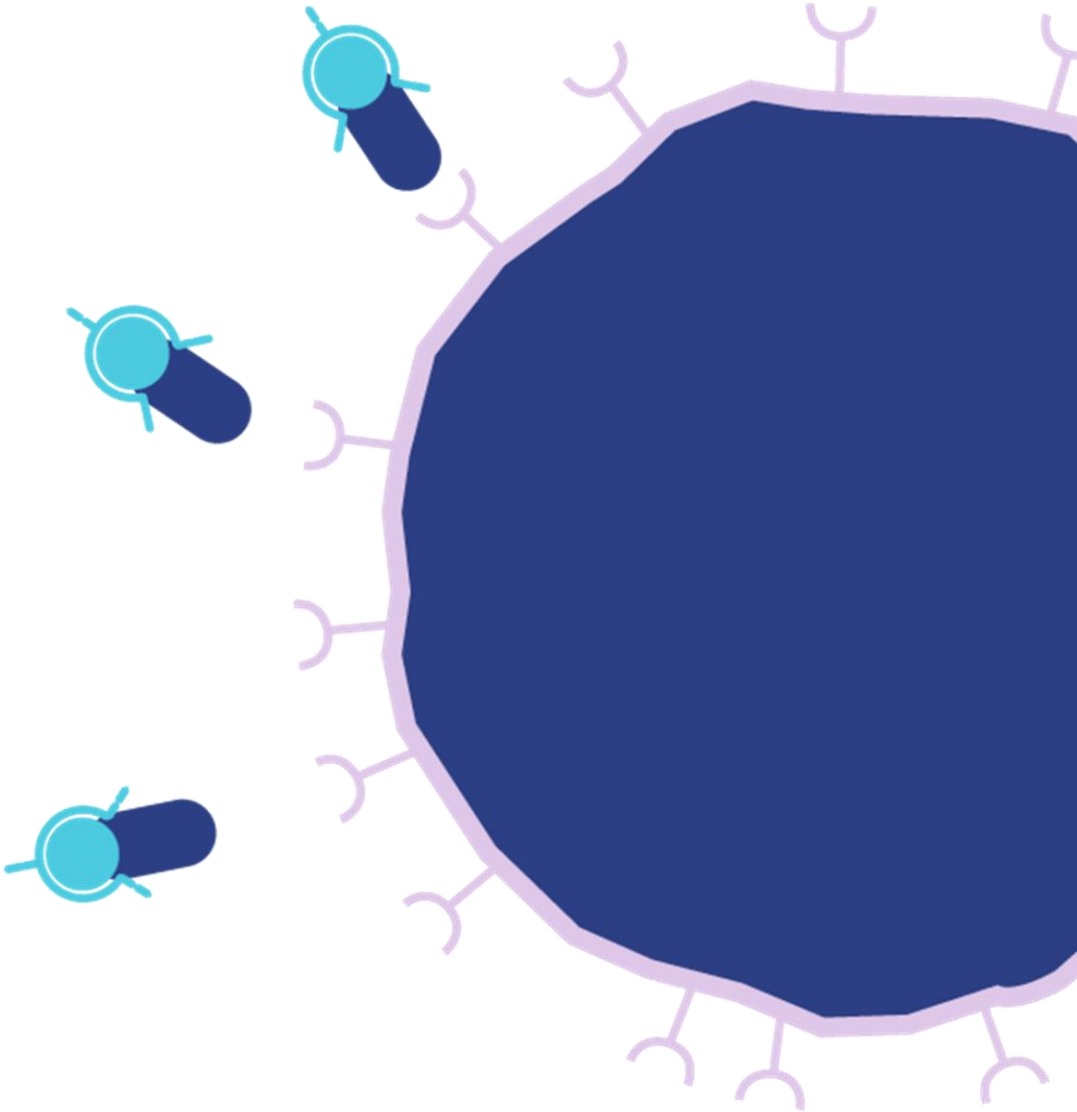

The Health Policy Partnership
[research, people, action]

Health system readiness for radioligand therapy in the US

Governance

Working paper

November 2021

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The Health Policy Partnership

Contents

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About this working paper

This working paper is part of a broader piece of work aiming to define what is needed to establish system-level readiness for radioligand therapy in the US. It explores current integration and future readiness for the therapy as it relates to governance, one of the five domains of the Radioligand Therapy Readiness Assessment Framework (*Figure 1*). The working paper provides answers to questions from the framework, with key findings from relevant subdomains outlined in a summary assessment at the start of each section. It captures relevant strategies and guidance for the management and delivery of radioligand therapy. Throughout the paper, we focus on the situation in neuroendocrine tumors, lymphoma, and prostate cancer.

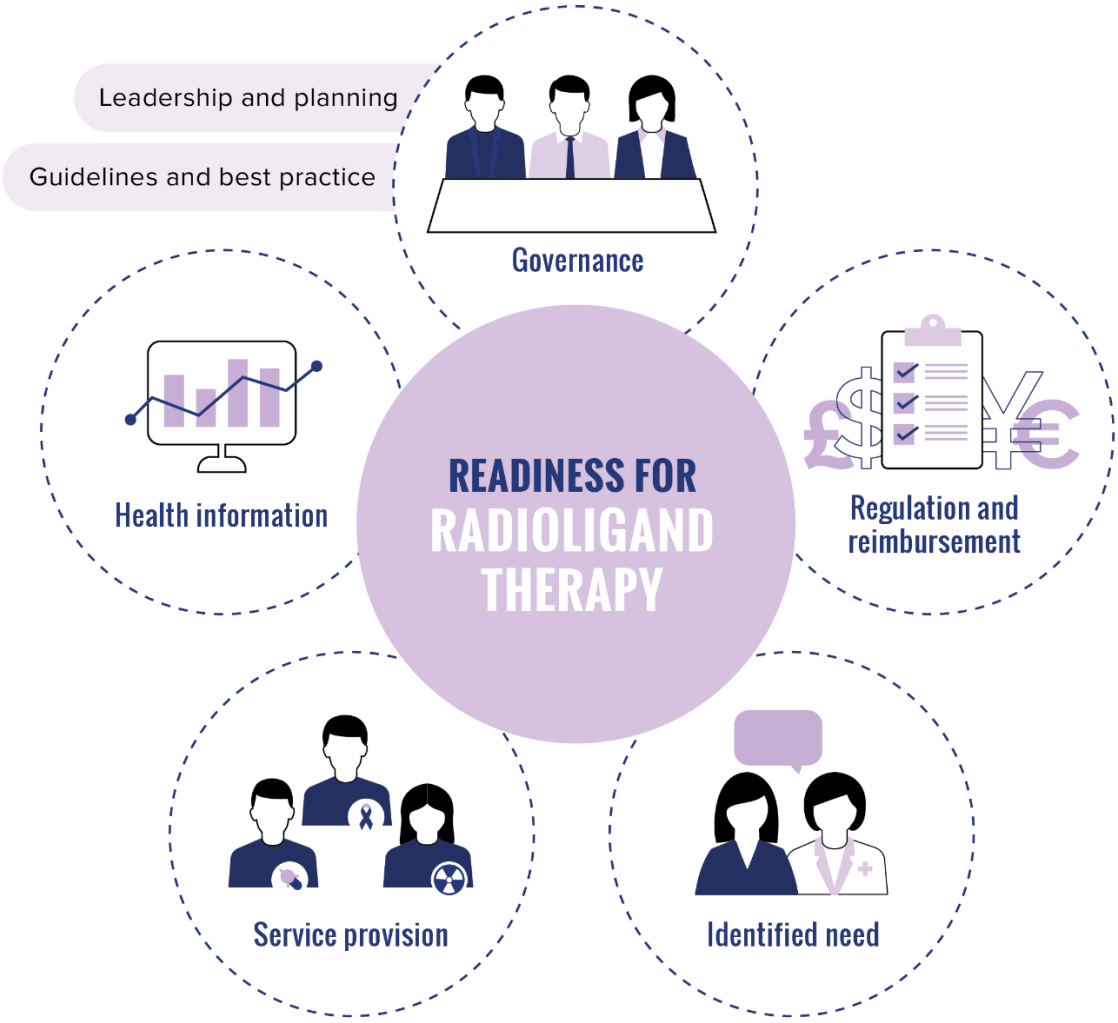
- This working paper is supported by other documents on health system readiness for radioligand therapy in the US. For more details, please visit: www.radioligandtherapy.com/framework/US

Terminology

This working paper uses the term radioligand therapy to refer to peptide-receptor radionuclide therapy (PRRT), prostate-specific membrane antigen (PSMA) therapy, and radioimmunotherapy. We appreciate that there are a variety of other terms that may be used for radioligand therapy.

Radioligand therapy is a specific subtype of radiopharmaceutical therapies. Where possible, this working paper includes data relating to radioligand therapy. However, where research about radioligand therapy is not specifically available, we may refer more broadly to radiopharmaceutical therapies.

Figure 1. Domains of the Radioligand Therapy Readiness Assessment Framework: US



What is governance?

Strong governance is an essential pillar of a functioning health system.[1] Governance is shaped by a country's specific context and history, and provides a value framework within which to act. However, it can be an elusive concept to define, assess and operationalize.[2] In cancer care, governance is the means by which services are organized and managed at the macro level, particularly with respect to improving quality and outcomes.[3]

Healthcare governance in the US encompasses a complex network of actors across various federal, state, and provider levels. While the federal government sets high-level ambitions for healthcare and research, it is left to a wide range of, often unconnected, institutions, providers and organizations to achieve these goals.[4] This decentralized approach leads to significant variation across the country. In the absence of a single governing body for cancer care in the US, a fragmented system poses a challenge to enacting system-wide healthcare improvements for cancer.[4]

What does good governance look like?

Effective governance for radioligand therapy requires federal and state-level leadership and strategic direction, in addition to well-defined guidance and protocols for its delivery in clinical practice. Federal cancer plans and strategies that consider radioligand therapy as a current component of cancer care, and commit to its future integration and funding, are essential for appropriate planning. Increasing political awareness of new therapies, such as radioligand therapy, will be critical for establishing their potential value for people with cancer, clinicians and payers, ultimately fostering leadership and readiness. Planning for effective integration of radioligand therapy also involves including it in clinical guidelines and care pathways, which should be actively used in practice.

1 Leadership and planning

Summary assessment

Indicators	Assessment
Are there any cancer strategies or plans in the US that include, or could include, radioligand therapy?	National cancer strategies determine research priorities and establish funding streams. But radioligand therapy is rarely addressed in these strategies or plans. Where it is mentioned, the therapy is addressed in the context of future areas of research rather than current use.
Are there any disease-specific strategies or plans in the US that include, or could include, radioligand therapy?	**Neuroendocrine tumors (NETs)**: No dedicated national plan or strategy for NETs, rare diseases or rare cancers was identified. **Lymphoma**: No dedicated national plan for lymphoma was identified. Regional cancer strategies occasionally mention personalized medicine for lymphoma, but do not specifically discuss radioligand therapy. **Prostate cancer:** No dedicated national plan specific to prostate cancer was identified. However, prostate cancer and radioligand therapy are occasionally included in the wider national cancer strategies, but only in the context of research or emerging therapies.
Is there national leadership and political support for radioligand therapy?	Patient and clinical organizations actively encourage recognition of, and funding for, radioligand therapy at a national and state level. However, these actions have yet to garner substantial political momentum.

There is no single national cancer plan that governs delivery of cancer care throughout the US. Recent high-level governmental initiatives include the Cancer Moonshot Blue Ribbon Panel[5] and the Annual Plan and Budget Proposal from the National Cancer Institute (NCI).[6] These can inform clinical research because they are seen as an indicator of where future funding strategies may be targeted.[7] Comprehensive Cancer Control (CCC) plans concretely outline how cancer should be addressed and optimally managed at the state level.[8] As this aspect of governance and planning is established for each state, prioritization of certain cancers or therapeutic approaches may differ widely depending on where a person lives.[9]

Radioligand therapy is infrequently discussed in state- or national-level strategies, but there is growing recognition of targeted therapies and personalized medicine, particularly in CCC plans. This recognition may mean that, despite a lack of explicit inclusion of radioligand

therapy, CCC plans are well placed to incorporate the therapy in the future. For example, some CCCs, such as those for Maryland and Michigan, discuss personalized medicine and targeted therapies.[10] [11] Other strategies contain relevant objectives for radioligand therapy, such as the NCI Annual Plan and Budget Proposal's aim to advance the development of precision radiotherapies.[6]

Initiatives are underway to improve awareness of and access to radioligand therapy. The NCI Radiation Research Program Targeted Radionuclide Therapy Working Group is just one group involved in this area.[12] Alongside the Society of Nuclear Medicine and Molecular Imaging (SNMMI), it has held three workshops about radiopharmaceutical therapies, including radioligand therapy (*Real-world example 1*).[13] Initiatives such as this can help establish a unified and multidisciplinary clinical perspective to present to policymakers and decision-makers. Lymphoma patient advocacy groups, such as the Leukemia & Lymphoma Society (LLS), seek to improve patient access to treatment through engagement with political decision-makers.[14] While current programs do not specifically address radioligand therapy, the approach is listed by LLS as a treatment for lymphoma.[14] This means that broad engagement programs focusing on reducing access barriers to lymphoma treatments may involve discussions around radioligand therapy. Political awareness of radioligand therapy seems to be slowly developing, but addressing access issues involves legislative action which, unfortunately, has yet to be realized.

Real-world example 1. Multidisciplinary clinical consensus building around radioligand therapy

NCI and SNMMI have hosted three joint workshops focusing on targeted radiopharmaceutical therapy between 2014 and 2019. The discussions aimed to establish a common terminology,[15] better understand combination therapies,[13] and highlight the importance of advocacy to ensure timely approval and adequate insurance coverage.[16]

Participants called attention to the importance of creating a multi-institutional infrastructure to facilitate the collection of data needed to support use of these therapies in the US.[15] Multi-institutional research networks can mitigate expertise gaps that exist within individual institutions, and a collaborative and multidisciplinary model can produce effective data to inform future research and policy.[15]

➔ For more information data collection in radioligand therapy, read the working paper on health information.

1.1 Neuroendocrine tumors

There is a lack of overarching policy prioritization and strategy for rare diseases, rare cancers and neuroendocrine tumors (NETs). Despite rare diseases, which include NETs, affecting an estimated 7% of the US population,[17] no national, regional or state plans for their management were identified in our research. While there are initiatives aiming to address specific challenges for rare cancers, such as the Orphan Drug Act of 1983[18] or the Rare Disease Act of 2002,[19] comprehensive governance or standard-setting at a federal level seems to be limited. However, the Rare Cancers Research Program, launched in 2020, may present opportunities for NETs research. It aims to prioritize research into prevention, detection, diagnosis, and treatment of rare cancers.[20]

Despite the lack of national strategies, the NETs clinical and advocacy communities have built significant momentum to prioritize research and treatment. The past decades have seen concerted interest and action from a policy perspective:

- In 2005, the Neuroendocrine Tumor Research Foundation (NETRF) was set up by a person with NETs[21] to directly support NETs research.[22]

- In 2011, the NCI produced research objectives for the treatment of NETs, which included radioligand therapy.[23]
- In 2013, a workshop of representatives of the NCI and SNMMI discussed the evidence and barriers to adoption of radioligand therapy for NETs.[15]
- In 2015, NETs research priorities were laid out by the NCI for the National Clinical Trials Network, and included systemic therapy using "targeted agents" for NETs.[24]
- In 2019, NETRF's research priorities led to the funding of new research projects on radioligand therapy.[22]

1.2 Lymphoma

There are no standalone national strategies for lymphoma but it is included in some state-level CCC plans. Most CCCs do not discuss lymphoma therapies, and if they do mention lymphoma, they do not refer to radioligand therapy.[25-27] However, Maryland's CCC plan notes that high-incidence cancers, such as lymphoma, can be treated with personalized medicine and targeted therapy.[10] As noted above, this could be taken to mean radioligand therapy.

To tackle limited political prioritization, patient advocacy groups have published national strategic plans to improve care for people with lymphoma. These typically focus on earlier diagnosis[28] and awareness raising.[29] While they do not specifically mention radioligand therapy or targeted therapies more generally, there are many relevant priorities for radioligand therapy within these plans:

- The Cutaneous Lymphoma Foundation published a national strategic plan for 2020–23, which focuses on improving education, community support, research, awareness, and advocacy.[29]
- The Leukemia & Lymphoma Society published its strategic plan in 2016, focusing on improving access to treatments through research and awareness-raising.[28]

1.3 Prostate cancer

A number of national and state CCC plans mention prostate cancer, but there is limited inclusion of therapeutic approaches. Efforts to address prostate cancer in the US are largely focused on prevention and early detection, and less on advanced prostate cancer or treatment. Healthy People 2030, a series of national health-related objectives set by the US Department of Health and Human Services, includes a goal of reducing death rates from prostate cancer but does not mention specific treatments or investigational therapies.[30] [31] This focus on prevention and early detection is also seen in CCC plans such as those for Florida and New York.[26] [27] Looking specifically at radioligand therapy, as it is under investigation in advanced prostate cancer, neither national nor CCC plans frequently include the approach – although some do in the context of research and trials, such as the congressionally directed Prostate Cancer Research Program.[32]

2 Guidelines

Summary assessment

Indicators	Assessment
Do national disease-specific guidelines, published by any US professional society or health body, include radioligand therapy?	**Neuroendocrine tumors (NETs):** Clinical guidance documents authored by the North American Neuroendocrine Tumor Society and the National Comprehensive Cancer Network (NCCN) include recommendations to use radioligand therapy for the management of NETs. **Lymphoma**: NCCN clinical guidelines for lymphoma include recommendations to use radioligand therapy as a first- and second-line treatment for certain types of lymphoma. No US-based lymphoma- or hematology-related professional societies have published clinical guidelines for lymphoma. **Prostate cancer:** While the NCCN, the American Society of Clinical Oncology and the American Urological Association have developed guidelines for advanced or metastatic castration-resistant prostate cancer, none mention radioligand therapy as it has not gained approval from the US Food and Drug Administration.
Is there guidance for the delivery of radioligand therapy across clinical indications that is publsiehd centrally by any US professional society or health body?	Multiple guidance documents exist to support the delivery of radioligand therapy which describe disease-specific delivery components as well as the wider workforce and infrastructure requirements. They are designed to allow sufficient flexibility for center-specific adaptation.

2.1 Radioligand therapy guidance in neuroendocrine tumors

Radioligand therapy is included in relevant national clinical guidelines for NETs. The North American Neuroendocrine Tumor Society (NANETS)[33-36] and the National Comprehensive Cancer Network (NCCN)[37] have authored separate clinical guidelines on the medical management of NETs, which recommend the use of radioligand therapy for people with somatostatin receptor-positive midgut NETs. The guidelines largely align, but differ in certain eligibility criteria. For example, the NCCN specifies additional eligibility criteria to NANETS, including a well-differentiated NET and adequate bone marrow, renal,

and hepatic function. Additional guidelines are expected in the near future as the American Society of Clinical Oncology (ASCO) identified advanced NETs as a priority area for guideline development in 2020–21.[38]

Clinicians and payers may rely on different guidelines, which may lead to variable approaches to radioligand therapy. Nuclear medicine specialists, medical oncologists, surgical oncologists, and radiation oncologists seem to commonly refer to both the NCCN and NANETS guidelines when managing NETs.[39] Nuclear medicine professionals also refer to the SNMMI delivery guidelines to provide guidance on procedures and use of radioligand therapy; for this reason, nuclear medicine professionals refer to them as part of their practice.[7] The NCCN guidelines are built on the experiences of comprehensive cancer centers in combination with more traditional guidance from systematic literature reviews,[40] and present a variety of possible therapeutic options. They are therefore considered a good reflection of real-world practice and are reported to be commonly used by payers when determining coverage and reimbursement policies. NCCN guidelines do not recommend a preferred sequence of therapeutic options, which may lead to clinical variability in tumor management across the country. A lack of consensus across guidelines may result in variable clinical approaches to disease management and choice of treatment.

2.2 Clinical guidelines for lymphoma

There are a limited number of lymphoma guidelines available to clinicians. While the NCCN has authored comprehensive guidelines for the management of lymphoma,[41] it is of note that no clinical guidelines for lymphoma have been published by the American Society of Hematology, the American Society for Radiation Oncology (ASTRO) or ASCO. This may suggest low prioritization for lymphoma in terms of guideline creation. Guidelines are published by the International Lymphoma Radiation Oncology Group (ILROG), but these focus on radiotherapy for lymphoma and do not mention radioligand therapy.[42-44] ILROG guidelines for lymphoma are widely used in a number of countries[45] and may represent an opportunity for future inclusion of radioligand therapy.

When radioligand therapy is referenced in lymphoma guidelines, it is positioned as a low-priority treatment, which impacts its use. The currently licensed radioligand therapy is included in NCCN guidelines for certain types of lymphoma,[41] but it is not listed as a preferred regimen. As research into novel uses of radioligand therapy in lymphoma is

underway, it will be important to ensure that any newly approved therapy is included appropriately in the guidelines so that it can be made available to all people who might benefit.

2.3 Clinical guidelines for prostate cancer

Prostate cancer management is governed by several clinical practice guidelines, but the optimal approach for advanced prostate cancer is not always clear**.** Guidelines have been published by the NCCN,[46] ASCO[47 48] and the American Urological Association (AUA, in collaboration with ASTRO and the Society of Urologic Oncology).[49] Experts report that these guidelines serve different purposes: the NCCN guidelines are algorithm-driven which can be helpful in the clinic setting, while the AUA guidelines undergo a broad evidence review to ensure they are data-driven in guiding the management of advanced prostate cancer.[50] Guidance for advanced prostate cancer is less straightforward than that for earlier stages of prostate cancer. One expert noted that this may be thanks to the multitude of therapies available for advanced prostate cancer, diversity of presentation, and the lack of evidence regarding which sequence of therapies is most effective.[51] Further research into therapies for advanced prostate cancer may help strengthen these guidelines and support evidence-based, personalized therapeutic approaches.

Clinical guidelines for prostate cancer do not yet explicitly discuss radioligand therapy. This is to be expected, as radioligand therapy for prostate cancer has yet to be reviewed by the FDA, and professional societies do not typically recommend non-FDA-approved therapies in their guidance. Should radioligand therapy be approved, recent experience suggests that inclusion in the guidelines would be relatively rapid. Specifically, a less-targeted radiopharmaceutical therapy, radium-223, was included in NCCN and AUA guidelines for prostate cancer just two months after FDA approval.[46 52]

2.4 Guidance for the delivery of radioligand therapy

Technical guidelines for radioligand therapy outline core delivery standards, but explicitly leave flexibility and autonomy to the clinicians and institutions. Various professional bodies have developed technical standards for the delivery of radioligand therapy that are either general, technical guidelines,[53] or disease-specific guidelines.[54 55] They are designed to guide patient selection; radiation safety; toxicity monitoring; waste

management; and roles, responsibilities and training requirements for the healthcare professionals involved. All guidance documents highlight the necessity of multidisciplinary collaboration for the optimal delivery of radioligand therapy, but are otherwise not designed to be strict protocols. They leave ample room for center-level adaptation, given the diversity of settings and institutions in which radioligand therapy is provided.[56] For example, documents suggest that radioligand therapy can be administered to inpatients or outpatients in the oncology infusion or nuclear medicine setting, as long as safe handling of radionuclides is ensured. Many experts have noted that they tailor the guidance based on their personal experience, each individual patient, and hospital processes.[33 39 51 56 57]

➔ For more information on multidisciplinary working, read the working paper on service provision.

Guideline flexibility may lead to variations in the delivery of radioligand therapy between different centers. These variations – based on institutional protocols, infrastructure, or individual interpretation of the guidelines – may lead to people with cancer who are treated at different sites receiving different standards of care. A patient advocacy expert noted that the variability in post-treatment protocols between centers is leading to confusion among people receiving radioligand therapy, with some patients taking unnecessarily stringent precautions under the assumption that they are following protocols.[58] To better prepare for the optimal integration of radioligand therapy into US health systems, there may need to be wider consensus building on minimum standards of care and processes for the multidisciplinary coordination of radioligand therapy. A recent publication from ASTRO focuses on this issue, highlighting the importance of a multidisciplinary approach for delivery of radioligand therapy in anticipation of increased availability of and demand for the therapy in the future (*Box 1*).

Box 1. A framework for patient-centered pathways for care for radiopharmaceutical therapy: An ASTRO Consensus Document

ASTRO convened a multidisciplinary group of experts in 2020 to develop a consensus statement addressing the projected growth of radiopharmaceutical therapy.[59] The goal is to ultimately provide guidance to inform future practice for these therapies.[59] Given the number of therapies in clinical use and in late-phase clinical trials, the approach will impact a larger number of people with cancer in the future. Furthermore, the likely complexity of such people's conditions means that it will be essential to provide highly coordinated multidisciplinary care.[59]

The group put forth a framework for developing pathways of care that can be broadly applied to all similar therapies, now and in the future. A central focus is to promote enhanced coordination and collaboration among appropriately qualified personnel with diverse expertise in radiologic care and multidisciplinary oncology care.[59]

Conclusion

The complex and fragmented approach to healthcare governance in the US has led to cancer care policy being decentralized. National groups and governmental agencies determine and fund research priorities, and professional societies outline clinical guidance, but there is no single overarching strategy specific to cancer care. The lack of top-down, cancer-specific, national strategies has led to a patchwork of state-level cancer plans. This variety of approaches may complicate the consistent integration of new therapies into daily practice. In time, radioligand therapy will need to be addressed across many different plans and policies.

Variability of care will require enhanced coordination across the system. Technical and clinical guidelines in the US are intended to be adapted based on the lead clinician's expertise and each institution's health infrastructure capacity. This means that care processes and approaches may vary between different specialists or centers. Developing standards to enhance care coordination and alignment across the health system will be important to support more consistent use of radioligand therapy in the future.

Inclusion in clinical guidelines is not the only requirement for timely integration of a therapeutic approach. Radioligand therapy was relatively quickly integrated into clinical care for NETs: clear clinical and delivery guidelines were certainly an important facilitator alongside pre-existing close multidisciplinary teams, but the process was aided by the fact that the patient population is small and there were few other therapeutic options. Treatment prioritization in guidelines may play a role in how much a treatment is used. Lymphoma guidelines include the use of radioligand therapy only as a peripheral treatment option; this may contribute to underuse of the approach and low awareness among clinicians. As prostate cancer affects a larger population, there may be more variability in care, and new challenges to timely integration may emerge. While newly approved therapies seem likely to be swiftly included in clinical guidelines, enhanced awareness and understanding of these new therapies among relevant clinicians and decision-makers will be necessary to ensure that inclusion in guidelines translates into use in practice.

Bringing radioligand therapy to the forefront of the policy agenda requires consensus and action from all parties. This places an imperative on collaboration across the clinical and advocacy communities, regardless of specialty. For radioligand therapy, as a complex and emerging therapy, such cross-sectoral efforts will be even more essential. This joint effort will take considerable time and work, but is an important step for cancer care in the future.

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