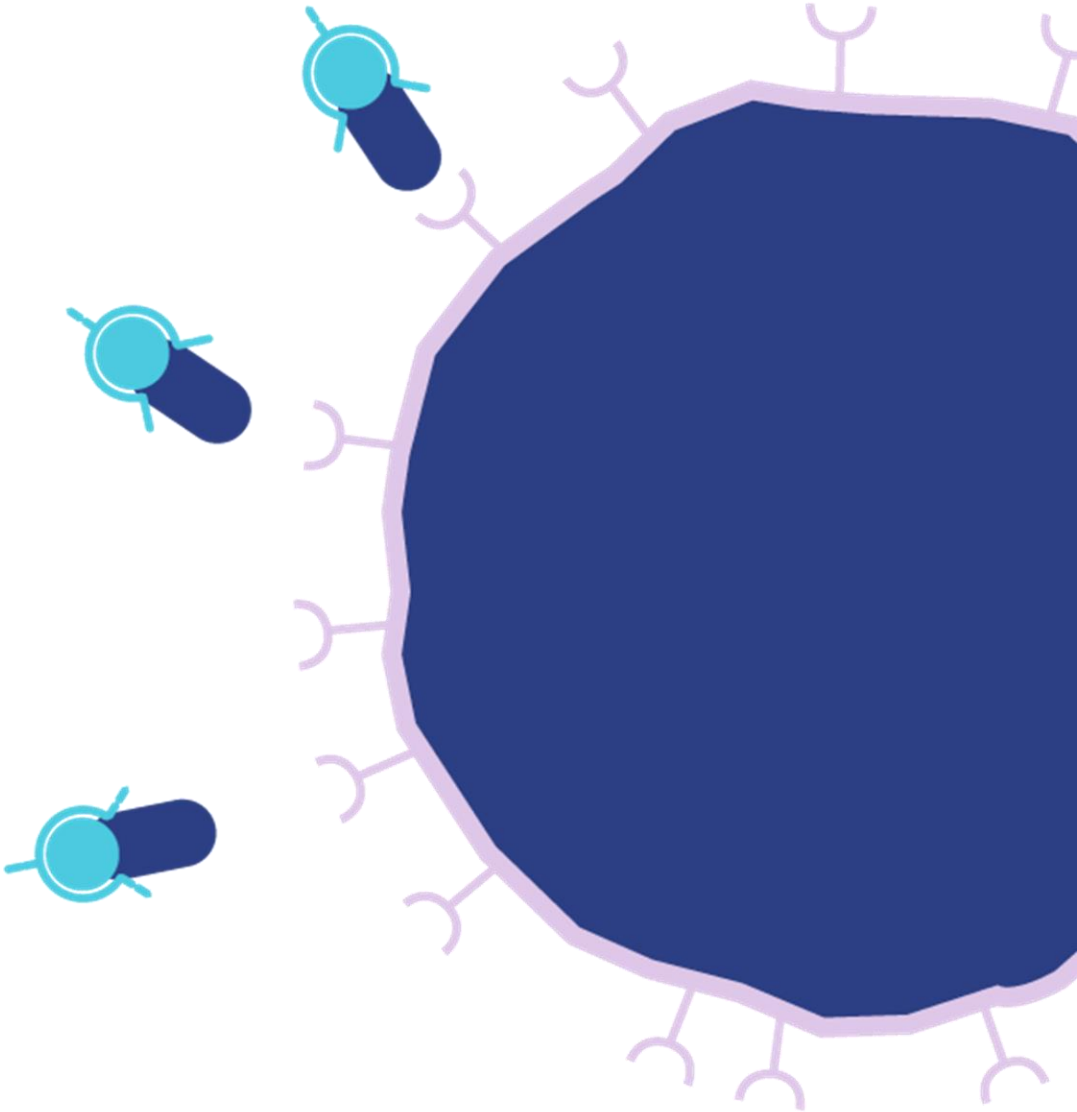


The Health Policy Partnership
[research, people, action]

Health system readiness for radioligand therapy in the US

Regulation and reimbursement

Working paper

November 2021

This working paper has been developed by The Health Policy Partnership and Avalere Health in collaboration with a US Expert Advisory Group. The group has had full editorial control over all national-level outputs. The project is supported through an unrestricted grant from Advanced Accelerator Applications, a Novartis Company, with additional support from Nordic Nanovector.

Contents

About this working paper 3
Terminology 3
What are regulation and reimbursement? 5
What do good regulation and reimbursement look like? 5
1 Regulation 7
1.1 Approval processes 8
1.2 Production and supply regulations 9
1.3 Regulations for administering radionuclides 11
1.4 Waste management regulations 12
2 Reimbursement and payment 14
2.1 Reimbursement and coverage frameworks 14
Conclusion 20
References 21

Please cite as: The Health Policy Partnership. 2021. *Health system readiness for radioligand therapy in the US: regulation and reimbursement (working paper).* London: The Health Policy Partnership.

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 regulation and reimbursement, 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 the regulation of radioligand therapy, its administration, the associated radionuclides and radioactive waste management. It also covers the reimbursement environment for radioligand therapy. Throughout the paper, we focus on the situation in neuroendocrine tumors, lymphoma, and prostate cancer.

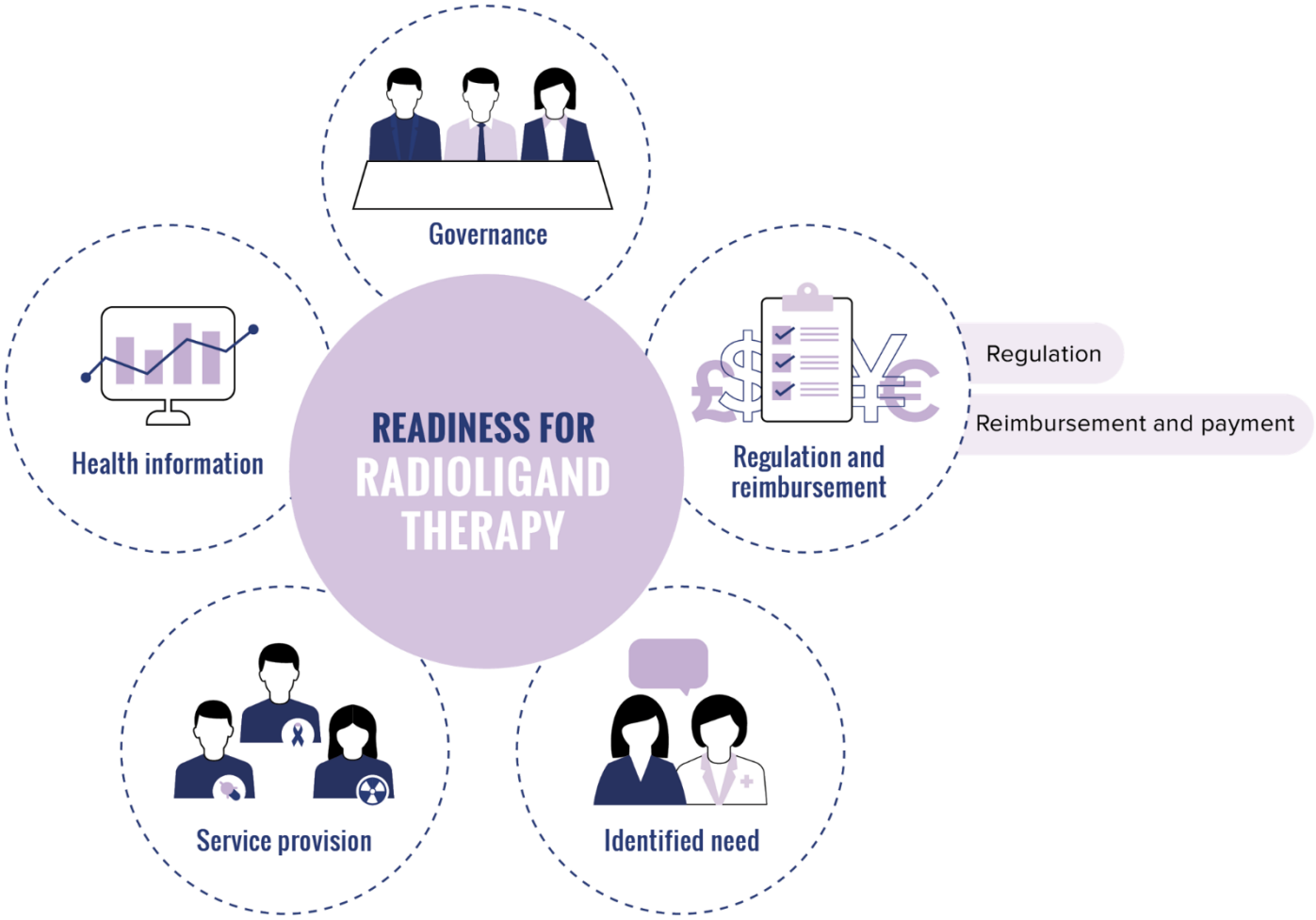
- This working paper is supported by other documents on health system readiness for radioligand therapy in the US. For more details, please visit: www.radioligandtherapy.com/framework/US

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 are regulation and reimbursement?

Transparent and appropriate regulation is an essential pillar of a functioning health system. Regulation in healthcare is a broad and dynamic concept, largely linked to overseeing and shaping behavior.[1] In this context, its goal is to clearly define why and when an 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. It also looks to address environmental concerns related to the use of radioactive materials.

Once radioligand therapy is approved for use in clinical practice, its payment or reimbursement also needs to be ensured. The US system has a decentralized model of reimbursement, where private health insurance companies or government agencies pay for healthcare services delivered by a hospital, clinician, diagnostic facility or other healthcare provider.[2] Potential payers include commercial insurance companies, Medicare, and Medicaid. The payment for services is informed by each payer's individual coverage policies, which determine whether a payer will pay for a drug or service based on whether the drug is deemed to be "reasonable and necessary."[3] Payers establish these criteria drawing on information from the US Food and Drug Administration (FDA) label, peer-reviewed literature, professional society guidelines, safety studies, cost or cost-effectiveness analyses, and stakeholder input.

What do good regulation and reimbursement look like?

Effective regulation of radioligand therapy requires objective, evidence-based assessments of the benefits and risks of the approach, ensuring that safety is appropriately ingrained in all steps. Regulations should be appropriate to different care settings and provide clear safety requirements that are appropriate for the unique qualities of each radionuclide.

The complex process of delivering radioligand therapy is reflected in the multiplicity of types of regulation and regulators involved. Regulation is conducted by a network of public and private entities at the federal, state and local levels.[4,5] Federal bodies include the Centers for Disease Control and Prevention and the FDA, which provide top-down oversight and coordination. State bodies, such as local public health and health services departments or state licensing boards, guide care to reflect local needs and issues. Specialist

organizations and independent bodies such as the American Medical Association may work across multiple levels providing specialist licensing and quality standards.

Additional licensing for radioligand therapy is required to ensure high quality and safety standards. This includes legislation from the energy and environmental sectors to ensure safe and secure production, transportation, administration, storage and disposal of radionuclides used. This additional regulation is led predominantly by the Nuclear Regulatory Commission (NRC) and affiliated regulators in Agreement States – who assume regulatory authority from the NRC – but also includes other regulatory bodies at the local, regional, and institutional level.

Optimal reimbursement for radioligand therapy would be a level of payment that could offset the cost of investing in safe and guideline-adherent delivery. Institutional investment costs of radioligand therapy may include specialist equipment and infrastructure, workforce training, and adherence to safety regulations. It is crucial that institutions not be discouraged from implementing radioligand therapy delivery programs; ensuring reimbursement processes for radioligand therapy are transparent and offer cost-neutrality can help mitigate any potential hesitancy.[6 7]

1 Regulation

Summary assessment

Indicators	Assessment
Are regulatory approval processes in the US suitable for radioligand therapy?	Radioligand therapy and other radiopharmaceutical therapies are classified as drugs by the FDA. Radioligand therapy is currently approved by the FDA for use in some types of neuroendocrine tumors (NETs) and lymphoma. Previous FDA reviews were designated “priority,” which suggests future indications will follow suit. Radioligand therapy and any associated imaging agents go through the same approval process as other drugs. However, there does not seem to be a link or coordination between the approval processes for a radioligand and its associated diagnostic pair.
Are regulations for the production and supply of radionuclides in the US appropriate for radioligand therapy?	Medical radionuclides can be produced by federal agencies, commercial suppliers and hospital-level producers, as well as coming from international sources. Mechanisms are in place to ensure adequate supply of radionuclides, guided by the Department of Energy (DOE). However, supply is ensured by both DOE bodies and private companies.
Are regulations for the administration of radionuclides in the US appropriate for radioligand therapy?	The NRC has clear training and experience requirements that enable certain healthcare professionals to become Authorized Users (AUs), licensing them to administer radioligand therapy and oversee all other technical support involved in delivering and using radionuclides. Medical practices and facilities must obtain materials licenses for their AUs and their radioligand therapy programs. Proposed changes to AU licensing state the intention of policymakers to expand the radioligand therapy delivery workforce in anticipation of increased future demand, although the need for an expanded workforce is not universally agreed on.
Are regulations for the management of medical radioactive waste in the US applicable to radioligand therapy?	At an institutional level, the management of waste from radioligand therapy is clearly outlined and regulated by the NRC and Agreement States. The regulations detail storage, transport and disposal requirements at the institution or with an authorized recipient. Once radiation levels are indistinguishable from background radiation levels, the waste can be disposed of alongside general medical waste.

	Administration regulations for AUs at the individual level also incorporate radioactive waste disposal.

1.1 Approval processes

Regulation of radioligand therapy is carried out by the FDA, which classifies the approach as a drug. The FDA is responsible for conducting regulatory reviews of new drugs, including radioligand therapy. As drugs, radioligand therapies and any paired imaging agents are governed by the same regulations as other drugs or biological products.[8] Regulatory requirements include that the drug is: proven to be safe and effective; manufactured in licensed, inspected facilities in accordance with Good Manufacturing Practices; and not adulterated or mislabeled, among other requirements.[8]

The FDA has approved radioligand therapies for use in some types of neuroendocrine tumors (NETs) and lymphoma via a "priority review" pathway. At the time of writing, radioligand therapy has been approved by the FDA for: people with advanced NETs that affect the pancreas or gastrointestinal tract;[9] and people with relapsed or refractory, low-grade or follicular B-cell lymphoma,[10] as well as people with previously untreated follicular lymphoma.[11] Both were reviewed in the prioritized pathway, meaning they were deemed to have the potential to significantly improve treatment or address significant unmet need. The FDA aims to complete priority reviews significantly faster than standard reviews.[12] In addition to this, the FDA recently designated radioligand therapy for advanced prostate cancer as a breakthrough therapy.[13] Breakthrough therapies undergo an expedited development and review process, and are selected based on their potential to deliver substantial improvement over current therapies.[14] This indicates that the FDA considers radioligand therapy to be of high importance and signals that future reviews of radioligand therapies for other indications may take the same path.

There is no clear link between approval processes for a radioligand therapy and its associated diagnostic pair, leaving enduring concerns around access. Associated imaging agents are also classified as drugs; however, there does not seem to be a link or coordination between the approval processes. This means that a situation may arise where the therapy is approved for use, but its paired diagnostic is not. This could hamper the clinician's ability to accurately identify people who would receive the most benefit from the therapy. It is encouraging for future indications that the regulatory approval process has

been successfully applied to radioligand therapy; however, the lack of coordination between approval processes for radioligands and their diagnostic pairs leaves concerns around access in the long term.

1.2 Production and supply regulations

The supply of radionuclides utilized for radioligand therapy is largely stable, but preparation is required to ensure a consistent supply in the future. Radionuclides for radioligand therapy are typically produced in nuclear reactors or cyclotron facilities and then transported to hospitals or clinics for use.[15] [16] These production centers may be run by the Department of Energy (DOE), domestic commercial companies or foreign suppliers. As an example, lutetium-177, the radionuclide utilized for radioligand therapy in NETs, is obtained from a variety of national and international sources, including a nuclear reactor in Europe,[17] at least one academic center in the US,[18] and various commercial US providers.[19] [20]

Demand for radionuclides for radioligand therapy is expected to grow, but there are concerns that anticipated renovations to current production facilities may impact supply. Even though the radionuclides used for radioligand therapy represent a relatively small share of all radionuclides currently used for medical applications, experts anticipate that demand for these radionuclides will increase. However, as two of the six European reactors producing lutetium-177 are expected to temporarily cease production within the next 15 years for renovation,[17] new sources will be required to maintain or increase production. Fortunately, it seems that domestic commercial companies are preparing to scale-up production of radionuclides.[21-23]

Despite national production efforts and safeguards, temporary shortages of certain radionuclides have occasionally occurred. Shortages of key radionuclides have been seen in recent years, such as for molybendum-99, actinium-225 and geranium-68.[24-26] Other radionuclides, such as yttrium, are heavily dependent on imports[27] and therefore at risk of future supply issues. Details on some of these shortages are outlined in *Box 1.* Causes are manifold and include unexpected reactor closures and flight suspensions due to COVID-19. In preparation for increased use of radioligand therapy in the US, it will be important to continually monitor policies that impact the production and distribution of radionuclides in general and mitigate potential risks. There are many examples of commercial and

government bodies working to ensure a consistent and smooth supply of radionuclides (*Real-world example 1*).

Box 1. Supply issues relating to key medical radionuclides

Actinium-225: While there have been trials examining use of actinium-225 for the treatment of various cancers, the global supply is insufficient for widespread routine application in hospitals worldwide. As a result, the DOE Office of Science's Isotope Program is leading efforts to find new ways to produce actinium-225.[25]

Yttrium: This is the radionuclide used in the only approved radioligand therapy for lymphoma. However, it is not currently produced in the US, leaving the US heavily reliant on overseas imports – 94% of which come from China.[27] With the vast majority of supply coming from one source, the yttrium supply chain is high risk. In February 2021, President Biden ordered a review of the supply chain for rare earth elements, including yttrium,[28] and some US mines claim to be developing capabilities to produce the material.[29] The current yttrium supply chain raises concerns around continuity of supply for radioligand therapy in lymphoma. However, future radioligand therapy in lymphoma uses the radionuclide lutetium-177, which somewhat mitigates broader concerns around the supply of radionuclides this indication.

Real-world example 1. The DOE Isotope Development and Production for Research and Applications Program (IDPRA)

The IDPRA aims to stabilize the supply of radionuclides for medical uses through three workstreams:[24]

- produce and/or distribute radioactive and stable nuclides that are in short supply
- maintain the infrastructure to produce and supply nuclide products and related services
- invest in research and development of new and improved nuclide production and processing techniques, enhancing the availability of radionuclides for research and other clinical applications.

The program explicitly does not aim to compete with commercial nuclide production; it will identify a deficit in supply and work to address it. Once commercial sources for radionuclides of interest are available, the IDPRA will shift focus to other radionuclides.

1.3 Regulations for administering radionuclides

Regulations to administer radioligand therapy are comprehensive, encompassing individuals and institutions. The regulations for working with radiopharmaceuticals are operationalized by the NRC and include the following:

- Materials licensing for institutions to receive and store radiopharmaceuticals.[30 31] These may have a “limited scope” for specific radionuclides or a “broad scope” for multiple types and quantities of radionuclides.
- Authorized User (AU) licensing for certain physicians to directly administer radioligand therapy.[31] Eligible physicians include nuclear medicine physicians, radiation oncologists and nuclear radiologists. Requirements include demonstration of training and clinical experience.
- Training specifications for radiation safety officers, authorized medical physicists and authorized nuclear pharmacists.[32 33] These specifications ensure that all personnel involved in delivering radioligand therapy are appropriately trained.

➔ For more information on the personnel involved in delivering radioligand therapy, read the working paper on service provision.

Discussions are ongoing over proposed changes to AU training requirements, which have the potential to increase the size of the delivery workforce. Currently, physicians can become an AU for radiopharmaceuticals via one of two pathways:[31 34]

- The "board certification pathway," in which a physician is certified by a medical specialty board recognized by the NRC or an Agreement State
- The "alternate pathway" approval, based on 700 hours of training and experience in safe handling of radionuclides used for medical purposes, including a minimum of 200 hours of classroom and laboratory training.

The optimal system for AU licensing would marry the need for good quality assurance and high standards with ensuring an adequately sized workforce to deliver radioligand therapy in future. Proposed changes to AU licensing would eliminate the alternate pathway for radionuclides used in radioligand therapy and allow the expansion of AU licenses to new specialties.[35] Discussions on these proposed changes are ongoing,[36 37] but they suggest policymakers' intention to grow the radioligand therapy delivery workforce. This could be a way to mitigate potential access issues in the future. Should these licensing changes be implemented, it will be important to evaluate how the workforce capacity changes. Regardless, it is encouraging that efforts are being made to address possible radioligand therapy workforce deficits as use of the therapy grows.

1.4 Waste management regulations

Regulations for the management of radioactive waste clearly outline reasonable safety requirements for safe disposal of different types of contaminated waste. Legislation requires each institution with an NRC license to dispose of any radioactive waste in accordance with the NRC regulations.[32] These describe how contaminated waste and radionuclides with different half-lives are to be held and disposed of.[30] For example, radionuclides with a half-life of below 120 days are allowed to decay in dedicated storage facilities in the hospital.[38] Once the radiation levels are indistinguishable from background radiation, the waste can be disposed of alongside other medical waste.[30] Regulations for waste management do not differ between inpatient and outpatient settings.

An increase in the use of radionuclides for medical purposes will lead to an increase in contaminated waste, but seems unlikely to require regulatory changes. An expert interviewed for this project anticipates that hospitals and physician practices with existing radiotherapy programs will be able to manage the increased amount of waste produced,[6] as any potential changes in models of care or patient numbers may not necessarily require adaptation of waste management regulations. Even though storage facilities for time-based decay are limited by the existing space dedicated to these rooms in a given hospital, increasing capacity is considered relatively achievable should use of radioligand therapy increase.[39]

2 Reimbursement and payment

Summary assessment

Indicator	Assessment
How are existing US reimbursement and payment mechanisms applied to radioligand therapy?	There are three main types of payers that may cover radiopharmaceutical therapies: commercial insurers, Medicare, and Medicaid. Most payers classify radioligand therapy as a drug and cover the approach under medical and/or hospital benefit. Payers determine coverage based on their assessment that a drug is reasonable and necessary.

2.1 Reimbursement and coverage frameworks

There are three main types of payers that may cover radioligand therapy, and each develops its own coverage and reimbursement criteria across settings of care. Commercial insurers, Medicare, and Medicaid all classify radioligand therapy as a drug and cover the approach under medical and/or hospital benefit. These payers establish their own payment criteria from a combination of information, including the FDA label, peer-reviewed literature, professional society guidelines, safety studies, cost or cost-effectiveness analyses, and stakeholder input. Once coverage criteria are met, commercial payers and Medicaid typically require prior authorization of higher-cost drugs, such as radioligand therapy, in order to approve payment. Prior authorization requires clinicians to provide diagnostic and lab test results, along with other patient information.[40] Once authorization is granted, the therapy can be furnished, billed and paid. Should prior authorization or coverage be denied, the patient may either pay out-of-pocket or the hospital may absorb the cost of the therapy.

Payers may classify radioligand therapy under medical or hospital benefits. Medical benefits provide coverage and payment for outpatient drugs and services, and hospital benefits cover inpatient drugs and services. Given the various models of care delivery, both benefits need to be considered for radioligand therapy. Both benefits typically account for radioligand therapy within the pharmacy or radiology cost center. However, services associated with delivery of the radioligand or other services furnished at the time (e.g., physical examination, diagnostic imaging, care planning) may be captured under different cost centers. The diversity of settings and benefits may make it challenging for payers to

navigate radioligand therapy reimbursement. This could act as a barrier to uptake and delivery of radioligand therapy.

Both approved radioligand therapy products are covered by the Healthcare Common Procedure Coding System (HCPCS), which is used by payers to facilitate insurance claims. All payers use HCPCS codes to identify therapies, and combine them with revenue codes to capture the costs associated with a specific hospital cost center. At the time of writing, two radioligand therapy products – Lutathera® for NETs and Zevalin® for lymphoma[41] – are covered under the HCPCS. Both are also covered by several health insurance plans.[42-45] *Real-world example 2* outlines how radioligand therapy is typically reimbursed for NETs. For all payers and regardless of benefit, hospitals may also qualify for outlier payment for high-cost cases, for example the Medicare new technology add-on payment, but there are strict criteria to qualify for such payments.[46] The number of technologies covered by this add-on payment has been increasing in recent years, particularly for oncology-related items.[47] This means there could be potential for radioligand therapy to qualify for the payment in future.

Real-world example 2. Reimbursement process for radioligand therapy in NETs

Insurance policies evaluated for NETs from the possible payers demonstrate that coverage does not seem to have specific limitations that would result in suboptimal access to radioligand therapy.[48] They simply specify criteria aligned to the product's FDA label. But different coverage exists based on the setting and benefit:

- **Outpatient setting and the medical benefit:** Medicare pays outpatient hospitals on a partially bundled prospective payment system, where payment rates are based on historical costs. Products and services are paid via ambulatory payment classifications (APCs), which group together therapies that are similar clinically and in cost. Commercial insurance and Medicaid may pay separately for services using APCs, fee-for-service, percent of charges, or per diem. APCs and prospective fee-for-service are the most common payment methodologies.
- **Inpatient setting and the hospital benefit:** Drugs are captured under a revenue code for the entire inpatient stay. Medicare pays inpatient hospitals on a bundled prospective payment system, which is set based on historical charges. Products and services are paid via a single payment based on average costs called Medicare Severity Diagnosis-Related Group (MS-DRG), and drugs are bundled into this single payment. Commercial insurance and Medicaid may pay for services using Diagnosis-Related Groups (DRGs), percent of charges, or per diem. DRGs are the most common form of payment for radioligand therapy by Medicaid and commercial insurers.

➔ For more on the models of care used to deliver radioligand therapy, please read the working paper on service provision.

The reimbursement process for radioligand therapy in lymphoma is similar to that for NETs. Radioligand therapy in lymphoma is currently only delivered in the outpatient setting. Since 2010, it has been reimbursed through Medicare via the same outpatient prospective payment system as described in *Real-world example 2*.[49] Some health insurance providers have deemed the use of radioligand therapy in lymphoma to be "medically necessary," thus qualifying it for coverage in some plans.[44 45] The circumstances for which radioligand therapy is deemed to be a medical necessity mirror those listed in the lymphoma guidelines from the National Comprehensive Cancer Network (NCCN).[50]

Despite established coverage and reimbursement policies for radioligand therapy, reimbursement processes could be improved. According to experts, reimbursement policy for radioligand therapy is key because if institutions lose money on a therapy then they will not readily adopt it.[51] A substantial barrier noted was a high cost price,[52] which triggers coverage reviews and limitations. To combat this, many centers are exploring how to reduce cancer care costs. One approach centers have been taking is bundling payments that require providers to collect the cost of services for one full episode of care, which can include services across settings and different providers. For example, the Center for Medicare and Medicaid Innovation runs the Oncology Care Model, which provides bundled monthly payments for a set of cancer care services.[53]

The introduction of a national Medicare price for radioligand therapy has resulted in some centers losing money if they provide the service. At first, Medicare reimbursed each hospital claim individually, resulting in varied reimbursement levels across different centers.[54] This approach was changed in 2008 when Medicare set a nationwide reimbursement price of $16,000 per treatment.[54] This set price meant that hospitals offering this treatment to Medicare patients may sometimes lose money on each treatment,[54 55] causing some hospitals to stop offering radioligand therapy for lymphoma.[55] If hospitals decide not to offer a treatment to Medicare patients, under federal law they are also unable to offer it to people with private insurance. The current reimbursement system is therefore leading to a decreased use of the approach and may be a contributing factor as to why larger centers with greater financial capability are more able to provide radioligand therapy. Various surveys have also shown that referring physicians were concerned about adverse economic effects of sending patients to other practices to receive radioligand therapy.[55 56] This shows the competing interests of medical oncologists and hematologists with the

physicians who deliver radioligand therapy. These economic issues, along with a variety of other factors, have led to the underuse of radioligand therapy historically and its limited use to this day.[55 57]

Financial incentives to keep therapy administration within institutions may be contributing to the underuse of radioligand therapy for lymphoma. Private community practices, where many people with lymphoma are treated, operate the "buy and bill" model of reimbursement which allows physicians to purchase medications and then directly bill payers for reimbursement.[58] During the billing phase, an institution can "mark up" the price of a medication to cover expenses relating to acquiring and administering it.[59] This allows for potential profitability and incentivizes physicians to treat patients with medications they can administer within that institution. According to one expert interviewed, this may contribute to fewer referrals for radioligand therapy, which typically requires administration in specialist centers.[60] With the current investigation of novel radioligand therapy for lymphoma, these economic factors should be considered if new therapies are approved in the future.

With less-than-optimal payment, institutions may simply choose not to provide radioligand therapy. Cumbersome billing practices often create additional reimbursement hurdles, and inconsistent payment for providers administering radioligand therapy may deter them from providing it to eligible patients.[6] Furthermore, radioligand therapy requires many investments to ensure optimal and safe care delivery, such as separate patient rooms, adequate facilities for waste disposal, and significant personnel training. These investments are considered by some care providers not to be adequately offset by current reimbursement levels.[61]

Developing an effective business case for radioligand therapy at the institutional level will be important. Experts have suggested that even if an institution makes a loss for delivering radioligand therapy itself, retaining the patient for the duration of their treatment is likely to be a net gain for the organization.[51] However, this may not be a sufficient incentive for community-based centers or smaller private practices that may see fewer patients or have effective referral networks with larger hospitals. Such centers may see less of a return on investment. At this stage, it is hard to tell how these institutional investment risk–benefit calculations will be changed by the potential approval of radioligand therapy for prostate cancer in the future.

Regardless of the reimbursement level, patients frequently experience significant costs related to the therapy. Even when institutions are able to cover the majority of costs for radioligand therapy, patients often remain responsible for substantial out-of-pocket costs.[62] In many cases, patients travel to different states to obtain treatment, which be very expensive. Some healthcare institutions are able to qualify for 340B drug pricing – a federal pricing program that helps institutions serving vulnerable populations to better afford expensive therapies – and many of these wider costs for patients are covered.[63] However, while it is easy to access information on how many 340B-qualifying institutions there are in each state, it is unclear which of these currently provide radioligand therapy. Identifying and mapping all US institutions that provide radioligand therapy could be a useful resource for people with cancer seeking the approach.

Conclusion

Regulation of radioligand therapy is comprehensive, and seems largely appropriate and proportionate to cover all aspects of production, supply, and delivery. Existing regulation to ensure safety before, during, and after administration of radioligand therapy seems suitable to the current use in NETs and lymphoma. Looking to the future, the wealth of experience with different medical radionuclides and close working between the NRC, nuclear medicine and radiation oncology specialists suggests that, if regulatory adaptations are required, adoption may be relatively smooth. Ongoing discussions regarding the AU licensing pathways are a positive step towards boosting the radioligand therapy delivery workforce, if needed, and maintaining access to radioligand therapy in future.

Securing a consistent supply of medical radionuclides remains an important aspect to monitor and evaluate. Given that each radionuclide has a unique and often global supply chain, an overall increase in the types and quantities of medical radionuclides used may add further complexity. Currently, it seems the US market and governmental bodies are very responsive to perceived supply chain issues. However, given the dynamic nature of supply and demand for radionuclides, risks will continually need to be mitigated, and open discussions and collaboration will be required among all relevant stakeholders.

Reimbursement of therapies in the US health system is complex, but more optimal reimbursement could potentially help ensure wider delivery of radioligand therapy. It is anticipated that coverage and reimbursement for radioligand therapy in other indications would be organized in a similar way to that in NETs and lymphoma, depending on the administration setting. While radioligand therapy is provided to certain people with NETs and lymphoma, reimbursement remains a challenging issue. Provision of radioligand therapy is most often found in academic centers that have the existing infrastructure and expertise, along with a large group of diverse patients. In contrast, few community-based settings have the experience or infrastructure to deliver radioligand therapy without careful planning and investment. Finding ways to improve referral pathways to specialists at institutions that deliver the therapy will be as important as ensuring return-on-investment for those institutions, or for those considering offering the therapy.

References

1. Dixon J. 2005. *Regulating Health Care: The Way Forward.* London, UK

2. Congressional Research Service. 2021. U.S. Health Care Coverage and Spending. [Updated March 15, 2021]. Available from: https://fas.org/sgp/crs/misc/IF10830.pdf [Accessed 10/29/21]

3. American Hospital Association. CMS codifies definition of 'reasonable and necessary' Medicare coverage. Available from: https://www.aha.org/news/headline/2021-01-13-cms-codifies-definition-reasonable-and-necessary-medicare-coverage [Accessed 03/15/21]

4. Rice T RLY, Unruh P, Barnes A J. 2017. United States of America: Regulation. Available from: https://www.who.int/health-laws/countries/usa-en.pdf?ua=1 [Accessed 10/28/21]

5. Field RI. 2008. Why is health care regulation so complex? *P T* 33(10): 607-08

6. Mittra E. 2020. Interview with Michelle Bruno at Avalere Health [Telephone]. 10/14/20

7. Morris M. 2020. Interview with Michelle Bruno at Avalere Health [Telephone]. 11/18/20

8. U.S. Food and Drug Administration. 2004. *Guidance for Industry: Developing Medical Imaging Drug and Biological Products. Part 2: Clinical Indications.* Silver Spring, MD: FDA

9. U.S Food and Drug Administration. FDA approves new treatment for certain digestive tract cancers. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-certain-digestive-tract-cancers [Accessed 07/16/21]

10. Grillo-López AJ. 2002. Zevalin: the first radioimmunotherapy approved for the treatment of lymphoma. *Expert Rev Anticancer Ther* 2(5): 485-93

11. Spectrum Pharmaceuticals. FDA Approves ZEVALIN(R) Expanded Label as Part of First-Line Therapy in Treatment of Follicular Non-Hodgkin's Lymphoma. Available from: https://investor.sppirx.com/news-releases/news-release-details/fda-approves-zevalinr-expanded-label-part-first-line-therapy [Accessed 07/16/21]

12. U.S Food and Drug Administration. Priority Review. Available from: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review [Accessed 07/16/21]

13. Reuters. 2021. Novartis prostate cancer drug receives U.S. FDA breakthrough designation [online]. *Reuters.* Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/novartis-prostate-cancer-drug-receives-us-fda-breakthrough-designation-2021-06-16/ [Accessed 08/02/21]

14. U.S Food and Drug Administration. Breakthrough Therapy. Available from: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy [Accessed 08/02/21]

15. Talip Z, Favaretto C, Geistlich S*, et al.* 2020. A step-by-step guide for the novel radiometal production for medical applications: case studies with (68)Ga, (44)Sc, (177)Lu and (161)Tb. *Molecules* 25(4): online

16. International Atomic Energy Agency. Radioisotope production in research reactors. Available from: https://www.iaea.org/topics/radioisotope-production-in-research-reactors [Accessed 09/11/20]

17. Hehakaya C, Moors EHM, Verkooijen HM*, et al.* 2020. (177)Lu-PSMA for advanced prostate cancer: are we ready to play big? *Eur J Nucl Med Mol Imaging*: 10.1007/s00259-020-05102-4

18. Advanced Accelerator Applications. Press Release: Advanced Accelerator Applications signs strategic supply agreement with University of Missouri for Lutetium 177. [Updated 30/03/17]. Available from: https://www.sec.gov/Archives/edgar/data/1611787/000095010317002935/dp74536_ex9901.htm [Accessed 10/30/20]

19. World Nuclear News. 2019. Shine to use 'novel' method for lutetium production [online]. [Updated 17//05/19]. Available from: https://world-nuclear-news.org/Articles/Shine-to-use-novel-method-for-lutetium-production [Accessed 18/11/20]

20. Dash A, Pillai MRA, Knapp FF, Jr. 2015. Production of (177)Lu for Targeted Radionuclide Therapy: Available Options. *Nucl Med Mol Imaging (2010)* 49(2): 85-107

21. Shine Medical Technologies. SHINE [online]. Available from: https://shinemed.com [Accessed 09/11/20]

22. NorthStar Medical Radioisotopes. 2021. NorthStar Medical Radioisotopes and IBA Expand Collaboration to Enable Global Availability of Diagnostic Radioisotope Technetium-99m (Tc-99m). Available from: https://www.northstarnm.com/northstar-medical-radioisotopes-and-iba-expand-collaboration-to-enable-global-availability-of-diagnostic-radioisotope-technetium-99m-tc-99m/ [Accessed 10/29/21]

23. Advanced Accelerator Applications. Press Release: Advanced Accelerator Applications to Build Targeted Radioligand Therapy

Production Facility in Indianapolis. [Updated 30/06/2020]. Available from: https://s3-adacap-product.s3.eu-west-1.amazonaws.com/wp-content/uploads/2020/06/30085248/AAA-Media-Release-IN-RLT-Facility-FINAL-June-v3-2020.pdf [Accessed 05/24/21]

24. The DOE/NSF Nuclear Science Advisory Committee Isotopes Subcommittee. 2015. *Meeting isotope needs and capturing opportunities for the future: The 2015 long range plan for the DOE-NP Isotope Program.* Washington, D.C.: Department of Energy

25. Energy.gov. The Journey of Actinium-225: How Scientists Discovered a New Way to Produce a Rare Medical Radioisotope. Available from: https://www.energy.gov/science/articles/journey-actinium-225-how-scientists-discovered-new-way-produce [Accessed 09/04/21]

26. Federal Register. 2014. Record of Decision To Withdraw From Production and Distribution of the Radioisotope Germanium-68 Used for Calibration Sources. Available from: https://www.federalregister.gov/documents/2014/09/02/2014-20749/record-of-decision-to-withdraw-from-production-and-distribution-of-the-radioisotope-germanium-68 [Accessed 10/28/21]

27. United States Geological Survey. 2021. *Rare Earths Statistics and Information - Yttrium.* Reston, Virginia: USGS

28. Shih W. 2021. It Might Take A Long Time For The U.S. To Become Self-Sufficient In Rare Earth Materials [online]. *Forbes.* Available from: https://www.forbes.com/sites/willyshih/2021/02/24/it-might-take-a-long-time-for-the-us-to-become-self-sufficient-in-rare-earth-materials/?sh=5174acc5192d [Accessed 07/16/21]

29. Scheyder E. China to buy rare earths from U.S. as part of trade pact [online]. *Reuters.* Available from: https://www.reuters.com/article/us-usa-trade-china-rareearths-idUSKBN1ZE2YQ [Accessed 08/17/21]

30. Burkhart M, Cockerham A, Cook J*, et al.* 2019. *NRC program-specific guidance about medical use licenses.* Washington, D.C.: United States Nuclear Regulatory Commission

31. Baldwin JA, Bag AK, White SL*, et al.* 2015. All you need to know as an Authorized User. *AJR Am J Roentgenol* 205(2): 251-8

32. NRC Regulations, Title 10, Code of Federal Regulations. 2020. United States of America: 15/09/20

33. United States Nuclear Regulatory Commission. Agreement state program. [Updated 02/03/20]. Available from: https://www.nrc.gov/about-nrc/state-tribal/agreement-states.html [Accessed 15/09/20]

34. Doane M. 2020. Rulemaking paln for training and experience purpose: requirements for unsealed byproduct material (10 CFR Part 35). Available from: https://www.nrc.gov/docs/ML1932/ML19321E358.pdf [Accessed 13/11/20]

35. American College of Radiology. NRC staff recommends revised authorized user T&E rules for unsealed materials. [Updated 01/23/20]. Available from: https://www.acr.org/Advocacy-and-Economics/Advocacy-News/Advocacy-News-Issues/In-the-January-25-2020-Issue/NRC-Staff-Recommends-Revised-Authorized-User-TE-Rules [Accessed 09/14/20]

36. Razmaria A, Calais J, Czernin J. 2019. Delivering radionuclide therapies requires extensive training and competence: send a firm message to the NRC and your representatives. *J Nucl Med* 60: 1-2

37. Segall G. 2019. ABNM statement on ACMUI changes in authorized user training and education. *J Nucl Med* 60: 17N

38. NRC regulations (10 CFR); Part 35—medical use of byproduct material. 2020. United States of America: 15/09/20

39. Ennis R. 2020. Interview with Michelle Bruno at Avalere Health [Telephone]. 10/16/20

40. Blue Cross Blue Shield of Massachusetts. Therapeutic Radiopharmaceuticals in Oncology for the Treatment of Gastroenteropancreatic, Bronchopulmonary, and Thymus Neuroendocrine Tumors (Lutetium 177 dotatate) Prior Authorization Request Form, #958. Available from: https://www.bluecrossma.org/medical-policies/sites/g/files/csphws2091/files/acquiadam-assets/958%20Prior%20Authorization%20Request%20Form%20for%20Therapeutic%20R

adiopharmaceuticals%20in%20Oncology%20Lutetium%20177%20prn.pdf [Accessed 09/10/21]

41. Centers for Medicare & Medicaid Services. 2021. *July 2021 Alpha-Numeric HCPCS File.* Baltimore: CMS

42. Aetna. 2021. Lutetium Lu 177 Dotatate (Lutathera). Available from: http://www.aetna.com/cpb/medical/data/900_999/0929.html [Accessed 09/21/21]

43. Blue Cross Blue Shield of North Carolina. 2021. *Therapeutic Radiopharmaceuticals in Oncology.* Durham, NC: Blue Cross Blue Shield of North Carolina

44. Premera. 2020. *Radioimmunotherapy in the Treatment of Non-Hodgkin Lymphoma.* Mountlake Terrace, Washington: Premera

45. Aetna. 2020. Ibritumomab Tiuxetan (Zevalin). Available from: http://www.aetna.com/cpb/medical/data/600_699/0659.html [Accessed 09/21/21]

46. Centers for Medicare & Medicaid Services. New Medical Services and New Technologies. [Updated 08/13/21]. Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/newtech [Accessed 09/30/21]

47. Manz CR, Bekelman JE, Doshi JA. 2020. The Changing Characteristics of Technologies Covered by Medicare's New Technology Add-on Payment Program. *JAMA Network Open* 3(8): e2012569-e69

48. Centers for Medicare & Medicaid Services. 2020. *Billing and coding: radiopharmaceutical agents.* Baltimore, MD: CMS

49. Spectrum Pharmaceuticals. ZEVALIN(R) Receives Positive Reimbursement Ruling Using Average Sales Price (ASP) Methodology. Available from: https://investor.sppirx.com/static-files/2d9ae134-d608-46d9-bb86-f2422e7dc955 [Accessed 07/16/21]

50. National Comprehensive Cancer Network. 2021. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): B-cell Lymphomas.* Plymouth Meeting, PA: NCCN

51. Morris M. 2020. Interview with Michelle Bruno at Avalere Health [Telephone]. 10/14/20

52. Centers for Medicare & Medicaid Services. 2021. *Addendum B.* Baltimore: Centers for Medicare & Medicaid Services

53. Centers for Medicare & Medicaid Services. Oncology Care Model. Available from: https://innovation.cms.gov/innovation-models/oncology-care [Accessed 06/29/21]

54. Berenson A. 2007. Medicare cuts payout on 2 cancer drugs [online]. *The New York Times.* Available from: https://www.nytimes.com/2007/12/07/business/07drug.html [Accessed 07/06/21]

55. Schaefer NG, Huang P, Buchanan JW, *et al.* 2011. Radioimmunotherapy in non-Hodgkin lymphoma: opinions of nuclear medicine physicians and radiation oncologists. *J Nucl Med* 52(5): 830-8

56. Schaefer NG, Ma J, Huang P*, et al.* 2010. Radioimmunotherapy in non-Hodgkin lymphoma: opinions of U.S. medical oncologists and hematologists. *J Nucl Med* 51(6): 987-94

57. Gordon L. 2021. Interview with Lucy Morgan at The Health Policy Partnership [Telephone]. 07/20/21

58. National Board of Prior Authorization Specialists. 2021. What is Buy and Bill. Available from: https://www.priorauthtraining.org/what-is-buy-and-bill/ [Accessed 09/02/21]

59. Weidner S, Diaz M, Schaedig C*, et al.* 2021. Observations Regarding the Average Sales Price Reimbursement Methodology. *Evidence-based Oncology* 27(4): 156-60

60. Mittra E. 2021. Personal communication by email: 08/24/21

61. Paivanas T. 2020. Interview with Michelle Bruno at Avalere Health [Telephone]. 10/06/20

62. Dunning D. 2021. Interview with Michelle Bruno at Avalere Health [Telephone]. 12/03/20

63. 340B Health. Overview of the 340B Drug Pricing Program. Available from: https://www.340bhealth.org/members/340b-program/overview/#:~:text=Specifically%2C%20the%20individual%20(1),referral%20for%20consultation)%20with%20the [Accessed 24/05/21]