How can we introduce innovative treatments into our publicly-funded healthcare system?

On April 28, Craig Earle, MD, MSc, from Sunnybrook Health Sciences Centre, Odette Cancer Centre in Toronto, presented the 2018 Cosbie lecture

Gerald Cosbie was a Canadian physician and pioneer in the treatment of gynecologic cancers. He cared for the first patients treated with radiotherapy at the Toronto General Hospital in 1921. He played an important role in the establishment of the Ontario Cancer Institute and served as Medical Director of the Ontario Cancer Research Foundation. The Cosbie lecture series, established by the Foundation and awarded to the Canadian Oncology Societies, was instituted in his honour in 1977. The series is currently sponsored by the Canadian Oncology Societies, Cancer Care Ontario and the Canadian Cancer Trials Group.

> “I’d like to think that if Dr. Cosbie and I were having a beer together, we would bond over a mutual passion for making sure that Canadians have the best possible access to cancer care.”

Dr. Craig Earle is a medical oncologist at Sunnybrook Health Sciences Centre, Odette Cancer Centre, in Toronto, Ontario. He is Vice-President of Cancer Control at the Canadian Partnership Against Cancer, a Senior Scientist at the Institute for Clinical Evaluative Sciences, and a Professor of Medicine at the University of Toronto. He is past Chair of the Ontario Steering Committee for Cancer Drug Programs and is a current member of the pan-Canadian Oncology Drug Review Expert Review Committee. His personal research focuses on evaluating and improving the quality of care received by patients with advanced cancer and cancer survivors, the effects of financial incentives on care delivery, and making linked, deidentified administrative data more available for health research. Dr. Earle originally trained and practiced in Ottawa, after which, beginning in 1998, he spent 10 years in Boston at Harvard Medical School and the Harvard School of Public Health. Between 2008–2017, he was Director of Health Services Research and Head of Clinical Translation at the Ontario Institute for Cancer Research.

The perception among people outside Canada is that our health care is completely paid for through the public system. However, the promise we have from the Canada Health Act is “reasonable access to necessary care” provided in hospitals or by physicians. Access to drugs remains variable and uncertain, which poses an increasing challenge in cancer care. There are considerable differences across provinces in the drugs covered by public plans, and Canada as a whole performs quite poorly in terms of assuring prompt access to cancer therapies that are shown to have benefit. A study published in 2012 comparing a number of countries found that Canada, represented by the province of Ontario, provided public funding for only half of 48 newer cancer therapies.[1]

The question I will explore today is: How can we introduce innovative treatments into our publicly-funded healthcare system? This is a considerable challenge—the prices of new therapies are threatening access and sustainability. We need strategies for quickly figuring out the added value of new drugs, without prolonging delays that deny people access to valuable treatments.

The advent of immunotherapy, using chimeric antigen receptor-modified T cells (CAR-T) to target tumour-associated antigen, is bringing increased attention to this challenge. In a recent article, Green and Saltz[2] look specifically at CAR-T cell therapy, which has a price tag of around $400,000 US for the drug itself, and additional costs associated with delivering the treatment, such as hospital and intensive care unit stays. We are therefore looking at million-dollar treatments. Green and Saltz consider that the price of CAR-T may force discussion around what minimal degree of efficacy will warrant such expense. They suggest that a more equitable pay-for-performance strategy for oncology drugs should be contemplated.

When graphing the price of cancer drugs over time, the curve will always slope steeply upwards, whether it refers to the price trajectory of a particular drug following approval,

or the overall cancer drug budget. And they are not always worth it. A study by Kelvin Chan and others published in March 2018[3] applies the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) value frameworks to drugs approved over the past few years and plots this alongside the price of a monthly dose of those drugs. While the average value score remains flat between 2006 and 2015, the average price triples over the same time period.

Dr. Peter Bach from Memorial Sloan-Kettering Cancer Center published an article in the *New York Times* a few years ago showing price variation in lung cancer drugs that we know, from an efficacy point of view, are more or less interchangeable; he found that price varied 6-fold between them. Other studies have looked at why prices vary to such a great extent and find little relation to novelty or effectiveness. Rather, current prices simply reflect what the market will bear.

In looking at the Canadian context in particular, it is helpful to first understand the various steps involved in a therapy's trajectory into the market.

HOW DO WE GET DRUGS INTO OUR PUBLICLY-FUNDED SYSTEM?

The first step belongs to Health Canada, which assesses a drug product's safety, quality of manufacturing and, to some extent, its efficacy. Following receipt of a Notice of Compliance from Health Canada, the next step is the Patented Medicines Pricing Review Board (PMPRB), which sets the maximum list price at which the drug may be sold in Canada. The PMPRB consults prices in 7 Organisation for Economic Co-operation and Development (OECD) countries and determines that the price in Canada cannot be more than the median of these prices; these list prices, we all know, are high. A new drug then undergoes an assessment of value, which falls under the Canadian Agency for Drugs and Technologies in Health (CADTH), and for cancer drugs, under the pan-Canadian Oncology Drug Review (pCODR). pCODR will makes a recommendation to the provinces about whether they should reimburse a particular drug. Following pCODR recommendations, decision-making moves to the provinces, which retain final decision-making power.

Decisions made around pricing for provincial public drug plans are taken by a committee called the Cancer Drug Implementation Advisory Committee (CDIAC), which used to be referred to as the "Secret Committee" because there was no information available on how deliberations were conducted or who was on the committee. It has since become somewhat more transparent. What the CDIAC does is to take the recommendations coming out of pCODR and prioritize them according to various factors: drugs are not assessed in the order in which they arrive. The next step, the pan-Canadian Drug Pricing Alliance (pCDPA), is where

TABLE 1: Public drug funding pathway

Requirement	Agency/Body	Output
1. Safety, efficacy, quality	Health Canada	Market authorization
2. List price	Patented Medicines Pricing Review Board (PMPRB)	Maximum price
3. Value (health technology assessment)	Canadian Agency for Drugs & Technologies in Health (CADTH) • Common Drug Review (CDR) • pan-Canadian Oncology Drug Review (pCODR)	Reimbursement recommendation to provinces
4. Value & affordability	Cancer Drug Implementation Advisory Committee (CDIAC) of Canadian Association of Provincial Cancer Agencies (CAPCA) • Provincial drug plans (CDIAC) • Private insurers	Reimbursement decision
5. Reimbursed price	• Pan-Canadian Drug Pricing Alliance (pCPA) • Product listing agreements	Best reimbursement price

the actual negotiations with the manufacturer occur to try to get the best reimbursed price. While provinces can at any point decide not to fund a drug, the idea is that all provinces will obtain a better deal if they negotiate together, and they lose negotiating power if too many drop out.

Effectiveness

pCODR looks at drugs with a deliberative framework that considers overall clinical benefit, alignment with patient values, cost effectiveness and feasibility of adoption. In terms of overall clinical benefit, the hope is that there are randomized controlled trials (RCTs) that provide very good information about a drug's benefits. Today, however, we face a real risk of innovation outpacing evidence. Some consider that the CAR-T technologies currently being investigated are already generations beyond the commercial products that are just starting to come through the regulatory and assessment process. Going forward, many pivotal decisions may end up being made on the basis of early-phase or even n-of-1 studies.

pCODR does have a track record of recommending funding for drugs that have not been studied in phase 3 RCTs. The rationale may be that they target a severe situation where there is no alternative treatment; that a randomized trial is judged to be infeasible; or that there has been loss of equipoise, where no one would ever allow themselves or their patients to be randomized. Another situation may be if there is good evidence of effectiveness early on, with very high rates of durable complete response. Looking at drugs that have been recommended for funding without phase 3 trials, we see that it is not enough to have high response rates; early studies need to show that people achieve clearly higher-than-expected survival, and preferably progression- and relapse-free survival. As well, recommendations favour drugs that are easier to take, with good quality of life and low toxicity.

Cost effectiveness

In Canada, we maintain that there is no cost-for-quality threshold with regard to public funding for a treatment. However, researchers have examined pCODR decisions and worked backwards to figure out the effective cost-for-quality threshold in recommendations for reimbursement.[4] It ends up at around $140,000 per quality-adjusted life year (QALY). That represents the list price, which is always higher than the negotiated price, but seems to be where the threshold currently sits.

Cost-effectiveness assessments are conditional on a great many factors. Looking at CAR-T therapy, it may actually be cost-effective for current indications that cure childhood leukemia, where treatment may produce a gain of 70 QALYs. However, if we start using the same therapy in the types of solid tumours most of us treat, the calculation will work out quite differently.

Feasibility

Feasibility of adoption is an interesting criterion. What usually comes to mind is budget impact. Increasingly, and certainly with CAR-T cells, feasibility challenges also appear in the availability of human resources, facilities and infrastructure, along with expertise in delivering a particular treatment. We can anticipate, especially if we wait for RCT results to initiate the funding consideration process, an additional several years delay as our systems ramps up to deliver these therapies. Some groups consider that running clinical trials to deliver CAR-T will get around these complications, but this raises questions around the ethics of favouring a home-grown CAR-T approach when there are proven commercially products available.

Budget impact is obviously a major factor in feasibility. In the guidelines, elements of budget impact include the number of patients; likely uptake; how long patients will be on treatment; and the cost of providing the drug: does it require a hospital stay, central venous access devices, or intensive care? The patent situation is also a consideration; when a drug is early in its patent life, the high price will persist for many years. Along with consideration of factors that increase budget impact, factors that offset overall costs are also considered. By delivering this treatment, can we save on something else, whether that may be downstream treatments, or means of caring for advanced cancer? Looking at how other jurisdictions are managing with the drug provides valuable information on some of these questions.[5]

The major factor in feasibility is, of course, the actual cost of the drug, and the reality is that almost no one knows what that is. The pan-Canadian Drug Pricing Alliance (pCDPA), conceived in August 2010 at a First Ministers' meeting, brings the provincial plans together to negotiate lower drug prices. It started operating in 2012, with Ontario and Nova Scotia as leads for the other provinces, and Quebec and the Federal government joining in somewhat later. The main idea is to use the increased leverage of larger numbers to achieve lower drug prices. The hope is that there will be more consistent availability of drugs across the country.

APPROACHES TO PRICE NEGOTIATION

Several approaches to negotiating price can be taken. The main one is value-based pricing. These negotiations are undertaken by the pharmacy representatives from the different jurisdictions, and not by professional negotiators, though that might be something to consider in the future. Calculations are made to establish the cost per QALY and the price that would render the drug cost-effective. On the pCODR expert review committee, I would often see manufacturers dispute the cost-effectiveness analysis, because they know it will affect later price negotiations.

Another approach that we do not see in Canada, but is used in some American insurance schemes, is value-based insurance. In these, either the manufacturer is reimbursed to a level of the least costly acceptable treatment or, when there is a new drug that is marginally more effective but not publicly funded, and the cost would need to be $1000 a month for it to be cost-effective, the patient is given that $1000 and pays the balance out of pocket or with private insurance. An advantage in this approach is that it requires some transparency in pricing and eventually exerts downward pressure on price, as individual patients, and not just public and private plans, have to decide what price point is acceptable.

Negotiations are likely not as effective in Canada as they could and should be. In the April 2018 report delivered to the House of Commons on Pharmacare, one interesting recommendation was that the government of Canada provide CADTH with additional funding to expand capacity to undertake therapeutic reviews of high-cost oncology drugs, as well as develop expertise to support the negotiation of managed-entry agreements for these drugs.

TABLE 2. Managed entry agreements = "adaptive" = "conditional" listing schemes

Health outcome-based	Non-outcome-based
• Pay for results: e.g., free drug initiation	• Volume discount
• Coverage with evidence development	• Utilization reviews → cap or discount if:
• Finance disease management programs, education, etc.	• budget impact
• Providing additional trial data as it becomes available	• per-patient cost
	• per-patient volume (mfr supplies beyond a certain # of doses) is exceeded

All of these are less common since the advent of the PCPA (↑ complexity)

MANAGED-ENTRY AGREEMENTS

Also called adaptive agreements or conditional listings schemes, these come in 2 types. One is based on health outcomes and involves some form of pay for results. The other involves non-outcome-based strategies.

Outcome-based strategies

A few years ago, the National Institute for Health and Care Excellence (NICE) in the UK attempted to negotiate a reimbursement strategy for multikinase inhibitors in renal cell carcinoma where the public plan would only pay if patients responded. In the end, that was not entirely applied, however it points to creative possibilities in this area. There are examples in other diseases: in Italy, some of the Alzheimer's drugs are provided free by the manufacturer for 3 months, after which public reimbursement kicks in, but only for patients whose disease has been stabilized.

Coverage with evidence development is another strategy. This was prompted a few years ago in Ontario, when a woman with a 9-mm HER-2-positive breast tumour objected to her exclusion from public coverage of trastuzumab. A new program was developed called the Evidence-Building Program, and trastuzumab is now covered for a broader population, with the idea that data is collected and will be analyzed centrally to assess whether benefits are achieved beyond the original target group.

Manufacturers can also be required to fund disease management programs as part of the listing agreement. When we prescribe EGFR inhibitors and our cancer centres magically seem to have these nice packets of skin creams, this was part of the negotiation for the manufacturer to provide a disease management program for the major side effect of the drug.

Another strategy is to require, as is common in Germany, that manufacturers collect additional trial data. After 1 year of public funding, the public insurer then reevaluates the drug based on everything the company has learned in the past year. The price can then be renegotiated, or funding can be stopped. It is also possible that the price will go up.

Non-outcome-based strategies

The other broad type of negotiation has nothing to do with whether or not the drug is effective. The main strategy in this category is the volume discount. Another type is utilization review, where the price is capped, or a discount is provided once the budget impact at jurisdictional level is known, or the per-patient, or per-patient volume (number of doses), is exceeded. When bevacizumab was made available in the US, one program stipulated that if a patient's drug costs exceeded $50,000 in a calendar year, the manufacturer would provide the balance of the drug for free. That program encountered a problem with mixed incentives that reduced uptake: in the US, most care providers actually make money on the markup of a drug, so even though the drug was being offered for free, the free drug was hardly ever used.

MANAGED-ENTRY AGREEMENTS IN CANADA

In Canada, there is a sense that since the pCDPA took on negotiations, fewer of these more creative types of agreement are being negotiated. The central strategy is simply the volume discount. I have no inside information, but my understanding is that most of the volume discounts are in the 20% to 30% range off the list price, though some are much more than that. The more creative approaches are not being used so much, as they become very complex when multiple jurisdictions are involved, especially with current data protection rules.

However, we may want to figure out how to improve the creativity of pan-Canadian negotiations. If we could make all our new-product listing agreements conditional, we might achieve a better balance between prompt access to new treatments and the need to evaluate them rigorously. It would allow us to iteratively generate new evidence and reduce some of the uncertainty we have about whether a treatment is worth the cost. For example, we could commit to funding a drug for 1 to 3 years, then analyze routinely collected data to see if the assumptions around the cost, effectiveness, uptake and complications have actually been borne out. If they were not, public insurers would reserve the right—established up front—to renegotiate the price, revise the eligibility criteria, make other amendments to conditional listing, or de-list the drug.

This kind of approach would move us from one-off, high-stakes decisions, to an ongoing process of evaluating drugs and determining whether they are worth paying for from public budgets.

What could we realistically assess?

This type of approach is based on an ability to collect information about a drug after it enters the market. Observational evaluations are limited by variables such as patient selection and intervention fidelity, and by ambiguity

around followup times and response. In many cases, response rates could likely be inferred. For example, when paclitaxel became available, physician-reported response to treatment was collected. Administrative claims data such as hospital discharge abstracts, billing data, etc., could be used to assess emergency room (ER) visits, hospitalizations, and stays in intensive care units. Duration on treatment could provide a proxy for progression-free survival (PFS). Most of the assumptions that underlie the budget impact analysis could be examined and tested using this type of routinely collected data. As well, some form of randomization could be embedded into the conditions of the listing. This was suggested with one of the checkpoint inhibitors, where the optimal duration of treatment is uncertain, and funding could be provided on the condition that it would be for randomly different durations to see if outcomes were detectably different. These are opportunities to bake real-world evidence into our drug approval process.

WHAT COULD MANAGED ENTRY LOOK LIKE FOR CAR-T CELL THERAPY?

In their article, Green and Salz state that the manufacturer (Novartis) has proposed an outcomes-based payment model where they would only be reimbursed if the patient responded within 30 days. However, given that 82% of patients will respond within that time, this does not completely solve the problem. Green and Salz propose other possible conditions, such as complete remission at 1 year, or setting a lower up-front price, and increasing payments as milestones—remission at 3 months, 6 months, etc.—are reached. Conditions would relate the effectiveness of the treatment to its cost.

The requirements for any of these approaches are, first, good data and reasonable sample size. Ideally this would be pan-Canadian data. Second, analysis would need to be transparent and rigorous because there is a lot at stake. Thresholds of efficacy or effectiveness, and the consequences of not meeting those thresholds, would need to be specified before making the listing decision, with agreement reached with the manufacturer on the definition of success and the interpretation of the data. And public plans would have to be prepared for the possibility that the price could increase as a result of the analysis, if a therapy performs better than expected. The process would need to gain the trust of manufacturers, and likely require sharing data with them, because results of the analysis could have an impact in markets much larger than Canada.

These types of approach require more resources than we currently have available. They need people with expertise to analyze and interpret data, as well as careful communication and education efforts with the public, patients and providers, around the process and the possibility that a drug that had been available could be de-listed. The message would need to emphasize that public health care involves a defined basket of goods and that we need to manage it responsibly. Ways to publicly communicate the analysis and reasons for decisions would be needed. As well, we would have to consider what to do for people who were already on the drug, and those who thought they would be able to get the drug. Perhaps our governments should sell supplemental insurance, plowing any profits back into the public healthcare system.

Once we start along this road, we will also need to assess the usefulness of evaluations, and the value of the information collected. Does it help us figure out which type of risk-sharing or cost-sharing agreements work, and in which situations, e.g. the most expensive drugs or the highest-volume drugs? Such work would help arrive at the simplest approaches for relating payments to the value of the treatment.

At the end of April, there was an interesting announcement from CADTH, that CAR-T cell therapies would be evaluated not as a drug through pCODR, but rather through the health technology assessment (HTA) process used for medical devices and clinical interventions. CAR-T cells are clearly evaluated by Health Canada as a drug and, in fact, Health Canada released a new definition to distinguish drugs and devices, seemingly to specifically address this therapy. It states that if something acts through the immune system, it is a drug, and will be regulated as such. However, CADTH determined that CAR-T cell therapy would be treated as a medical device/intervention. The other assessment group in Canada, Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) has taken the same approach.

While I cannot pretend to know the internal discussion around that decision, a few possible reasons come to mind. For one, CAR-T requires much more than just the administration of a drug, but if reviewed as a drug, would funding for all these other implementation issues also have to come out of drug budgets? The decision might also have been made to allow flexibility for home-grown CAR-T cell therapies, being more philosophically in line with allowing such approaches down the road. Or it could be as simple as providing a way to get around pCODR's very strict timelines for recommendations, given the novelty of the therapy and uncertainty about how to evaluate it. Timelines are more flexible in the medical device review process.

CONCLUSION

Introducing innovative treatments into our publicly-funded healthcare system will require being more creative and thoughtful about how we fund therapies and make decisions around funding. There is a need to move away from one-off high-stakes decisions. However, the alternative approaches discussed here will need resources, people power, analytic capacity and courage.

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