Health system readiness for radioligand therapy in the US

SITUATION ANALYSIS REPORT

November 2021

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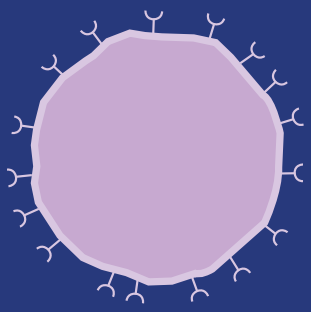
The Health Policy Partnership
[research, people, action]



ABOUT THE RADIOLIGAND THERAPY READINESS ASSESSMENT PROJECT

This report 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 is supported by other documents including a policy action blueprint on health system readiness for radioligand therapy in the US, an associated national framework, and five working papers. For more details, please visit **www.radioligandtherapy.com**

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With many thanks to our US Expert Advisory Group members:

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ABOUT THE HEALTH POLICY PARTNERSHIP

The Health Policy Partnership (HPP) is an independent research organization, working with partners across the health spectrum to drive the policy and system changes that will improve people's health.

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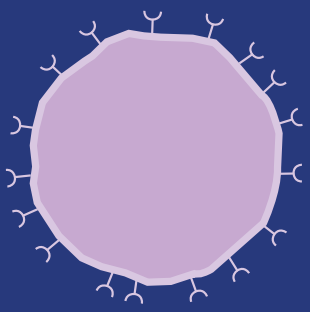


Foreword

Radioligand therapy is a promising, targeted cancer therapy that we have seen improve the lives of people with certain types of cancer. The therapy is currently used in neuroendocrine tumors and is being explored in metastatic prostate cancer, lymphoma, and other cancers. As many new applications of radioligand therapy are currently under investigation, the number of people who could benefit from it may grow substantially in the future.

Healthcare provision in the US is a mosaic; an individual's experience is influenced by where they live, their socioeconomic status, race, and more. We have seen how current provision of radioligand therapy can be inequitable and inconsistent. Without careful and considered planning, and education of medical professionals and decision-makers, approval of new therapies may exacerbate existing inequalities. Existing models of care are unlikely to be suitable for larger patient populations; we need to adapt referral pathways and reimbursement practices to ensure that the US is ready for the future of radioligand therapy. Without these changes, eligible patients may not receive a potentially beneficial therapy.

This report aims to clarify the overarching challenges and opportunities for greater readiness and integration of radioligand therapy, both now and in the future. It provides insight into where changes in delivery and infrastructure are needed, with a concrete way forward provided in the accompanying policy action blueprint: *Creating a ready health system for radioligand therapy in the US*. Because the barriers to integration of radioligand therapy are system-wide, we need representatives from all groups involved in developing, planning, and delivering radioligand therapy to work together to overcome them. We hope that these materials help to prompt health policy discussions and facilitate planning for radioligand therapy, ultimately contributing to wider health system readiness.

The COVID-19 pandemic has exacerbated existing challenges in cancer care. However, it has also led to rapid changes in how we think about and manage healthcare. Now is the time to act, working together to make sure that people with cancer can promptly get the care they need.

Josh Mailman,
NorCal CarciNET

Dr. Michael Morris,
Memorial Sloan Kettering Cancer Center

Executive summary

Radioligand therapy is a highly targeted cancer therapy that has been shown to significantly improve survival and quality of life for people with certain types of neuroendocrine tumors (NETs), lymphoma and prostate cancer.[1-6] In the US, radioligand therapy is approved for use in NETs and lymphoma. The therapy is under investigation for use in these and many other types of cancer and system changes will be required for its delivery to larger patient populations in the future.

The US needs to be ready for the wider use of radioligand therapy. Planning for the expansion of radioligand therapy requires multidisciplinary and multi-sectoral collaboration. Everyone involved in cancer care must work together to actively integrate radioligand therapy into all areas of the health system to ensure that it is made available to all people who could benefit from it.

STAKEHOLDERS IN THE US WILL NEED TO COMMIT TO:

- **Improving awareness and training** opportunities to ensure radioligand therapy is considered for all people who might benefit
- **Greater consensus building and multidisciplinary working** to make sure best practice is well communicated and radioligand therapy is included appropriately in relevant guidelines
- **Supporting the development of clear and adaptable pathways** for referrals and care delivery to guarantee every eligible person can receive radioligand therapy seamlessly as part of their ongoing care
- **Clarifying the financial feasibility** of radioligand therapy referrals and delivery to help expand the number of centers providing the approach
- **Careful planning** for future radioligand therapy services to ensure equitable access for all people who need it, regardless of where they live
- **Expanding data collection and analysis** to inform appropriate sequencing, resourcing and service planning for radioligand therapy

This report aims to support policymakers, decision-makers and the wider cancer community in taking action to build readiness for radioligand therapy in the US.

Introduction

What is radioligand therapy?

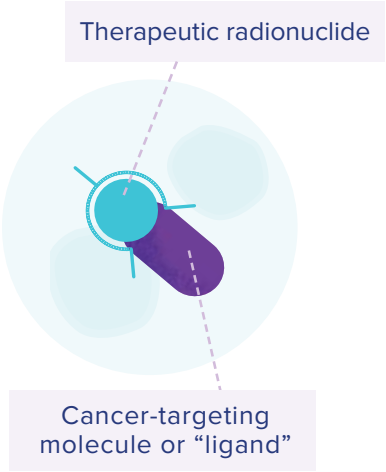


FIGURE 1. Radioligand

Radioligand therapy is a highly targeted therapy that has demonstrated positive outcomes for people with certain types of cancer. A radioligand is made up of two parts: a ligand, which is able to find cancer cells that present a particular receptor, and a radionuclide, which is able to treat the cancer (*Figure 1*).[7,8] Radioligand therapy has been shown to improve progression-free survival and health-related quality of life for people with certain types of neuroendocrine tumors (NETs), lymphoma, and prostate cancer.[1-5,9]

Therapies involving radionuclides are commonly used in cancer care. Radionuclides have been used to treat differentiated thyroid cancers and bone metastases for decades.[10,11] Radioligand therapy has evolved from this general approach; it has enhanced precision not just at an organ level, but at a cellular level. This targeting leaves healthy cells largely unaffected, reducing side effects of treatment.[7,9]

The US Food and Drug Administration (FDA) has recognized radioligand therapy's clinical benefits for patients. The FDA reviewed radioligand therapy for NETs and lymphoma through the prioritized pathway, which is designed for therapies with the potential to significantly improve treatment or address an unmet need.[12,13] In June 2021, the FDA granted the therapy breakthrough designation in metastatic castration-resistant prostate cancer (mCRPC), which means that a full review of the therapy may be expedited.[14]

Use of radioligand therapy

Radioligand therapy is currently approved in NETs and lymphoma, but its use varies in practice. In 2014, estimates suggested that over 170,000 people in the US were living with NETs;[15] radioligand therapy is commonly administered to eligible patients at some point in their treatment pathway. By contrast, for various reasons, the therapy is rarely used in lymphoma,[16] a condition which affected an estimated 960,000 people in 2018.[17,18] New applications of radioligand therapy are being explored in both types of cancer,[19-22] potentially increasing the number of people who will be eligible for the therapy in the future.

Preparing for the future

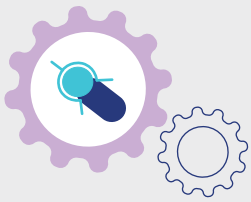
Ensuring system readiness for radioligand therapy

Radioligand therapy is currently under investigation in many cancers. In addition to NETs and lymphoma, studies are ongoing for mCRPC, metastatic breast cancer, and cancers of the central nervous system, among many others.[23-26] Combined, these cancers affect much larger patient populations than those for which radioligand therapy is currently indicated. Even if radioligand therapy will not be appropriate for everyone with these cancers, its approval would still spark an increase in the number of people who could benefit (see *Appendix*). Careful planning is therefore needed to ensure it can be integrated into care systems quickly and equitably, and that appropriate models of care are adopted to facilitate this.

Proactive planning can help ensure that provision of radioligand therapy does not exacerbate inequalities in access to care. It is widely acknowledged that race, socioeconomic status, and geographical location impact experiences with health services in the US,[27] and cancer care is no exception. Once the current and potential future inequalities have been identified, service providers, patients, and regulators can work together to overcome them and enable equitable provision of radioligand therapy and other innovative treatments. The January 2021 Executive Order on Advancing Racial Equity and Support for Underserved Communities[28] may help increase the amount of federal attention and funding that such initiatives receive.

Readiness for radioligand therapy means the necessary people, policies, processes, infrastructure, and resources are in place to facilitate its prompt adoption into clinical practice. These components must have sufficient flexibility to ensure that the approach can be integrated in the most effective way within an ever-evolving context (*Box 1*). To achieve readiness for radioligand therapy, we have developed the Radioligand Therapy Readiness Assessment Framework.[29] It allows us to investigate what is needed to integrate radioligand therapy into the US health system, and is built around five domains of cancer care: governance, regulation and reimbursement, identified need, service provision, and health information.

BOX 1.



What do we mean by integration and readiness for radioligand therapy?

Integration is the adoption and assimilation of radioligand therapy into every aspect of a health system (i.e. governance, regulation, reimbursement, funding, and service delivery frameworks) in order to ensure its availability to all people who may benefit from it.

Readiness is the ability of the health system to rapidly and sustainably adapt policies, processes, and infrastructure to support integration of a new radioligand therapy.

This document outlines the policy barriers to and opportunities for better integration of radioligand therapy within cancer care in the US, today and in the future. It comprehensively summarizes the current integration of radioligand therapy, looking specifically at NETs, lymphoma and prostate cancer. The document also clarifies the necessary system-level components that need to be aligned to ensure readiness. We hope it will support policymakers, decision-makers, and the wider cancer community in understanding which areas of the health system require policy action to improve integration of radioligand therapy.

Integration and readiness for radioligand therapy: strategic challenges

Awareness and training

There is mixed awareness and understanding of radioligand therapy among people who might benefit from it. People with cancer and their loved ones can play an important role in advocating for the equitable availability of novel therapies, such as radioligand therapy. In the US, limited information is available about radioligand therapy for prostate cancer,[30] and the existing information about lymphoma does not account for ongoing clinical trials.[31-33] As such, people with these cancers may not be aware of the therapy or know that it is currently being investigated. Many people with NETs are aware of radioligand therapy,[34] as the treatment is well established and often discussed on research, advocacy and national cancer organizations' websites. However, information about the therapy is inconsistent, with eligibility criteria varying between patient advocacy and national clinical organization sources.[35-37] Consistent and accurate information is required to ensure that people with cancer understand, and can discuss, their treatment options, and advocate for themselves.

"We need to ensure that information about different therapies is readily available and accessible to people with cancer, so that they can make informed decisions about the most appropriate treatment path."

PETER FRIEND,
Us TOO International

Referring physicians are not always educated on approved radioligand therapy, which may mean they are not aware of it. Endocrinologists, gastroenterologists, medical oncologists, or hematologists are responsible, on their own or with other specialists, for recommending a treatment plan for people with NETs and lymphoma. Despite being a well-established treatment for these cancers, radioligand therapy is not routinely included in physician training,[38-44] for reasons that remain unclear. As a result, some of them may not always be aware of, or familiar with, the therapy. Without physician awareness, people who might benefit from radioligand therapy may not be identified, informed about this treatment option, or referred to professionals who can deliver it. Training curricula for referring physicians should be regularly updated to include relevant information about approved therapies.

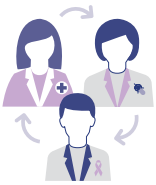
"Younger physicians who weren't involved in early clinical trials in lymphoma haven't even thought about [radioligand therapy]. And if their mentors or institutions haven't used it, they're never going to use it. They're never going to look into it."

DR. LEO GORDON,
Northwestern Medicine

Training for healthcare professionals who can deliver radioligand therapy is extensive. As part of their general training, nuclear medicine physicians, radiation oncologists, and nuclear radiologists are trained in the use of radioligand therapy for lymphoma,[45] [46] and radiopharmaceuticals more broadly.[45-47] However, formal training on radioligand therapy in NETs only occurs as part of additional training, for example if clinicians become higher-level Authorized Users (AUs) licensed to deliver injectable radiopharmaceuticals. AUs must demonstrate extensive clinical and training experience, and these requirements may discourage some professionals from pursuing the qualification. It is crucial that AU training equips physicians to deliver radiopharmaceuticals safely and appropriately. Efforts should also be made to ensure that AU training is accessible and that there are enough licensed professionals to meet growing demand for radioligand therapy. Although the need for more AUs is not universally acknowledged, discussions are ongoing around the potential expansion of AU licenses to new specialties,[48-50] which may ultimately help expand the radioligand therapy delivery workforce.

→ To find out more, please refer to the working paper on identified need

→ To find out more, please refer to the working paper on regulation and reimbursement



Consensus building and multidisciplinary working

Multidisciplinary working early in the care pathway can help ensure that all people who might benefit from radioligand therapy are identified. Aside from training, some ways in which referring physicians can become aware of radioligand therapy is through tumor boards, professional and journal committees, and other (formal or informal) multidisciplinary working patterns.[51-54] While radiation oncologists may already work closely with medical oncologists and other specialists, the involvement of nuclear medicine physicians has historically been more limited, and they are not as ingrained in multidisciplinary care processes or tumor boards.[54-56] Ensuring that nuclear medicine physicians and radiation oncologists who are aware of radioligand therapy are included in treatment decisions from an early stage will help increase overall awareness of the therapy. Currently, these specialists are not present in every center or clinic.[54] [57-59] As radioligand

"I think that we need to have more teamwork in the management of patients. If nuclear medicine physicians can work together with oncologists, then we would be better at managing these patients."

DR. SUZANNE LAPI,
The University of Alabama at Birmingham

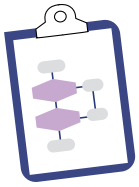
therapy is explored in new indications, and more specialists and centers become involved in its delivery, ensuring multidisciplinary care may become increasingly challenging. Telemedicine and virtual tumor boards, which gained traction during the COVID-19 pandemic,[60] have the potential to improve engagement with nuclear medicine physicians and radiation oncologists who are familiar with radioligand therapy.

It will be important to support the review and appropriate incorporation of any newly approved therapy into guidelines for relevant indications. Guidelines can help standardize care and increase awareness of a therapy. Oncologists and nuclear medicine specialists treating NETs commonly use guidelines from the North American Neuroendocrine Tumor Society (NANETS) and the National Comprehensive Cancer Network (NCCN).[55 58] Both guidelines recommend the use of radioligand therapy,[61-65] though the NCCN eligibility criteria contain more requirements (such as renal and hepatic function) than the NANETS equivalent. NCCN guidelines for lymphoma recommend radioligand therapy, although it is not listed as a preferred regimen.[66] As further data are collected on the use of radioligand therapy in NETs, lymphoma, and prostate cancer, it will be important to support swift and standardized updates to guidelines. Consistent inclusion of physicians who manage and deliver radioligand therapy in relevant guideline development committees would help ensure that treatments are appropriately considered during drafting or updates and that guidelines include the consensus opinion on when therapies should be considered and the practicalities of their use. Ultimately, this would enable physicians with limited access to multidisciplinary working to be exposed to diverse treatment options.

→ To find out more, please refer to the working paper on governance

"Everyone who's going to be involved in the care needs to be at the tumor board and on guideline committees. That leads to a collaborative environment and new things get integrated. When you're more disparate and you're not participating, that's when opportunities for innovation are missed."

DR. RONALD ENNIS,
Rutgers Cancer Institute of New Jersey



Referrals and care delivery

Successful delivery of radioligand therapy requires collaboration between healthcare professionals and streamlined coordination of services. Once the referring physician has identified a person who may benefit from radioligand therapy, a formal eligibility assessment is completed. For people with NETs or prostate cancer, this includes specialized positron emission tomography–computed tomography (PET-CT) or gamma imaging with a diagnostic radionuclide.[67-70] This type of imaging is not always available, especially in more rural or remote communities,[59 71] which may be a barrier to patient identification. Once appropriately identified, eligible patients can be referred to a facility or physician who is authorized to deliver radioligand therapy (the AU).[72] Having confirmed the patient's eligibility, the AU works with the referring physician and a multidisciplinary team to develop a personalized treatment plan, order radioligand therapy, and deliver it in line with appropriate regulations.[72] Given the complex processes and interactions required, clear referral pathways and models of care are essential to ensure consistency of care and enable appropriate use of the therapy.

"Radioligand therapy and imaging agents need to be ordered ahead of time, sometimes several days [earlier], and there are also regulatory requirements. It requires a lot of communication, planning, and coordination to walk through the entire workflow."

DR. DANIEL LEE,
Ochsner Medical Center

There are currently no standard referral pathways for radioligand therapy in NETs or lymphoma. As such, processes for prescribing, referring people for, and delivering radioligand therapy may vary.[54 73] While a certain level of flexibility can help ensure that care best fits the unique attributes of a given health facility, the absence of any overarching referral process makes it difficult for new centers to start offering the therapy. Recognizing the lack of adequate referral pathways, in 2020 the American Society for Radiation Oncology (ASTRO) convened a multidisciplinary group of experts to create a framework for developing these pathways.[72] The framework can be broadly applied to all radiopharmaceutical therapies.

→ To find out more, please refer to the working paper on service provision

Standard referral pathways for different settings will be particularly important if radioligand therapy is used in prostate cancer and its use is expanded in lymphoma.

The current systems for delivering the therapy in NETs seems largely appropriate to meet the needs of the rare cancer population. However, new referral pathways will be essential if there is increased use of radioligand therapy in lymphoma, prostate cancer, and other cancers that are predominantly treated in community settings. There is evidence that physicians in these settings may face greater barriers to referrals,[74] though research is not specific to radioligand therapy. An expert has noted that, in addition to identifying people who may benefit from radioligand therapy, physicians in community settings must navigate an unknown referral process and may not have existing referral network or professional connections.[16] Creating referral pathways that account for the additional challenges in these settings will help ensure that radioligand therapy is considered for all people who might benefit from it, regardless of geographical location or immediate access to an academic or specialist center.

"You have referral pathways that you need to focus on, and that requires strong data-driven guidelines, especially when involving different sub-specialists. In the large private clinical practice environment, that internal referral can more readily happen. But you also must look at the smaller urology practice environment and how they access sites that can deliver radioligand therapy (destination service providers). So, you have those different cost and care models all functioning in the community medical marketplace."

THOMAS PAIVANAS,
The CUSP Group

Effective referral pathways should be simple, clearly outlining the role of the referring physician.

Even in centers where referral pathways for radioligand therapy exist, physicians may be reluctant to use them if they are too complex or unclear.[16] This is particularly important for physicians who must refer their patients for treatment outside of their center or hospital network. Referring physicians can and should be involved in treatment planning, and be kept informed of a patient's progress throughout treatment. Without this regular communication and collaboration, referring physicians may not always know their role and may be reluctant to recommend radioligand therapy for fear of losing the patient to another institution or physician.[55] Clarifying the role of the referring physician, and creating opportunities for referring physicians to become professionally familiar with AUs, may increase their willingness to consider the therapy.

Financial feasibility

Ensuring that institutions, physicians, and patients are adequately reimbursed for all aspects of radioligand therapy is essential for the therapy's use. Establishing a radioligand therapy service requires investment for set-up, including separate patient rooms, adequate facilities for imaging and waste disposal, significant personnel training, and administration. Hospitals may qualify for financial support to cover some aspects of this, for example through the Medicare New Technology Add-on Payment, but there are strict eligibility criteria.[75] Where such funding is not available, some care providers may not consider the set-up costs to be adequately offset by the current level of reimbursement.[53 76] Once the necessary set-up is complete, the cost of radioligand therapy, which is set by the pharmaceutical industry, may be covered by Medicare and Medicaid, or by private insurers. Medicare has set a national reimbursement amount for radioligand therapy in NETs and lymphoma,[77 78] but the current reimbursement for the therapy and associated imaging may not be sufficient for all providers. This means that some hospitals lose money – sometimes up to $15,000[77] – on each procedure.[53 79] Radioligand therapy for use in NETs and lymphoma is also included in several private health insurance plans.[80-83] However, an expert has noted that patients can still incur substantial out-of-pocket costs, which vary between states, institutions and insurance providers.[84] Without adequate reimbursement for all aspects of radioligand therapy delivery, patients, physicians, and institutions may be unable or unwilling to use the therapy. More clinical and economic data are required to fully understand the cost of radioligand therapy and support reimbursement decisions.

→ To find out more, please refer to the working paper on regulation and reimbursement

"Physicians and institutions are – consciously or unconsciously – going to be motivated by providing therapies that are reimbursed to a level that will allow them to keep their doors open."

DR. MICHAEL MORRIS,
Memorial Sloan Kettering Cancer Center

Complex reimbursement processes and perverse incentives may further discourage hospitals and physicians from providing radioligand therapy. Once services are established, the therapy's high price can trigger coverage reviews, and many private insurers will require extensive evidence to pre-authorize the therapy.[85 86] Further, policies around payment bundling may mean that cancer therapies such as radioligand therapy are not fully reimbursed.[58 87] An expert has suggested that retaining patients for the duration of their treatment is likely to be a net gain, which may encourage some centers to provide radioligand therapy even if reimbursement is insufficient or complex.[51] However, this may not be enough of an incentive for community-based centers or smaller private practices that see fewer patients or lack effective referral and reimbursement networks with larger hospitals. Physicians at these centers may face administrative and economic barriers to referring patients,[79 88] which may prevent them from prescribing or referring their patients for radioligand therapy.

"When costs are bundled, we're getting back a small fraction of the actual price, if that. If institutions do their business modeling and see this, they're unlikely to make radioligand therapy available."

DR. ERIK MITTRA,
Oregon Health & Science University

Equitable access

Radioligand therapy is predominantly provided in large centers, which may limit its availability for certain populations. When radioligand therapy is delivered, whether in clinical practice to people with NETs or in clinical trials, this typically takes place in large academic or integrated centers via highly centralized care models.[89] This results in geographic inequality in access and an inequitable system, with many people having to travel long distances to receive radioligand therapy. As use of the therapy extends to more common cancers, the number of people needing to travel for treatment will grow and the current models of care will become unsuitable. New models for delivering radioligand therapy in community-based or less centralized settings will be valuable. Planning for new centers should be carried out in a way that supports equitable geographical distribution and ensures that people need to travel less to receive treatment.

Telemedicine and other healthcare innovations may help reduce disparities in access to specialist expertise and availability of radioligand therapy. Variation in use of radioligand therapy is linked to restricted geographic availability of specialists who can advise on and deliver the therapy. The COVID-19 pandemic has catalyzed rapid uptake of telemedicine and greater use of virtual meetings, with regulations shifting to allow healthcare coverage across state borders.[60 90] These innovations could increase the extent to which nuclear medicine physicians and radiation oncologists can connect with smaller medical centers, ensuring that referring physicians at these centers are kept aware of and can consider relevant radioligand therapy for appropriate patients. Virtual consultations before and after treatment could also substantially reduce how often people with cancer must travel to specialist centers, and may improve their quality of life, ultimately making it easier for them to receive the care they need.

Clear care guidelines can further improve consistency in care and provision of radioligand therapy. Care models and pathways for radioligand therapy depend on the patient's health insurance, geographic location, and healthcare institution. As a result, treatment may vary between centers[58] and it may be difficult for people with cancer to know what to expect from their care.[91] Given the diversity of care settings in the US, a level of flexibility in guidelines and referral pathways is essential to ensure that each institution can provide care in the most efficient way. For radioligand therapy specifically, wider consensus building based on relevant data and the creation of guidelines that outline minimum standards of care would be helpful to ensure consistency in delivery and adherence to safety standards. Such guidelines would help to optimally prepare new centers and healthcare professionals to deliver the therapy.

"Depending on the institution you are at, and even on the physician you see, you could be offered radioligand therapy early in your cancer journey or as a last therapy. It could be the same institution and how you are being guided is completely different."

JOSH MAILMAN,
NorCal CarciNET

Data collection and analysis

Collection of data specific to radioligand therapy is increasing, but more can be done to ensure that the therapy is included in all relevant databases. Various ongoing and recently completed trials in NETs, lymphoma and prostate cancer are expanding the amount of clinical data available on radioligand therapy.[4 5 19 26 92-95] Collection of real-world data is also underway, as use of radioligand therapy is captured through electronic health records (EHRs) at institutions that provide it.[34] In addition, the University of Iowa has been granted funding to conduct a comparative effectiveness research study focusing on NETs therapies, which will include radioligand therapy.[96] However – unlike other, more commonly used therapies – radioligand therapy does not appear to be included in the Surveillance, Epidemiology, and End Results (SEER) Program or the National Program of Cancer Registries (NPCR),[97 98] which are the primary cancer registries in the US. There are also limited economic data on use of the therapy in NETs and lymphoma. Wider incorporation of radioligand therapy into national databases, and a concerted effort to collect economic data, would improve decision-makers' understanding of the impact of using the therapy on healthcare resources and help ensure it can be used in the most efficient way.

"We need to be collecting data on radioligand therapy. Data showing that it is an effective therapy will help increase awareness and make sure that it is covered."

DR. TODD MORGAN,
Rogel Cancer Center

Where data on radioligand therapy are available, they are highly fragmented, which limits analysis. Data on radioligand therapy – whether from clinical trials, EHRs or stand-alone studies – are collected via numerous operating systems. This variety of data collection systems, and inconsistencies in the type and amount of data collected, makes it difficult to conduct meaningful analysis.[99] There is also limited funding for data analysis, particularly in NETs.[34] The siloed nature of data collection is well recognized in the US, and attempts are being made to create more unified data collection systems across cancer care and the wider health system. For example, the National COVID Cohort Collaborative collects and standardizes data from EHRs across the US, covering approximately 8.6 million patient records.[100 101] Creating a similar national data set for cancer care, and ensuring that it includes radioligand therapy, would substantially improve researchers' ability to explore outcomes associated with the use of the therapy. Ultimately, this would help to optimize its delivery.

→ To find out more, please refer to the working paper on health information

Good-quality data collection and analysis are fundamental to ensuring the appropriate sequencing and safe delivery of radioligand therapy. There is currently no consensus on which guidelines to use for the management of NETs,[55] and this may contribute to uncertainty around appropriate use of radioligand therapy. Targeted collection of data on when radioligand therapy should be provided relative to other therapies, such as that being collected in the University of Iowa study,[96] could help clarify the optimal timing for delivery of radioligand therapy. More studies like this will be needed in lymphoma, prostate cancer, and other indications where radioligand therapy may become available. Investigator-initiated studies to generate clinical and patient-reported outcomes data would help support the development of clinical guidelines and models of care that are consistent and appropriate for a variety of settings. Such data collection requires careful planning, and data analysis requires sufficient funding. It is important to consider that in order to ensure equitable availability of the therapy, data collection must cover a diverse population and a range of settings, and analysis must be completed with a view to overcoming inequalities. Use of these data to inform planning and clinical practice can help ensure that the right people are referred for, and receive, radioligand therapy at the right time.

"There are huge gaps that reflect a lack of knowledge or lack of data. In other words, how one treatment compares with another treatment, how to sequence treatments, how to prioritize treatments – that information is lacking. But there are also no good data to address that."

DR. JONATHAN STROSBERG,
Moffitt Cancer Center

Conclusion

Radioligand therapy may become an important treatment choice for an increasing number of people with cancer.
As with all cancer treatments, its integration into care requires alignment of different components of the health system: governance, regulation, reimbursement, workforce planning, healthcare professional and patient awareness, and data collection. There are unique challenges to aligning each of these components of the US health system, and as such integration of, and readiness for, radioligand therapy must be assessed from a systems perspective.

Efforts are needed in several areas to prepare the US health system for integration on radioligand therapy into cancer care. We need to improve training and awareness, build consensus and encourage multidisciplinary collaboration, create clear referral pathways and appropriate reimbursement frameworks, and ensure equity in access to care and availability of data. To ensure progress across all of those areas, it will be important that the entire cancer community works together to advocate for appropriate use of radioligand therapy. Importantly, institutions, physicians, and people with cancer must have evidence of the value of the therapy if they are to consider using it. New or clearer models of care are needed, along with more accurate and up-to-date epidemiological and outcomes data, to clarify the business case for radioligand therapy.

Clear leadership, alongside close multidisciplinary coordination and planning, will be required to ensure that the US is ready for future uses of radioligand therapy.
Given the historically fragmented nature of the US health system, concerted efforts must be made to bring together the professionals involved in managing and delivering radioligand therapy, as well as policymakers and those involved in regulation and funding. Different sectors, healthcare institutions, and specialties will need to work together to create evidence-based and person-centered care pathways for radioligand therapy. Clear communication between different stakeholders can lead to consensus on the optimal way to integrate radioligand therapy into care. Ultimately, this consensus and appropriate leadership can help to ensure that the therapy is readily available to people who could benefit from it.

Glossary

This glossary provides definitions of terms as they are used in this document. They are derived from existing sources and adapted for the purposes of this project.

Authorized Users (AUs) are healthcare professionals who are licensed to administer radiopharmaceuticals such as radioligand therapy, as well as overseeing all technical support involved in using radionuclides. There are different levels of AU status which impact the therapies an AU is licensed to delivery.

Breakthrough designation is given to a therapy that treats a life-threatening condition where preliminary clinical evidence suggests that the therapy may improve specific patient outcomes over alternative available therapies.

Care pathways are the clinical processes that patients go through, from eligibility for treatment to follow-up after treatment has been completed.

Clinical indication is a health condition that could benefit from a specific test, therapy or procedure. If a therapy has been established and approved by regulatory bodies, the therapy is said to be approved for a specific indication.

Community practice is a privately owned healthcare setting that is not part of a hospital or academic center.

Computed tomography (CT) scans use X-rays to create images of the body at different angles. A computer uses these images to develop a 3D image. X-rays help identify changes to bones and tissue caused by cancer or other disease.

Electronic health record (EHR) is any digital document or system that collects medical information about an individual's health and care. EHRs include information about patient history such as diagnoses, treatment plans, and tests completed.

Eligibility assessment is used to evaluate whether radioligand therapy is a suitable treatment option for a particular individual based on the outcome of specific, often imaging, tests.

Governance refers to a range of policies, standards and ways of working that directly impact the availability, accessibility, and standards of delivery for any therapy, ultimately influencing health outcomes.

Health information refers to data that are collected, analyzed and synthesized to support health-related decision-making.

Identified need is the potential need and demand for a specific healthcare intervention.

Ligand is a small molecule that selectively binds to a specific different molecule. Examples are a hormone binding to a receptor on a cell, or an antibody binding to an antigen.

Lymphoma is a type of blood cancer that affects the lymphatic system. Lymphoma develops when white blood cells grow uncontrollably. There are over 60 types of lymphoma, with different treatment requirements.

Metastatic cancer occurs when a cancer has spread to different parts of the body from where it originated.

Metastatic castration-resistant prostate cancer is an advanced type of prostate cancer that has spread to the bone and has become resistant to hormonal cancer therapy.

Multidisciplinary care occurs when healthcare professionals from different disciplines work closely together to deliver comprehensive patient care.

Neuroendocrine tumors (NETs) are a group of cancers which occur in neuroendocrine cells. NETs arise from cells of the hormonal and nervous system that can develop in many different organs of the body.

Nuclear medicine is a medical discipline that involves the application of radioactive substances to assess bodily functions, and diagnose and treat disease.

Payment bundling is a payment structure in which various healthcare providers who are treating an individual for the same or related conditions are paid a sum of money for multiple tests, therapies, and procedures rather than being paid for each individual treatment.

Positron-emission tomography (PET) scans use radioactive tracers to produce 3D images of the inside of the body. The scan shows how organs and tissues function, and can also provide evidence of the presence or absence of cancer.

Priority review is given to therapies where preliminary evidence suggests that a therapy has the potential for significant improvements in safety or effectiveness of treatment compared with alternative available therapies. A priority review designation means that the FDA will direct resources and attention to an application to ensure it is reviewed within six months rather than the standard ten months.

Radiation is the emission of energy as electromagnetic waves or subatomic particles. This energy can be emitted by radionuclides and used to diagnose or treat disease.

Radiation oncology is a medical discipline that involves the use of radiation to diagnose, treat and manage cancer.

Radionuclide is an unstable form of a chemical element that emits radiation as it breaks down to a stable form. Radionuclides may occur naturally or be made in a laboratory. Different radionuclides have different properties and applications – for example, different radionuclides would be used for diagnosing or treating cancer.

Radioligand is a cancer-targeting molecule, or ligand, attached to a radionuclide. By choosing different radionuclides to attach to the same type of ligand, the process can be tailored to either diagnose or treat different types of cancer.

Referring physician is a medical professional who sends a patient to a different specialist for additional information, imaging, or treatment. In the case of radioligand therapy the referring physician might be a urologist, gastroenterologist, or hematologist, among others.

Referral pathway is the process through which a patient is sent by a physician to another physician or healthcare institution for additional healthcare services.

Regulation defines why and when a healthcare intervention should be provided and how it can be delivered safely to patients, including the appropriate rules and safeguards that need to be in place.

Service provision encompasses the inputs (such as the health workforce, infrastructure, and equipment) and outputs (such as diagnostic, therapeutic, and follow-up services) required for the provision of healthcare.

Targeted therapy is a category of cancer treatment that exploits differences between healthy and cancerous cells. It can be used to target a treatment to cancerous cells with minimal effect on healthy cells.

Telemedicine is the practice of remote diagnosis, treatment, and monitoring by means of digital technologies.

Tumor board is a group of healthcare professionals who work closely together to deliver comprehensive patient care. The tumor board is responsible for each patient's diagnosis, management plan, and assessment of treatment. It may include medical and radiation oncologists, surgeons, pathologists, nurses, and other healthcare professionals.

Appendix

TABLE A1. Radioligand therapies licensed in the US

Indication (estimated US prevalence)	Description of indication	Therapy licensed by FDA for use in clinical practice in the US
Gastroenteropancreatic neuroendocrine tumors (35 per 100,000 in 2017)[102]	A rare type of neuroendocrine tumor that can form in the pancreas or in other parts of the gastrointestinal tract, including the stomach, small intestine, colon, rectum, and appendix	Lutetium-177 oxodotreotide
Follicular lymphoma (1 per 3,000 in 2010)[103]	The most common type of slow-growing non-Hodgkin's lymphoma that develops from B cells. The abnormal B cells typically form in clumps inside lymph nodes	Yttrium-90 ibritumomab tiuxetan
Pheochromocytoma and paraganglioma (between 1 per 2,500 and 1 per 6,500 in 2010)[104]	Rare types of neuroendocrine tumors that develop in or on the adrenal glands	Iobenguane iodine-131

FDA, US Food and Drug Administration.

TABLE A2. Clinical indications for radioligand therapy in international phase II and III clinical trials

Indication in phase II clinical trials[a] (estimated US prevalence)	Indication in phase III clinical trials[b]	Description
Carcinoid heart disease[105] (data unavailable)		Carcinoid heart disease is a rare condition that is related to raised levels of peptides and hormones produced by neuroendocrine cancer cells. It usually affects the right-sided heart valves and leads to right heart failure
Central nervous system cancer [23 24 106] (173,400 in 2018)[107]		Central nervous system cancer begins in the brain or the spinal cord. It encompasses over 100 distinct tumor types
Lymphoma subtypes including relapsed indolent non-Hodgkin's lymphoma and relapsed/refractory follicular lymphoma[19] (960,000 in 2018)[17 18]		Lymphoma is a type of cancer that develops in the lymphatic system
Neuroendocrine tumor sub-types including paraganglioma, pheochromocytoma and neuroendocrine breast tumors, among many others[20 108-110] (171,300 in 2014)[15]	Gastroenteropancreatic neuroendocrine tumors[94]	Neuroendocrine tumors arise from cells of the hormonal and nervous system that can develop in many different organs of the body
Meningioma[23 106 111] (97.5 per 100,000 in 2010)[112]		A meningioma is a tumor that grows from the tissues that line the brain
Metastatic breast cancer[25] (154,800 in 2017)[113]		Metastatic breast cancer is breast cancer that has spread to other parts of the body
Metastatic castration-resistant prostate cancer[114] (13,800 of prostate cancer cases in 2018)[115]	Metastatic castration-resistant prostate cancer[116c]	Metastatic castration-resistant prostate cancer is a cancer that has spread beyond the prostate gland and where hormone therapy is no longer effective in stopping or slowing the disease
Peritoneal solid tumors[117] (data unavailable)		Peritoneal solid tumors are a rare type of cancer that are found in the lining tissue of the abdomen

a. Phase II at the time of publication (2021).
b. Phase III at the time of publication (2021).
c. Study closed on January 27, 2021.

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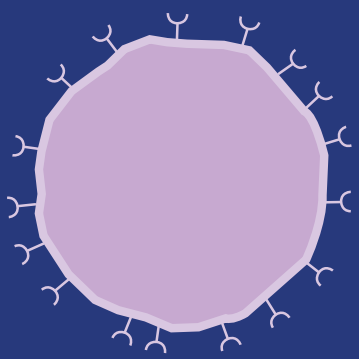

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