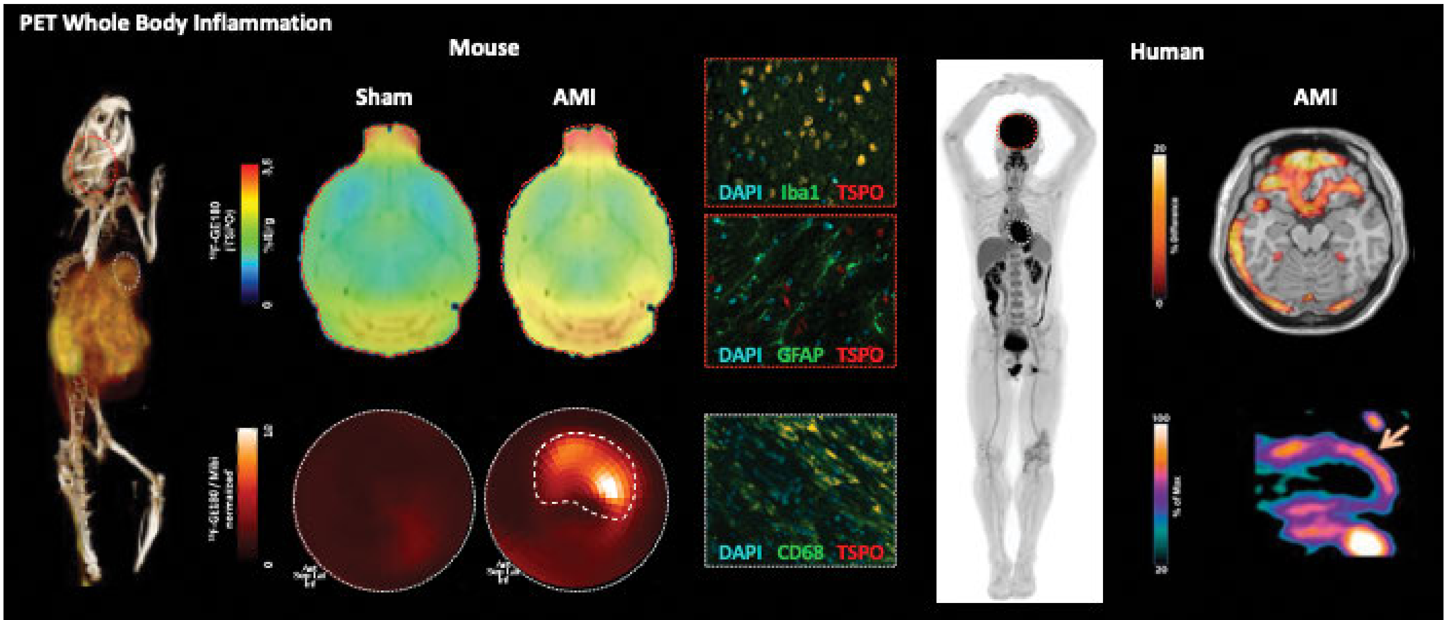
FEBRUARY 2022 ▪ NEWSLETTER
VALUE INITIATIVE



2022: A Milestone Achieved. A Call to Action Awaits

SATOSHI MINOSHIMA, MD, PhD; VALUE INITIATIVE BOARD CHAIR

2022 represents a significant milestone for the SNMMI Value Initiative: five years of partnering with our volunteer leaders and industry partners to advance nuclear medicine, molecular imaging, and radiopharmaceutical therapy.

In these five years, I've seen our volunteer leaders embrace their strategic role in driving positive change. I've seen tremendous growth, collaboration, and participation from our industry partners. I've seen recognition of the critical role and value of SNMMI in supporting the profession. Thanks to these partnerships and tireless efforts, we have:

- Bolstered SNMMI's focus on precision medicine with the creation of the Radiopharmaceutical Therapy, AI, and Dosimetry Task Forces
- Created and held multiple therapeutics-specific conferences
- Launched new SNMMI resources, including the 'Radiopharmaceutical Therapy Central' and 'Resident and Medical Student' websites, and the 'One's to Watch' recognition program
- Successfully advocated to retire FDG F-18 PET for infection and inflammation beginning in 2021 and the exclusionary language for non-oncologic PET in 2022
- Along with our society partners, succeeded in maintaining the training and experience requirements for Authorized Users
- Provided a forum for start-up companies with the creation of the Small Business Pavilion on the exhibit floor at SNMMI's Annual Meeting
- Saw the approval of new radiopharmaceuticals, including Lutathera (Lu177-dotatate); Azedra (I131-iobenguane); Ga68-dotatoc (U of Iowa); Pylarify (F18-DCFPyL); Ga68-PSMA (UCSF and UCLA) ; Tauvid (F18 flortaucipir); Cerianna (F18-FES); and Illuccix (Ga68-PSMA kits)

In recognition that our initiatives are achieving positive outcomes, we have seen a steady increase in industry support, with participation increasing from 5 industry alliance companies in 2018 to 37 (and counting) in 2022. This tremendous support powers the engine that will drive transformative change.

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NorthStar and its Future with Electron Accelerator Technology

An Interview with James Harvey, PhD and James McCarter, PhD

NorthStar Medical Radioisotopes is poised to become the first-in-class production supply chain for the future of therapeutic radiopharmaceuticals. In September 2019, the company broke ground on a 30,000 ft. building that now houses the company's first pair of electron beam accelerators. This past September 2021, the company celebrated the successful installation of the accelerators as well as all the equipment installed in an adjoining building, which will serve as the dissolution, processing, and filling facility. During our celebratory event this past September, we invited investors, customers, members of local and federal government and special guests to take a tour of these buildings. The feedback was so positive and garnered so much interest in our facilities that we decided to share the highlights with the membership of SNMMI. The following is an interview with James McCarter, PhD, Manager, Irradiation and James Harvey, PhD, Senior Vice President & Chief Science Officer, who have been leading the accelerator program at NorthStar.

Q. Why don't you start with an introduction, and tell us what your role is at NorthStar.

JM: I am James McCarter, Manager of our Irradiation team at NorthStar. Our Irradiation Group has a blended focus on nuclear physics and engineering, providing support throughout various processes along the production pathway. Our team is responsible for NorthStar's production of Molybdenum-99 using electron accelerators and applying the same accelerator technologies to future radioisotope programs.

JH: I am James Harvey, NorthStar's Senior Vice President and Chief Science Officer. I work with NorthStar's engineering, manufacturing and development teams to bring new products to the company in a Business Development capacity. I have been in this role at NorthStar since the inception of the Company more than 17 years ago.

Q. How does NorthStar currently produce Mo-99?

JM: Mo-99 is currently produced in partnership with The University of Missouri Research Reactor, or MURR®, as we call it. This process involves the addition of a neutron to naturally occurring Mo-98 to create Mo-99. Our new electron accelerators will create electron beams that produce x-rays that will knock neutrons off, known as neutron knock-off. This process takes a naturally occurring and abundant natural resource, Molybdenum-100, knocking off a neutron to create the radioactive Mo-99. In summary – we currently add a neutron to Mo-98 in the MURR® reactor; additionally, in the future, we will remove a neutron from Mo-100 using the electron accelerators.

Q. When thinking of new ways to produce domestic, non-uranium Mo-99, how did you and your team begin to think about electron accelerator technology? What were the goals you had in mind or issues that you thought through to solve using accelerator technology?

JM: The Program was already underway when I joined NorthStar. I come from a background of accelerator physics. I have my PhD in Engineering Physics that I received through the University of Virginia and Thomas Jefferson National Accelerator Facility, working on accelerators for many years at a few different companies before coming to NorthStar.

I have always been interested in the space and am aware of the many ways that accelerators can help society and have meaningful impact. When I learned of NorthStar's approach to use accelerators to produce Mo-99 and pursue other medical radioisotopes, I was intrigued. When I learned about the accelerator project, how NorthStar operated, and its management team and resources, I decided this was the place I wanted to pursue my career and advance the growth of a domestic Mo-99 supply chain.

JH: We knew as far back as the first major shortage of Mo-99 after Canada's National Research Universal (NRU) reactor at Chalk River outage in late 2007 that we had something special – the technology that has become the FDA approved isotope separation platform known as the RadioGenix® System. We also understood then that we could combine this technology with two different non-uranium production technologies, either reactor neutron capture or electron accelerator neutron "knock-out" to produce a domestic, non-uranium, non-HEU Mo-99 at a commercial scale. We knew we needed to establish two distinctly separate production technologies that could provide dual production pathways – sourcing Mo-99 that would be reliable for our customers and most importantly, for the patients they serve.

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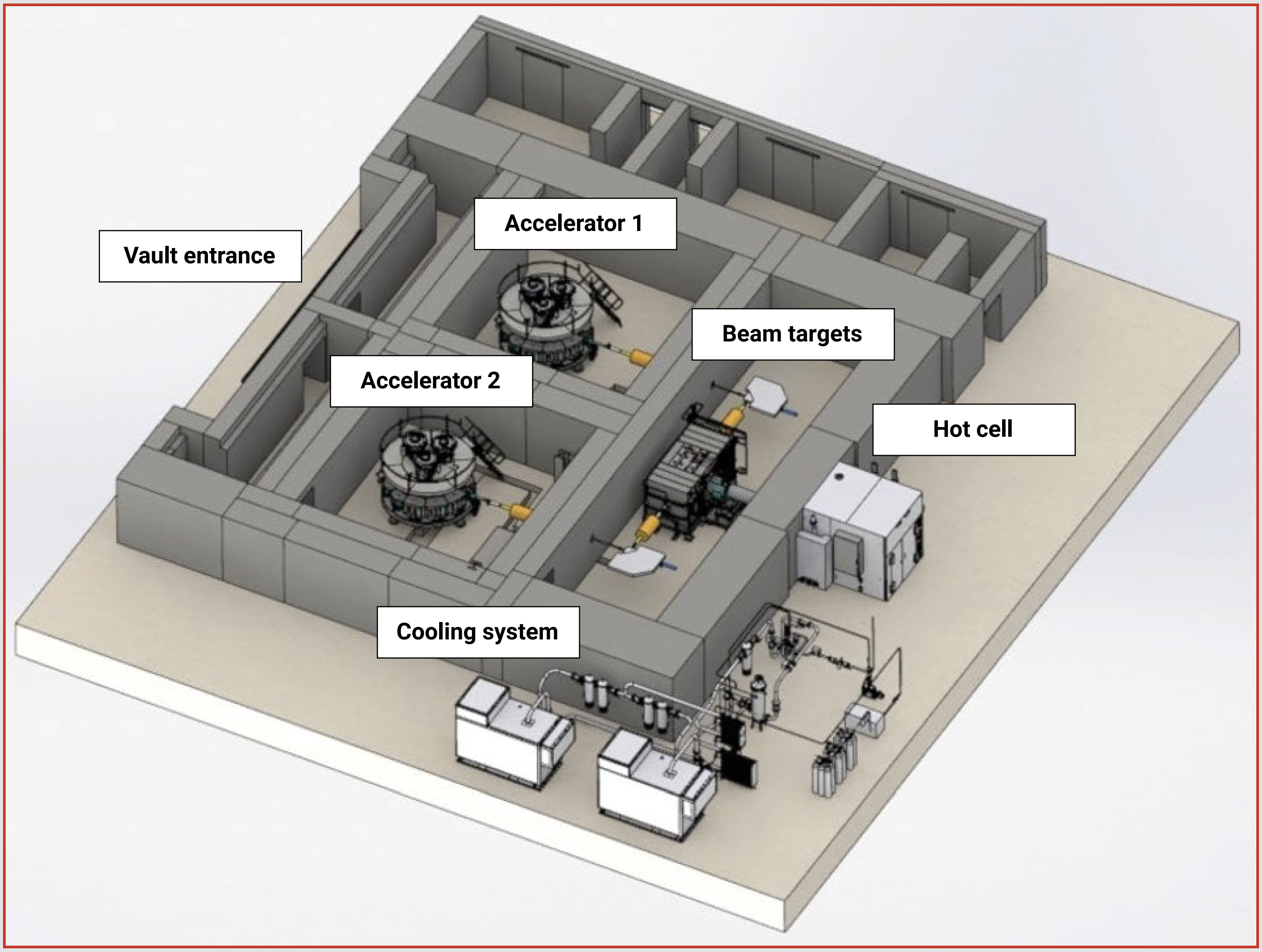

Q. How is accelerator technology different from what you are doing now?

JM: I think the accelerator technology is different primarily because it gives NorthStar complete control over the supply chain – true vertical integration. We are still fully committed to a long-term relationship with MURR® because it ensures reliability of the supply chain, and at the same time we will have access to that material from start to end; from generation of the raw Mo-100 all the way through to the RadioGenix® System-produced Technetium-99m (Tc-99m) that our radiopharmacy customers use to compound patient doses. Another important added benefit of vertical integration is the ability to adapt our production timelines to meet customer schedules. We will control what days we produce and ship Mo-99. We can increase supply of Mo-99 on short notice and we can produce Mo-99 every day of the week, if that is what customers require, or we can go to a more traditional Sunday production run, adding another day if needed.

Q. Why two accelerators?

JM: To understand the NorthStar accelerator production process it helps to start with the target. Our target is a series of Mo-100 cylindrical discs, approximately one-inch in diameter. The stack of discs resembles a roll of quarters. To maximize production efficiencies, it helps to shoot the electron beam from both sides. That is the way we can maximize the most efficient production of Mo-99. If we irradiate the starting material from two sides, it makes sense to use two different accelerators instead of trying to use one singular beam, split it in half, then recombine it. That technology would have been even more challenging. With two accelerators, we are

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NorthStar's accelerator production facility houses two custom-built, 24-ton Rhodotron®TT 300-HE (High Energy) electron beam accelerators. Each 10' diameter x 11' high accelerator weighs 48,000 pounds, or the weight of four African bush elephants. The accelerators were custom-built in Belgium for NorthStar by IBA (Ion Beam Applications S.A., EURONEXT). The accelerators began their 5,700-mile journey in Louvain-la-Neuve, Belgium and were transported via truck to Antwerp. They travelled in separate container ships to Baltimore, Maryland where, after clearing U.S. Customs, they were loaded onto oversized flatbed trucks to travel as a convoy from Baltimore to Beloit. The convoy arrived April 20, 2021 and the vaults and rest of the building were built around them. NorthStar expects equipment qualification and regulatory approvals for aMo-99 production to be completed by the end of 2022 with commercial production beginning in 2023. Up to three additional mirror image, accelerator facilities are planned to support increased market demand for Mo-99 and other radioisotopes.

NorthStar's unique and proprietary electron accelerator production facility and processes are designed to provide efficiencies throughout the production process, thereby enabling the production of multiple radioisotopes utilizing the same equipment. With this in mind, production of radiochemical grade Copper-67 (Cu-67) is expected in late 2022.

able to use twice the beam power and create material with higher specific activity than would be possible using other accelerator methods.

In line with NorthStar's efforts to be a reliable producer and supplier of Mo-99, we made the decision to separate the accelerators from the target. Therefore, we have our accelerator and our target housed in a concrete vault. This vault actually is three separate rooms. One room for each accelerator and the third room is for the target. This separation allows for maintenance even during operation of the accelerators.

Q. Can you tell us more about the accelerator and the systems required to maintain them.

JM: Our accelerator vault is similar to other accelerator labs, but we have a very high beam power. We have 250 kilowatts of total beam power at 40 MeV of electron energy. To contain that radiation, we built concrete walls that are 7.5 feet-thick of high-density concrete, which is equivalent to 12 to 15 feet of standard density concrete. In addition, we have local shielding around the target itself, which consists of a series of boxes, similar to Legos stacked on top of each other, and those boxes are filled with a combination of steel pellets and water or steel plates and concrete.

The accelerator facility itself was then built around the vault, which is the center of our process. Our production process also uses very high pressure, high flow helium to cool the target. The facility has a specialized room to house the helium equipment, which ranges from compressors and blowers, to purification and monitoring equipment, all located adjacent to the vault. There is also hot cell space, which the targets are placed into, moved out of the vault and delivered to NorthStar's adjacent Isotope Processing facility.

The entire accelerator facility is built on a 56-inch concrete foundation, which supports the 15 million pound vaults, the accelerators, and other associated equipment.

Q. The facility must require a lot of power.

JM: The accelerator facility will use approximately 1.5-2.0 megawatts of power to run the accelerators and the associated HVAC and other building systems. It is a lot of power for a very small footprint! You might see that kind of power at a car factory that is spread across several hundred thousand square feet. In comparison, our facility is 25,000 square feet, so it is "energy-dense." We have a dedicated power substation located adjacent to our facility, which will handle current and future needs including additional accelerators.

Given the enormity of power to dissipate, our chilled water system is very important. The colder temperatures in Wisconsin allow us to utilize a dry cooling system. Similar to how a car radiator works, we pump the water outside to let the cold air of the Wisconsin winter chill the water for us. This provides significant electricity cost savings and helps with sustainability.

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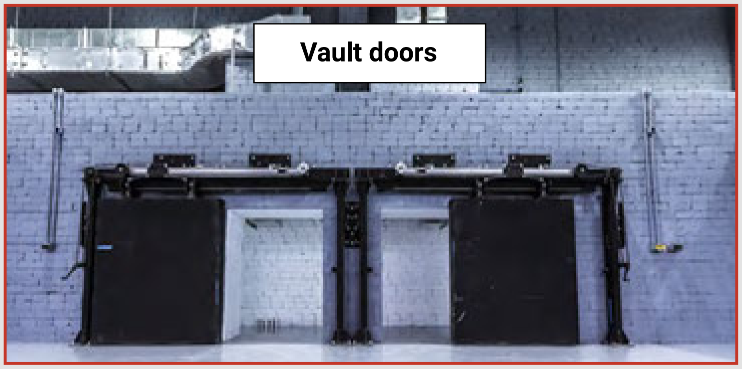

NorthStar's Electron Accelerator Vault Quick Facts

- 1600 yards of concrete were used in one continuous pour over 10 hours – that's 168 truckloads of concrete for the foundation that weighs as much as 333 African bush elephants.
- 400,000 high-density steel impregnated blocks were used in the construction of the vault over five months – that's an average of 25,000 blocks laid per week.
- The vault weighs 15 million pounds – as much as 760 school buses.
- 70' x 70' footprint, which is slightly bigger than two standard volleyball courts side by side. In some places, the vault reaches 25' tall.

We are equipped through an Uninterruptable Power Supply (UPS) system to handle short power outages. This allows us to safely shut down our accelerators and monitor all equipment and the status of all measurements and instrumentation in our facility. In the event of a power failure, the UPS is able to sustain operations until our facility generators and backup generators turn on.

Q. After the discs are irradiated, can you give an overview of the dissolution, processing, packaging and shipping processes?

JM: To recap, the Mo-100 starting material is pressed into discs, loaded into a holder and irradiated on both sides using our two electron accelerators. The irradiated targets, which are now a combination of Mo-99 and Mo-100, are removed through our hot cells (where we push the targets in and out of the accelerator), placed into a shielded transfer cask and moved from our Accelerator Production facility to our Isotope Processing facility, which is next door. In our Isotope Processing Facility, the discs are removed, and placed into a dissolution chamber where robotic arms are used to remove the discs and process the Mo-99. The material is then moved over to our filling lines, placed in tungsten shielded source vessels, packaged, and then shipped to radiopharmacies across the country.

An important item to note is that any unused Mo-100 is reclaimed and reused. This occurs both at the point of production and any unused Mo-99 that remains in the source vessels that are returned from customers is also reclaimed and reused. This is yet another example of NorthStar's focus on being an environmentally conscious company.

Q. Are electron accelerators more environmentally sound than traditional Mo-99 production methods?

JM: Absolutely. NorthStar's accelerator production technology is more environmentally sound than legacy production using fission methods. The critical distinction is that our process does not use uranium. We do not create uranium fission fragments or any problematic by-products. We have very limited long-term radioactive waste material and a benign chemical waste stream.

NorthStar's radioisotope production programs rely solely on methods that do not involve use of uranium and the fission process. We believe developing environmentally sound radioisotope production methods is important to the sustainability of nuclear medicine. Radioisotopes we produce now or plan to produce in the future will continue to use non-uranium target material and production processes.

Q. What are plans for expansion at NorthStar? Will there be additional accelerators and what will they be used to produce?

JM: We believe we will have extra capacity with the two accelerators and our current target design. If there are gaps between what the Mo-99 customer base demands and what we can supply in any given time, we are able

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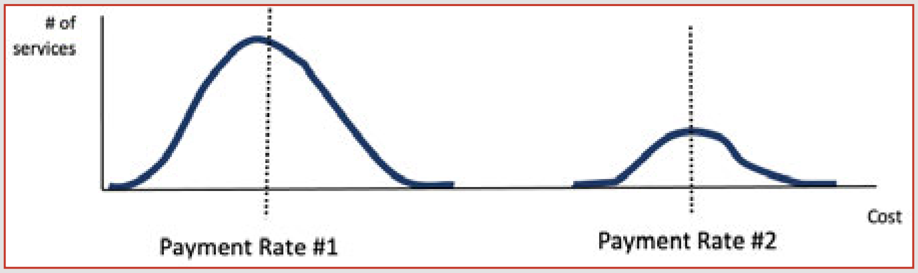

Figure 2: Split into Two APCs

outcome and other downstream costs for the underlying disease. For an apt comparison, the analysis would probably have to be disease-specific. It would not necessarily have to be set up as a clinical comparative trial; instead it might be able draw on longitudinal Medicare claims data as a principle source of information, using comparison techniques (for instance, propensity-matched samples) and estimating methodologies. Any stakeholder interested in pursuing such analysis should recognize the need for an expert, sophisticated effort.

Assuming robust, positive results, what good would this do? Surprising as it may seem, CMS does not usually pay much attention to cost-effectiveness. CMS eschews attention to costs in coverage determinations, and the main thrust of payment rate determinations is, within limits, to establish rates that capture the resource requirements of packages of items and services, not on the effects of those services on decreasing — or increasing — overall costs. So, given CMS posture that DxRPs are supplies, a cost effectiveness study may not be the missing link that will impel CMS adopt separate payment for DxRPs.

However, even though CMS does not take costs explicitly into account, its view might still be swayed by evidence pointing to a significant savings potential, and a study with at least moderately robust results could influence the agency's willingness to provide some accommodation. While the likelihood of CMS wholly abandoning a packaged approach in this instance does not appear high, the agency could conceivably revise the current APCs depending on whether a particular product is used. For example, CMS could split a single APC for diagnostic scans, which is not now differentiated by the DxRP used, into two APCs, one for scans using high cost DxRPs and another for scans using low cost DxRPs. This could allow a higher payment to hospitals for the diagnostic service as a whole in particular instances, while not going as far as providing for separate payment for the DxRP. One stylized example of this is shown in Figure 2.

Further, such a study could help in securing support in Congress for the FIND Act. It may also help with securing more adequate payment rates from capitated plans — Medicare Advantage and many private insurance plans.

NorthStar. Continued from page 14.

to use the accelerators for other projects. Those other projects can be improvements to our current design for a more efficient production process, to make more Mo-99 per target, or produce other radioisotopes that serve other markets. Our accelerators are agnostic as to what their target is. They are designed to run 7 days a week, 24 hours a day. For example, if we only need 5 days of Mo-99 production, then there are two days of production that can be used to produce other radioisotopes. NorthStar will be able to meet our commitment to provide domestic Mo-99 as well as our commitment to future medical radioisotope partners.

Throughout our current commissioning projects we are learning and refining along the way and will apply lessons learned to expand into the therapeutics business. In the near term, we just broke ground on our Actinium-225 Production facility that will house an electron accelerator to produce non-carrier-added Actinium-225 (n.c.a Ac-225).

I think the future of NorthStar and our electron accelerator technology is very bright. In 2023, after receiving all necessary approvals, we will be delivering radioisotopes to the community produced at NorthStar's own facilities in tandem with the Mo-99 produced from our partners at MURR®. Relying on that expertise will help us bring a dual-sourced domestic, efficient, reliable, and environmentally sound Mo-99 supply. Mo-99 has been the workhorse of the United States nuclear imaging community for years. When we apply the depth and breadth of our knowledge and experience in new and former technologies to the future of radiodiagnotics and radiotherapeutics, you can envision the direct impact that NorthStar will have on the lives of the patients we work so hard to serve.

For additional information on NorthStar's accelerator technology, and to take a virtual tour of the facilities discussed here, please visit us at www.NorthStarnm.com.

James McCarter, PhD
Manager, Irradiation

James Harvey, PhD
Senior Vice President & Chief Science Officer

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