Sustainability of F18 medical isotope production in small Canadian cities

Daniel Banks (TVB Associates Inc)
Joe Huser (TRIUMF)
Dale Schick-Martin (Fedoruk Centre)
Drew Marquardt (University of Windsor)

University of Windsor
Faculty of Science

Sustainability of F-18 medical isotope production in small Canadian cities

Authors: Daniel Banks (TVB Associates Inc), Joe Huser (TRIUMF), Dale Schick-Martin (Fedoruk Centre), and Drew Marquardt (University of Windsor)

Acknowledgements: The authors acknowledge contributions to the development of the business model reported in this paper from Constantinos Economou (AtomVie), and Manny Subramanian (TeamBest). The authors thank the Windsor Regional Hospital for helpful discussions. This work was funded by the Natural Sciences and Engineering Research Council and the Ontario Centres of Excellence via a VIP Alliance grant.

Introduction

Canada's small population distributed across its very large geography poses significant challenges in providing equitable medical care across its rural and urban areas. A notable challenge is provision of cancer diagnosis techniques that rely on short-lived radioisotopes, such as Fluorine-18 (F-18), which is required for Positron Emission Tomography (PET) scanning. Such nuclear diagnostic techniques are typically only available at centralized locations.

Without access to a PET scanner locally, cancer patients must travel to receive their diagnosis. Such travel can burden patients and complicate their condition—and, during an epidemic or pandemic, may be discouraged or forbidden to reduce the transmission of pathogens from one local medical system to another. Thus, greater access to PET scanning for patients in rural areas and small cities would be a step toward more equitable medical care and self-sufficiency of local medical systems.

The medical importance of PET scanning is growing, as cases of cancer continue to increase and as Health Canada and other regulatory bodies continue to approve new indications for PET scanning in cancer diagnosis and other medical applications.

Typically, sustainable PET scanning requires a large population nearby, not only because of the high capital cost of PET scanners (e.g. $3-4M), but also the high cost of facilities to produce F-18 and convert it to the radiopharmaceutical needed for PET scanning: [^{18}F]-fluorodeoxyglucose, known as FDG. Such radiopharmaceutical manufacturing requires a costly particle accelerator, typically a cyclotron, and a lab that is equipped with hot cells and certified for Good Manufacturing Practices (GMP).

Two small cities in Ontario each have a PET scanner but do not have a local supply of FDG, namely, Windsor and Sudbury (serving catchment populations of 420,000 and 200,000, respectively).[1] In these cases, FDG must be just-in-time shipped from larger centres such as London, Hamilton, or Toronto. Well over half of the FDG in such shipments is lost during transit through radioactive decay due to the 110-minute half-life of the F-18. These losses in transit drive up the per-patient cost of PET scans at the receiving hospital and limit the number of patients that can be served from a single production run of FDG from the supplier.

[1] All population numbers are as reported by Statistics Canada, 2021 Census of Population, for the respective district health unit.

Thunder Bay, Ontario, serving a catchment population of 150,000, has a PET scanner as well, but it has acquired its own local supply of FDG because its considerable distance from major cities would make reliance on outside FDG suppliers impractical. In other words, producing the FDG locally is less expensive, on a per-scan basis, than bringing in FDG from elsewhere. Thunder Bay is an exception, as most similarly sized populations in Canada have neither their own PET scanner nor FDG supply.

Windsor has a strategic interest in hosting its own FDG supply. Its PET scanner has been well supplied with FDG from London for its current number of patients. However, projected growth in the demand for PET scans over the next several years could overtake the current limit on the number of patients that can be served each day in Windsor within the current delivery arrangements, leading to either increased costs or the need for patients to travel elsewhere for a PET scan. Further, Windsor was especially hard-hit by the COVID-19 pandemic, which may have been related to its role as a major international border community and highlights a need for the self-sufficiency of its medical system during epidemics or pandemics.

Thus, we examined the sustainability of local FDG production in Windsor, looking for insights that will apply generally to the sustainability of FDG production in other small Canadian cities.

Achieving sustainability

Strategies to secure local supplies of FDG include diversification of the business model beyond sales to supply a local hospital. One option is to sell to other cities that have PET scanners but not their own FDG production capability. Another option is to use the F-18 production accelerator, and the isotopes produced from it, for research and industrial purposes, and thus generate revenues from other non-medical sources. The Saskatchewan Centre for Cyclotron Sciences is an example of a cyclotron-based facility with a diversified mission that includes research and innovation as well as supplying a clinical PET scanner with FDG. These strategies for sustainability have worked well in some cases, but are not always viable solutions.

Pricing is often the determining factor in whether a medical isotope supply is sustainable. The price points of the isotope itself (e.g. F-18), the radiopharmaceutical made from it (e.g. FDG), and the medical procedure (e.g. PET scanning) are all important factors. Each price needs to be high enough to sustain the suppliers of these medical goods and services. When prices are too low, they pose a risk to the sustainability of any radiopharmaceutical supply chain.

A case in point is the global supply of technetium (Tc-99m) needed for SPECT scans. Tc-99m is by far the most used medical isotope. Over 85% of all diagnostic nuclear medicine procedures use Tc-99m (i.e. about 30 million scans around the world every year). Yet the global supply chain of Tc-99m has been unreliable over the past 15 years, ever since the severe supply crisis in 2009 and 2010 caused by unexpected outages and extended maintenance periods of its few central production facilities (nuclear research reactors). In 2010, the Nuclear Energy Agency (NEA) identified the root cause of this unreliability: Unsustainably low prices at the point of isotope production.[2] The same study showed that it would take a nine-fold price increase of the isotopes at the point of production in order to sustain reactors fully dedicated to isotope production, without a need for subsidies or other revenue sources on

[2] NEA (2010). The Supply of Medical Radioisotopes: An Economic Study of the Molybdenum-99 Supply Chain. OECD Publishing, Paris.

which such production facilities (i.e. reactors) typically rely. But what is most revealing is that this seemingly extreme jump in price would make only about a 1% difference in the reimbursement rates for the medical diagnostic procedures that use Tc-99m. That is because the cost to provide the radiopharmaceuticals used in the scans is only a small part of the procedure's overall cost, and in turn, the cost of the isotope production (performed by the reactor) is a small part of the radiopharmaceutical cost. The NEA points to complexities in the supply chain for an explanation of why the unsustainable pricing still persists today, despite the apparently easy solution of raising isotope prices.[3]

Fortunately, in the case of FDG, the supply chain and pricing system are simpler, often with only three parties involved: The party that produces the isotope, F-18, typically produces the radiopharmaceutical, FDG, as well. That producer sells and ships the FDG to hospitals for use in PET scans. The provincial government, acting as the single payer, sets the policies for reimbursing the hospitals.

Our research questions and approach

This simple supply chain provides hope that sustainability of FDG production in small Canadian cities could be reduced to a pricing problem. As such, *At what increase in cost of the FDG to the payer does local FDG production become sustainable? How much difference would the requisite price increase make in the cost of the PET scan?* And, *How dependent are these findings on the local demand for PET scans?* We sought to answer these questions by developing a cost model for FDG production in Canada, to which we add information about the cost of PET scans in Windsor.

As was the case for the NEA assessment of Tc-99m, our main strategy was to talk to industry experts. We relied on advice from FDG suppliers, suppliers of FDG production equipment, and cancer care providers about the many individual cost factors involved, and using this information we built our model from the bottom up. Information that was not disclosed to us for commercial reasons (e.g. the price of a batch of FDG) was inferred with good approximation from other information.

In our analysis, we distinguish between two levels of sustainability: (1) *full sustainability*; and (2) *essential operations*. In the full sustainability scenario, we calculate the price of FDG needed to recover all capital costs of an FDG production facility, including a building, a commercial cyclotron to produce F-18, and equipment to produce the FDG over the facility's expected lifetime. We also include start-up costs to be recovered over 40 years. Start-up costs include a decommissioning bond, licensing fees, personnel, and other operating costs during a two-year start-up phase before significant revenues from sales of FDG can be expected.

In the essential operations scenario, we take the building, cyclotron, and start-up investment as provided, without expectation of cost recovery. The essential operations scenario is relevant to a situation in which government grants, donations from the public (i.e. fundraising), and in-kind contributions from a university or hospital are used to offset the capital and start-up costs of healthcare provision. Even in this scenario, FDG revenues must be sufficient to replace the FDG production equipment as needed, which can be as often as every 10 years.

In our model, we made simplifying assumptions that are applicable to a facility operated by a university or by a hospital in cooperation with a university. Most notably, we assumed that the FDG production

[3] OECD/NEA (2019). *The Supply of Medical Isotopes: An Economic Diagnosis and Possible Solutions*. OECD Publishing, Paris. *https://doi.org/10.1787/9b326195-en*

personnel can be shared with the host for other nuclear medicine or research purposes when they are not engaged in FDG production. This is a critical assumption at low production volumes because it enables us to convert the otherwise fixed cost of full-time staff into a variable cost that scales with the demand for PET scans. Such a facility operated by a university or by a hospital would also be eligible for much lower regulatory fees.

Our model includes all operating costs, such as production and administrative personnel, raw materials and other consumables, maintenance of the cyclotron and other equipment, overhead costs such as safety and regulatory costs, quality assurance, host space charges, decommissioning set-asides, and backup costs of failed production runs.

Results and discussion

A key finding of our analysis is that the current arrangements for FDG supply and PET scans are not far off from the price points required to reach essential operations in the case of Windsor (Figure 1). The price of a batch of FDG would need to rise 56%, but the resulting cost of all supplies for the PET scans on a per-patient basis would rise only 34%, after accounting for the savings in shipping costs by producing the FDG locally, and for other supply costs incurred by the hospital for PET scanning. This 34% increase, in turn, would raise the total cost of a PET scan in Windsor by only 17% (the total cost includes supplies, labour, amortization of capital equipment, and 50% overhead on labour and supplies).

To reach the full sustainability level, at which all capital costs are recovered, higher increases are required but may still be feasible (Figure 2): The batch price of the FDG would need to rise 150%, resulting in a 110% increase in PET supply costs and a 54% increase in the total cost of a PET scan in Windsor.

We also considered how the sustainable FDG price would change with the demand for PET scans. The data shown in Figure 1 is based on the current PET scan schedule in Windsor: In 2021, Windsor's PET scanner operated 3 days per week over 48 weeks, serving 5 or 6 patients per day (i.e. about 730 patients per year). We defined a *baseline scenario* in which Windsor continues to import FDG from London as demand grows. In this baseline scenario, an average of 5.5 patients per day are served, and the number of days in the year that PET scans are provided—and FDG is produced—is determined by demand. When demand reaches 1,320 PET scans per year, a second shipment of FDG later in the day from London would be required, enabling 11 patients per day to be served on some days. We have made the conservative assumption that the second batch of FDG can be obtained at the same cost (although the cost of a second batch would likely be higher).

If the FDG is produced locally, however, more patients can be served with a single batch of FDG by avoiding losses that occur during shipment. Hence, we define a *normal PET schedule* as one in which PET scans are initially limited to 3 days per week for 48 weeks per year, and the number of patients is allowed to rise to 11 patients per day. Additional days per week are added only after this PET schedule is saturated by demand, which occurs at about 1,600 PET scans per year. In Figure 1, we show the difference in FDG price required for essential operations for this normal PET schedule, compared to the current price continuing as in the baseline scenario. Our calculations show that the required price increase for FDG in an essential operations scenario makes no difference to the cost of a PET scan once demand reaches 1,100 PET scans per year, which is the *break-even point* from the perspective of the

single payer. At higher demand, the cost of a PET scan drops, since the FDG can be used much more efficiently when produced locally.

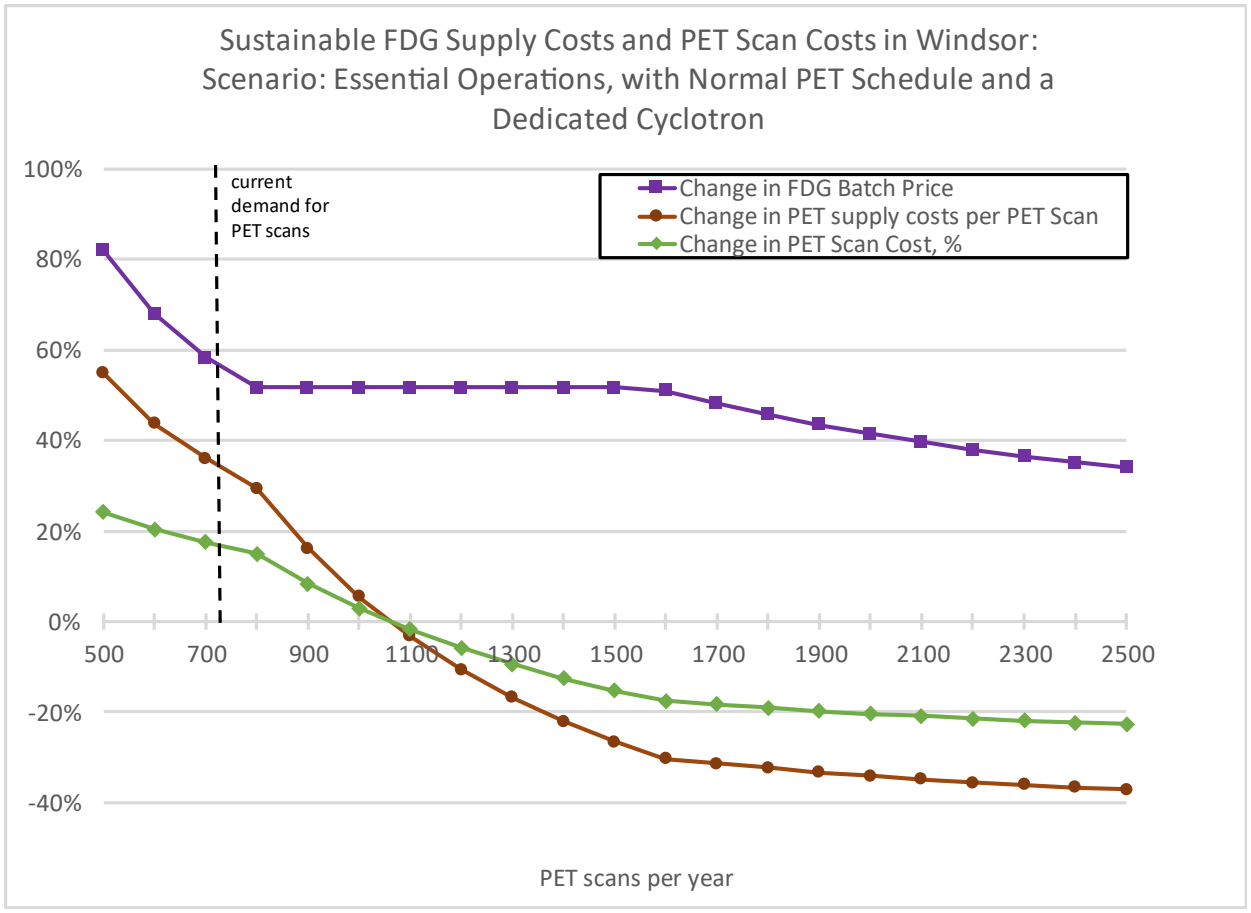

*Figure 1. Change in FDG batch price (compared to the baseline scenario) required to achieve sustainability in the **essential operations scenario**, and the resulting changes in PET supply costs per scan and in PET scan costs.*

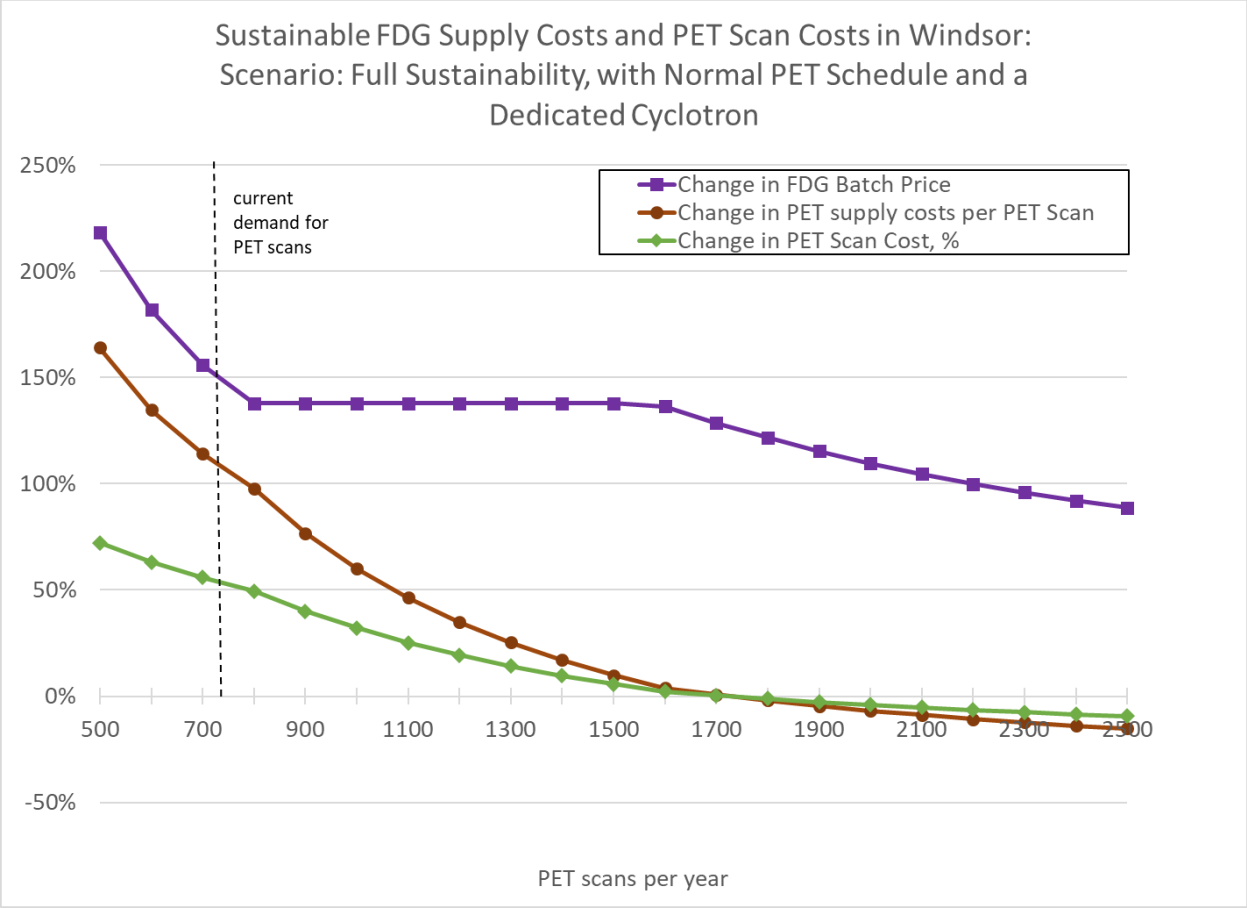

*Figure 2. Change in FDG batch price (compared to the baseline scenario) required to achieve **full sustainability**, and the resulting changes in PET supply costs per scan and in PET scan costs.*

We also examined an even more efficient *compact PET schedule* in which PET scans are offered for only an average of 1.5 days per week until demand saturates this schedule at 11 patients per day, corresponding to 800 PET scans per year, after which additional days would be added. For this compact schedule, the break-even point for the single payer is reached much earlier, at only 700 PET scans per year, even though a 100% increase in the price of an FDG batch would be required for essential operations of the FDG production facility.

As the above scenario shows, a local FDG production facility could be sustained in Windsor today without increasing net cost to the public health system, if the capital costs of a building, cyclotron, and start-up are excluded. If those costs are to be recovered, then a 36% increase in the cost of a PET scan would be required to sustain such a facility today.

We did not perform a benefit analysis, leaving that to healthcare policy experts. However, the cost increases for the scenarios we examined appear to suggest that a full cost-benefit analysis may be worthwhile for small cities on the scale of Windsor.

We did not consider the possibility, mentioned above, of diversifying the missions of the cyclotron-based facility to generate other revenue streams. Such streams could make local production more attractive but would need to be examined on a case-by-case basis.

Conclusion

A local FDG production facility might be sustainable in Windsor today without increasing net cost to the public health system, if:

(a) the capital costs of a building, cyclotron, and start-up are provided from other sources, such as fundraising, government grants, and in-kind support from local partners (e.g. universities, hospitals);

(b) the PET scanning schedule is adjusted to fully exploit every batch of FDG produced locally; and

(c) the local producer is a university or hospital that can employ FDG production staff elsewhere on days that FDG is not being produced.

While this analysis has focused on Windsor, the findings suggest that similar degrees of sustainability of FDG production might be achieved in small population centres across Canada that require as few as 700 PET scans per year, provided that the current cost of PET scans in Windsor is acceptable to the various provincial payers. Yet each situation should be examined carefully on a case-by-case basis, and options for other sources of revenue should be explored to enhance each case for sustainability.

University of Windsor
Faculty of Science