

HEALTHCARE

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*Health Services, Management and Policy Research
Services de santé, gestion et recherche de politique*

Volume 17 + Number 4

**University Technology Transfer Has Failed to Improve Access to
Global Health Products during the COVID-19 Pandemic**

MATTHEW HERDER, E. RICHARD GOLD AND SRINIVAS MURTHY

**Propelled by the Pandemic: Responses and Shifts in Primary
Healthcare Models for Indigenous Peoples**

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Healthcare Policy/Politiques de Santé seeks to bridge the worlds of research and decision making by presenting research, analysis and information that speak to both audiences. Accordingly, our manuscript review and editorial processes include researchers and decision-makers.

We publish original scholarly and research papers that support health policy development and decision making in spheres ranging from governance, organization and service delivery to financing, funding and resource allocation. The journal welcomes submissions from researchers across a broad spectrum of disciplines in health sciences, social sciences, management and the humanities and from interdisciplinary research teams. We encourage submissions from decision-makers or researcher–decision-maker collaborations that address knowledge application and exchange.

While *Healthcare Policy/Politiques de Santé* encourages submissions that are theoretically grounded and methodologically innovative, we emphasize applied research rather than theoretical work and methods development. The journal maintains a distinctly Canadian flavour by focusing on Canadian health services and policy issues. We also publish research and analysis involving international comparisons or set in other jurisdictions that are relevant to the Canadian context.

Politiques de Santé/Healthcare Policy cherche à rapprocher le monde de la recherche et celui des décideurs en présentant des travaux de recherche, des analyses et des renseignements qui s'adressent aux deux auditoires. Ainsi donc, nos processus rédactionnel et d'examen des manuscrits font intervenir à la fois des chercheurs et des décideurs.

Nous publions des articles savants et des rapports de recherche qui appuient l'élaboration de politiques et le processus décisionnel dans le domaine de la santé et qui abordent des aspects aussi variés que la gouvernance, l'organisation et la prestation des services, le financement et la répartition des ressources. La revue accueille favorablement les articles rédigés par des chercheurs provenant d'un large éventail de disciplines dans les sciences de la santé, les sciences sociales et la gestion, et par des équipes de recherche interdisciplinaires. Nous invitons également les décideurs ou les membres d'équipes formées de chercheurs et de décideurs à nous envoyer des articles qui traitent de l'échange et de l'application des connaissances.

Bien que *Politiques de Santé/Healthcare Policy* encourage l'envoi d'articles ayant un solide fondement théorique et innovateurs sur le plan méthodologique, nous privilégions la recherche appliquée plutôt que les travaux théoriques et l'élaboration de méthodes. La revue veut maintenir une saveur distinctement canadienne en mettant l'accent sur les questions liées aux services et aux politiques de santé au Canada. Nous publions aussi des travaux de recherche et des analyses présentant des comparaisons internationales qui sont pertinentes pour le contexte canadien.

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New Spending Programs and Old Frustrations: Where Is the Vision?

THE SPRING HAS USHERED IN AN UNEXPECTED NUMBER OF MAJOR HEALTH POLICY announcements compared with the last 10 years. They are led by the federal government's outlines of a national pharmacare program, an unexpected dental care program (Prime Minister of Canada Justin Trudeau 2022), plus "top-up" funding for clearing provincial surgical and imaging backlogs. These announcements are on top of the voices expressing concerns about COVID-19-related healthcare expenditure trends (Bailey 2022). Without a doubt, taxpayer money is flowing freely into healthcare (Labby 2020).

The major policy initiatives occur in the backdrop of a receding pandemic whose social and economic policies to combat the spread of COVID-19 wrought a severe toll on many Canadians. The impact has not been equally distributed – infirm seniors, the economically or socially marginalized, healthcare workers and others who disproportionately experienced the pandemic's burden.

From my vantage point, I am surprised by the lack of anger and frustration with the provincial and territorial healthcare delivery systems' return to the same modus operandi. I am surprised that there are no loud voices demanding meaningful reform among the families of long-term care residents isolated during the pandemic, among dependents of overworked healthcare professionals shuffled into gut-wrenching situations and among surgical patients enduring prolonged waits for surgery, who are now also demonstrating symptoms of depression and anxiety (HQCA 2019; Rubinoff 2022; Silas and McKenna 2021).

As public spending on health services and products accelerates with these policy announcements, I expected a commensurate quid pro quo, with taxpayers demanding that the foundation of provincial healthcare delivery be strengthened. New government spending should purchase not only more of the same but some of the new funding should fix, or meaningfully reduce, the silo-based delivery system's faults.

Many are clear about the most important problems facing healthcare delivery in Canada. Though researchers may argue over the relative ranking of problems, the list of suspects usually

includes lack of access to high-quality primary care especially among marginalized groups; lack of coordination between primary care and other healthcare providers such as allied health, mental health or specialist care; long waits for specialty care such as allergists and surgeons; and lack of coordination and cooperation between healthcare and social care sectors.

Improved access to prescribed drugs and dental care are important pieces of the healthcare safety net, but they alone do not improve access to primary care, reduce fragmentation between primary and secondary care or address regional disparities in access or health outcomes, nor do the pharmacare or dental care policies target social factors associated with health and well-being, such as food and job insecurity or affordable housing.

A Path Forward

There are green shoots amid the status quo in most provinces. Ontario has embarked on a journey to create community-based structures of healthcare that span a range of provider types, including coordination among hospitals, physicians and community-based physical and mental healthcare providers. Similar to Alberta's smaller scale initiative (HQCA 2019), province-wide reforms in Ontario will need a long-term horizon, patience from politicians, policy makers and the public and additional public spending to reduce bottlenecks, improve coordination or care and address system-level disequilibrium between demand and supply of healthcare services. We should cheer for their efforts.

There is a complementary need to evaluate the COVID-19-induced rapid-cycle innovations that occurred across the county. The federal government can establish a time-limited commission to evaluate healthcare delivery innovations whose task is to arm provincial and territorial policy makers with answers to questions of "what worked and why?" Successful local innovations can be broadly transmitted to other settings to avoid duplication of effort. Without speedy action, identifying factors associated with provinces' successes, such as widespread adoption of video-based consultations, may be lost.

Potential solutions to serious healthcare delivery problems were not touched upon in the new policies' media releases. The focus of the new policies was squarely on "adding" more programs. That is fine because a preponderance of evidence suggests that they will improve access to care and health outcomes. However, governments should not overlook existing problems and their potential to positively change the trajectory of future healthcare consumption and spending growth.

In my opinion, the demand for change is extremely high from many quarters and the policy window of opportunity is still open. Without speedy action and clear vision for change from decision makers, we allow Canadians to continue experiencing the same problems with their healthcare that they have always faced.

In This Issue

The focus of this issue is on important system-level factors associated with healthcare access, equity and advanced technology. In the first Discussion and Debate article, Herder and

colleagues (2022a) express the point of view that the process of transferring publicly funded university-developed technology to low- and middle-income countries is not effective. The authors cite the example of the lipid nanoparticle delivery technology incorporated into COVID-19 vaccines. The authors conclude that the federal government should take a number of steps to improve, and make more transparent, university and government technology transfer practices.

In the next article, Stevens (2022) has crafted a rejoinder to Herder and colleagues' (2022a) Discussion and Debate article. In contrast with the original article, Stevens describes a counter-example of Oxford University and Vaccitech as a more effective university technology transfer vis-à-vis the societal objective of lowering financial barriers to access new therapies in low- and middle-income countries. The rejoinder concludes that Herder and colleagues' (2022a) interpretation is based on an overly narrow example; Stevens writes that technology development is a complex give-and-take among researchers, government funders and industry manufacturers or distributors, each with different objectives. The article concludes that improving access to innovative therapies requires a deliberate weighing of pros and cons of different options for which there is currently no clear winning strategy.

Consistent with the original article, a second rejoinder by Ramachandran (2022) articulates that the field of university technology transfer experiences "... pervasive failure of universities in implementing their public pledges to use licensing strategies that prioritize global access to technologies developed on their campuses even with significant federal funding support" (p. 38). Ramachandran states that governments should take additional steps to comply university-based research and researchers to enact access-oriented licensing and transparency measures, inferring that these steps would improve access to therapies in low- and middle-income countries.

The topic of technology transfer practices is concluded with a brief response by Herder et al. (2022b) that argues that university technology transfer policies need substantial strengthening by the government.

A second Discussion and Debate article by Barnabe et al. (2022) recounts Indigenous communities' response to the first wave of the COVID-19 pandemic in southern Alberta. Multiple stakeholders were assembled to develop and implement a response plan to reduce the pandemic's impact on Indigenous communities. The article posits that the learnings from the strong response to the pandemic can be harnessed to establish and strengthen self-determined models of health-care delivery that reflect Indigenous culture and identity.

A rejoinder by Oster and Lightning (2022) reinforces the importance of relationships in Indigenous health research. Oster and Lightning (2022) extend the discussion on Indigenous culture and self-determined models of healthcare delivery by emphasizing that trust-based relationships between Indigenous communities and researchers are requisite to research-informed Indigenous health transformation. The article concludes with the authors' perspectives on possible approaches to reframing Western approaches to research in order to successfully engage Indigenous communities in health-related research.

This issue's final research article examines the safety of health-related artificial intelligence (AI) products (Da Silva et al. 2022) by presenting risks in the evaluation of AI products and

the complementary perspective of whether the AI products are safely used by the health-care industry. The authors describe an existing patchwork of laws and regulations spanning safety, privacy, anti-discrimination and standards of care, which, when taken together, make for a complex regulatory environment. The article concludes with a number of specific recommendations that can be used by Health Canada as a basis for reforming regulations for health-related AI products.

JASON M. SUTHERLAND, PHD

Editor-in-Chief

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Nouveaux programmes de dépenses et vieilles frustrations : où est la vision?

Le printemps a vu un nombre inattendu d'annonces majeures en matière de politiques de santé, par rapport aux 10 dernières années. On y trouve les grandes lignes d'un programme national d'assurance médicaments, d'un programme de soins dentaires inattendu (premier ministre du Canada Justin Trudeau 2022), ainsi que d'un financement « complémentaire » pour éliminer les retards provinciaux en matière de chirurgie et d'imagerie. Ces annonces s'ajoutent aux voix qui expriment leur inquiétude quant aux tendances des dépenses de santé liées à la COVID-19 (Bailey 2022). De toute évidence, l'argent des contribuables circule librement dans les soins de santé (Labby 2020).

Ces initiatives se déroulent dans le contexte d'une pandémie en recul dont les politiques sociales et économiques pour lutter contre la propagation de la COVID-19 ont fait des ravages chez de nombreux Canadiens. L'impact n'a pas été ressenti de manière égale : les personnes âgées fragiles, les personnes économiquement ou socialement marginalisées, les travailleurs de la santé et d'autres personnes ont subi de manière disproportionnée le fardeau de la pandémie.

De mon point de vue, je suis surpris par le peu de colère et de frustration face au retour du même modus operandi dans les systèmes de santé provinciaux et territoriaux. Je suis surpris qu'il n'y ait pas de voix exigeant une réforme significative chez les familles des résidents des établissements de soins de longue durée isolés pendant la pandémie, chez les personnes dépendant de professionnels de la santé surchargés de travail et qui se retrouvent dans des situations déchirantes ou encore chez les patients qui doivent attendre longtemps avant d'être opérés, qui montrent aussi des signes de dépression et d'anxiété (HQCA 2019; Rubinoff 2022; Silas et McKenna 2021).

Alors que les dépenses publiques pour les services et produits de santé s'accroissent avec ces annonces politiques, je m'attends à une contrepartie proportionnelle, c'est-à-dire que les contribuables exigeront un renforcement de la base pour la prestation des soins de santé provinciaux. Les nouvelles dépenses gouvernementales devraient non seulement permettre

de poursuivre dans la voie habituelle, mais une partie du nouveau financement devrait venir corriger, ou réduire de manière significative, les défauts d'un système de prestations qui fonctionne en cloisons.

Plusieurs personnes pointent clairement du doigt les problèmes les plus importants auxquels fait face la prestation des services de santé au Canada. Bien que les chercheurs puissent discuter du classement relatif des problèmes, la liste des suspects comprend généralement le manque d'accès à des soins primaires de haute qualité, en particulier parmi les groupes marginalisés; le manque de coordination entre les soins primaires et les autres types de soins tels que les soins paramédicaux, la santé mentale ou les soins spécialisés; les longues attentes pour des soins spécialisés tels que l'allergologie et la chirurgie; et le manque de coordination et de coopération entre les secteurs de la santé et de l'aide sociale.

L'amélioration de l'accès aux médicaments sur ordonnance et aux soins dentaires est un élément important du filet de sécurité des soins de santé, mais ces initiatives n'améliorent pas l'accès aux soins primaires, ne réduisent pas la fragmentation entre les soins primaires et secondaires, ni ne résolvent les disparités régionales en matière d'accès ou de résultats en matière de santé. Les politiques d'assurance médicaments ou de soins dentaires ne ciblent pas non plus les facteurs sociaux associés à la santé et au bien-être, comme l'insécurité alimentaire, la précarité d'emploi ou le logement abordable.

Une voie à suivre

Dans la plupart des provinces, on peut voir des signes précurseurs au milieu du statu quo. L'Ontario s'est lancé dans une démarche visant à créer des structures de soins de santé communautaires qui couvrent une gamme de types de fournisseurs, notamment par la coordination entre les hôpitaux, les médecins et les fournisseurs communautaires de soins de santé physiques et mentaux. Tout comme l'initiative à plus petite échelle de l'Alberta (HQCA 2019), les réformes en Ontario nécessiteront un horizon à long terme, la patience des politiciens, des décideurs et du public ainsi que des dépenses publiques supplémentaires pour réduire les goulots d'étranglement, améliorer la coordination ou le système de soins et s'attaquer au déséquilibre de niveau entre la demande et l'offre de services de santé. Nous devrions applaudir ces efforts.

En parallèle, il faut aussi évaluer les innovations à cycle rapide induites par la COVID-19 qui ont eu lieu au pays. Le gouvernement fédéral pourrait créer une commission d'une durée limitée afin d'évaluer les innovations en matière de prestation de soins de santé dont la tâche est d'offrir aux décideurs provinciaux et territoriaux une réponse à la question « qu'est-ce qui a fonctionné et pourquoi? ». Les innovations locales pourraient être transmises à d'autres contextes pour éviter la duplication des efforts. Sans une action rapide, l'identification des facteurs associés aux succès des provinces, comme l'adoption généralisée des consultations par vidéo, pourrait se perdre.

Les solutions possibles aux graves problèmes dans la prestation de soins de santé n'ont pas été abordées dans les communiqués de presse qui accompagnaient l'annonce des nouvelles

politiques. Ces politiques étaient surtout axées sur « l'ajout » de programmes supplémentaires. C'est bien parce qu'un grand nombre de données suggèrent que ces programmes permettront d'améliorer l'accès aux soins et les résultats en matière de santé. Cependant, les gouvernements ne doivent pas négliger les problèmes existants et leur potentiel à modifier la trajectoire de la croissance de la consommation de services de santé et des dépenses de santé.

À mon avis, le besoin de changement est extrêmement élevé dans nombre de milieux et la fenêtre d'opportunité politique est encore ouverte. Sans une action rapide et une vision claire du changement de la part des décideurs, nous laisserons les Canadiens continuer à vivre avec les mêmes problèmes auxquels ils ont toujours été confrontés dans les services de santé.

Dans ce numéro

Ce numéro met l'accent sur d'importants facteurs au niveau du système associés à l'accès aux soins de santé, à l'équité et à la technologie de pointe. Dans le premier article de la section Discussions et Débat, Herder et collègues (2022a) expriment le point de vue selon lequel le processus de transfert de technologies financées par des fonds publics vers les pays à revenu faible ou intermédiaire n'est pas efficace. Les auteurs citent l'exemple de la technologie à nanoparticules lipidiques incorporée dans les vaccins contre la COVID-19. Les auteurs concluent que le gouvernement fédéral devrait prendre un certain nombre de mesures pour améliorer et rendre plus transparentes les pratiques universitaires et gouvernementales en matière de transfert de technologie.

Dans l'article suivant, Stevens (2022) a rédigé une réplique à l'article de Herder et collègues (2022a). Contrairement à l'article original, Stevens décrit le contre-exemple de l'Université d'Oxford et de Vaccitech, considéré comme un transfert de technologie universitaire plus efficace pour atteindre l'objectif sociétal d'abaisser les obstacles financiers à l'accès aux nouvelles thérapies dans les pays à revenu faible et intermédiaire. Cette réplique conclut que l'interprétation de Herder et collègues (2022a) se fonde sur un exemple trop étroit. Stevens explique que le développement technologique est un échange complexe entre les chercheurs, les bailleurs de fonds gouvernementaux et les fabricants ou distributeurs de l'industrie, chacun ayant des objectifs distincts. L'article conclut que l'amélioration de l'accès aux thérapies innovantes nécessite une évaluation du pour et du contre des différentes possibilités, évaluation pour laquelle il n'existe actuellement aucune stratégie gagnante claire.

Plus conforme à l'esprit de l'article original, une deuxième réplique de Ramachandran (2022) fait état d'« un échec généralisé des universités dans la mise en œuvre de leurs promesses publiques d'employer des stratégies d'octroi de licences qui donnent la priorité à l'accès universel aux technologies développées sur leur campus, et ce, même avec un soutien financier fédéral important » (p. 38). Ramachandran ajoute que les gouvernements devraient prendre des mesures supplémentaires pour inciter la recherche universitaire et les chercheurs à adopter des mesures d'octroi de licences et de transparence axées sur l'accès, en déduisant que ces mesures pourraient améliorer l'accès aux thérapies dans les pays à revenu faible et intermédiaire.

Le sujet du transfert de technologie se termine par une brève réponse de Herder et al. (2022b) qui soutient que les politiques de transfert de technologie universitaire doivent être considérablement renforcées par le gouvernement.

Un deuxième article de la section Discussion et Débat, par Barnabe et al. (2022), fait état de la réaction des communautés autochtones à la première vague de la pandémie de COVID-19 dans le sud de l'Alberta. Plusieurs intervenants ont été réunis pour élaborer et mettre en œuvre un plan d'intervention visant à réduire l'impact de la pandémie sur les communautés autochtones. L'article postule que les enseignements tirés de la forte réaction à la pandémie peuvent être exploités pour établir et renforcer des modèles autodéterminés de prestation de soins de santé qui reflètent la culture et l'identité autochtones.

Une réplique d'Oster et Lightning (2022) renforce l'importance des relations dans la recherche en santé autochtone. Oster et Lightning (2022) prolongent la discussion sur la culture autochtone et les modèles autodéterminés de prestation de soins de santé, en soulignant que des relations fondées sur la confiance entre les communautés autochtones et les chercheurs sont essentielles pour une transformation de la santé autochtone fondée sur la recherche. L'article se termine par les points de vue des auteurs sur les approches possibles pour recadrer les approches occidentales de la recherche afin d'engager avec succès les communautés autochtones dans la recherche liée à la santé.

Le dernier article de ce numéro examine la sécurité des produits d'intelligence artificielle liés à la santé (Da Silva et al. 2022) en présentant les risques liés à leur évaluation et en cherchant à savoir s'ils sont utilisés en toute sécurité par l'industrie de la santé. Les auteurs décrivent le patchwork des lois et réglementations actuelles qui portent sur les questions de sécurité, de confidentialité, de lutte contre la discrimination et de normes de soins. Ensemble, ces lois et réglementations créent un environnement réglementaire complexe. L'article se termine par un certain nombre de recommandations que Santé Canada pourrait utiliser pour réformer la réglementation des produits d'intelligence artificielle liés à la santé.

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University Technology Transfer Has Failed to Improve Access to Global Health Products during the COVID-19 Pandemic

Le transfert de technologie universitaire n'est pas parvenu à améliorer l'accès mondial aux produits de santé pendant la pandémie de la COVID-19



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Abstract

Publicly funded research has contributed enormously to many products that were developed in the face of the COVID-19 pandemic. Yet universities' technology transfer practices have failed to ensure that these products are available in low- and middle-income settings. Drawing upon the example of the lipid nanoparticle delivery technology – which was

developed in and around the University of British Columbia in Vancouver, BC, and incorporated into the Pfizer/BioNTech COVID-19 vaccine – we show the divide between the university's stated principles to serve global health and technology transfer in practice. We outline three policy actions to realign universities' technology transfer practices in the service of global health.

Résumé

La recherche financée par l'État a grandement contribué au développement de nombreux produits face à la pandémie de la COVID-19. Pourtant, les pratiques de transfert de technologie des universités n'ont pas réussi à garantir que ces produits soient disponibles dans les pays à revenu faible ou intermédiaire. L'exemple de la technologie à nanoparticules lipidiques – qui a été développée entre autre par l'Université de la Colombie-Britannique, à Vancouver, et incorporée au vaccin Pfizer/BioNTech contre la COVID-19 – montre le fossé entre, d'une part, les principes énoncés par l'université au service de la santé mondiale et, d'autre part, le transfert de technologie dans la pratique. Nous décrivons trois actions politiques pour réaligner les pratiques de transfert de technologie des universités au service de la santé mondiale.

Introduction

While Canada has imported more doses from Pfizer/BioNTech than from any other COVID-19 vaccine makers, many may be unaware that a crucial component of the mRNA vaccine was developed domestically. The vaccine incorporates a “lipid nanoparticle” (LNP) delivery system that was invented and developed by researchers embedded in a web of biotechnology companies (Box 1), which sprang out of the University of British Columbia (UBC) (Dolgin 2021; Vardi 2021) in Vancouver, BC. It is uncertain as to who controls the technology. The validity of some of the patents pertaining to the LNP technology remains the subject of an ongoing legal dispute between one of UBC's spin-off companies (Arbutus Biopharma) and the American biopharmaceutical company Moderna, Inc., which in collaboration with the National Institutes of Health (NIH) in the US, produced the other COVID-19 mRNA vaccine (“Moderna Loses Key Patent” 2020). But without the LNP delivery system, Pfizer/BioNTech's life-saving vaccine (and likely also the NIH/Moderna mRNA vaccine [Vardi 2021]) would not work (Buschmann et al. 2021).

Against a background of an insufficient supply of COVID-19 vaccines to meet global need and vaccine-makers resisting efforts to share the underlying knowledge (Furlong 2021), we trace how the LNP technology came to be privately controlled. In the past, observers lauded UBC for its global health-oriented approach to technology transfer, which focused on licensing biomedical discoveries in ways that promote access in low- and middle-income countries (LMICs) (“University Global Health Impact” n.d.). However, the COVID-19 pandemic reveals a departure from this goal and a gap between technology transfer in principle and technology transfer in practice. We focus on this gap in order to motivate policy change.

BOX 1. Developing the LNP delivery system: A complex backstory

The story behind the development of the LNP delivery system is complex. According to patent filings, the LNP technology was originally invented in the mid-2000s by several scientists, including Ian MacLachlan, who were then employed at Protiva Biotherapeutics. Understanding who controls the LNP delivery system and what products it has been integrated into is, however, clouded by an array of corporate transactions, trade secrecy, regulatory rules and multiple rounds of litigation.

The litigation mainly appears to be the product of interpersonal rivalry and corporate manoeuvring. Protiva was spun out of another company, Inex Pharmaceuticals (later renamed Tekmira), which had been co-founded by UBC biochemist Pieter Cullis in the 1990s (considered a pioneer in the field of LNPs and other technologies, Cullis has been involved in multiple companies' efforts to commercialize promising therapeutics). As MacLachlan (through Protiva) pursued the development of a gene therapy with a Massachusetts-based company, Alnylam Pharmaceuticals Inc., demonstrating the first effective "gene silencing" therapy in monkeys using the LNP system, his former Inex colleague-turned rival, Thomas Madden, vied for Alnylam's attention. Lawsuits followed, eventually resulting in Alnylam assigning ownership of the LNP patents back to Protiva/Tekmira and paying \$65 million to settle the case. Importantly, the biotechnology company AICana Therapeutics (created by Madden and Cullis), which later became Acuitas Therapeutics, was also granted a licence under the 2012

settlement to utilize MacLachlan's LNP delivery system for the purposes of developing novel mRNA products. In 2015, AICana/Acuitas sub-licensed the LNP technology to Moderna, Inc., for the development of an mRNA influenza vaccine, precipitating another round of litigation between Tekmira (then renamed Arbutus Biopharma) and Acuitas. As part of a new settlement in 2018, Acuitas' licence to the LNP technology was terminated. But the core LNP technology, through various partnerships, appears to be embedded in a range of products, including a regulatory-approved rare disease gene therapy, mRNA-based cancer treatments currently in development and at least one COVID-19 vaccine. Arbutus and Moderna meanwhile continue to dispute their respective patent rights before the US Patent Trial and Appeal Board.

Moderna has indicated it will not enforce any COVID-19 patent rights during the pandemic. But neither Arbutus (the owner of MacLachlan's patents on the LNP system) nor Acuitas (which worked with Pfizer/BioNTech to develop its COVID-19 vaccine delivery technology) has signalled the same forbearance. None of these companies has shared the precise details of the LNP delivery system that is incorporated into the mRNA COVID-19 vaccines. Arbutus' LNP delivery system patents have been filed in South Africa, India and China, among other places, where key would-be producers of COVID-19 vaccines have thus far struggled to re-engineer the underlying LNP technology.

The information contained in Box 1 derives from multiple sources (Aizenman 2021; Akinc et al. 2019; Dolgin 2021; Vardi 2021; Zimmermann et al. 2006), including patent applications pertaining to the LNP delivery system (Yaworski et al. 2011, 2016).

Technology Transfer and Global Health

Technology transfer encapsulates a range of activities designed to move a discovery from "bench to bedside." The predominant approach to technology transfer relies upon intellectual property (IP), especially patents (Table 1), as a tool to attract investment and create agreements between two or more parties, all with an intention of spurring follow-on research (Burk and Lemley 2003; Herder et al. 2020). The process can consume many years spanning discovery through pre-clinical research, clinical trials involving humans and, eventually, regulatory approval. Most drugs and vaccines fail along this path, but the process often begins with a discovery in a university lab, which is patented and transferred into a newly formed "spin-off" company, hoping to attract partners and investment on the strength of its IP position.

Many drugs and vaccines in use today, especially those that are important for public health, emanate from publicly funded environments (Herder et al. 2020). This does not necessarily mean that technology transfer is functioning optimally. On the contrary, there are several instances where the current, IP-focused approach to technology transfer has slowed

TABLE 1. A glossary of IP and related legal instruments

Type of IP	Description	Duration	Example
Patents	A set of exclusive rights to use, make, sell and import an “invention” that must be applied for and, if the criteria of the <i>Patent Act</i> (1985) are met, granted; patent rights are country- or region-specific	20 (or more) years from the date of filing a patent application with the potential for extensions due to regulatory delays	A novel lipid-nucleic acid particulate complex that is useful for <i>in vitro</i> or <i>in vivo</i> gene transfer
Trade secrets and confidential business information (CBI)	An exclusive right pertaining to information, scientific or technical, with respect to trade secrets and business in the case of CBI, that is valuable to its owner due to its secrecy and which its holder has taken reasonable steps to keep confidential; no application is required	Unlimited unless the information is no longer kept secret or is independently created. In addition, CBI protection is unavailable if the regulator deems it no longer to be CBI under the <i>Food and Drug Regulations</i> (2022) in Canada	Trade secrets include information pertaining to vaccine manufacturing processes – that is, manufacturing “know-how”, while CBI includes unpublished clinical trial results
IP assignments, patent licences and cross-licences, research collaboration agreements, etc.	Contractual agreements that involve the transfer of IP or granting another party permission to use IP rights (whether patents, trade secrets and/or CBI)	The term specified by the parties to the contractual agreement	A licensed agreement granting permission to use patented LNP technology for the development of gene therapies

None of these forms of IP are mutually exclusive from one another; rather, in practice, actors often utilize these diverse forms of IP and IP-related contracting in conjunction with one another.

or stifled research. Gene patenting is a classic, but contested, example (Bubela et al. 2015). Other IP rights, such as contracts that treat research data as trade secrets, can also be detrimental to knowledge translation (Williams 2013). Even when a useful product is invented, access to it by populations in need, particularly in LMICs, may be limited by IP, high product pricing, or both (Padmanabhan et al. 2010).

Scientists at Yale University, Connecticut, US, developed d4T – one of the historically most important therapies for HIV/AIDS. By 2001, d4T had been licensed by the university’s technology transfer office on an exclusive basis to the American biopharmaceutical company Bristol Myers Squibb, which priced the drug in a way to render it inaccessible to millions suffering with HIV/AIDS in much of the world (Kapczynski et al. 2005). Through concerted advocacy efforts, however, Bristol Myers Squibb eventually allowed for generic production of d4T by a South African company, triggering a 30-fold reduction in price and huge scale-up in global access.

Building upon this success, a global movement in favour of open access to university-generated health products coalesced. UBC was the Canadian leader in this effort, creating a set of “Global Access Principles” in 2007 (Wasan et al. 2009) that directly informed how it licensed a low-cost, oral formulation of amphotericin B – a novel treatment for leishmaniasis

that nearly exclusively occurs in LMICs (Chen et al. 2010). How often these principles were actually implemented into technology transfer practices is not known, however, because technology transfer activities are typically kept confidential, and universities do not track their adherence to these principles. But it is apparent that without access to the LNP delivery system incorporated into the mRNA vaccines, would-be LMIC-based manufacturers are struggling to produce their own COVID-19 vaccines (Aizenman 2021).

The Development of the LNP Delivery System at the University–Industry Boundary

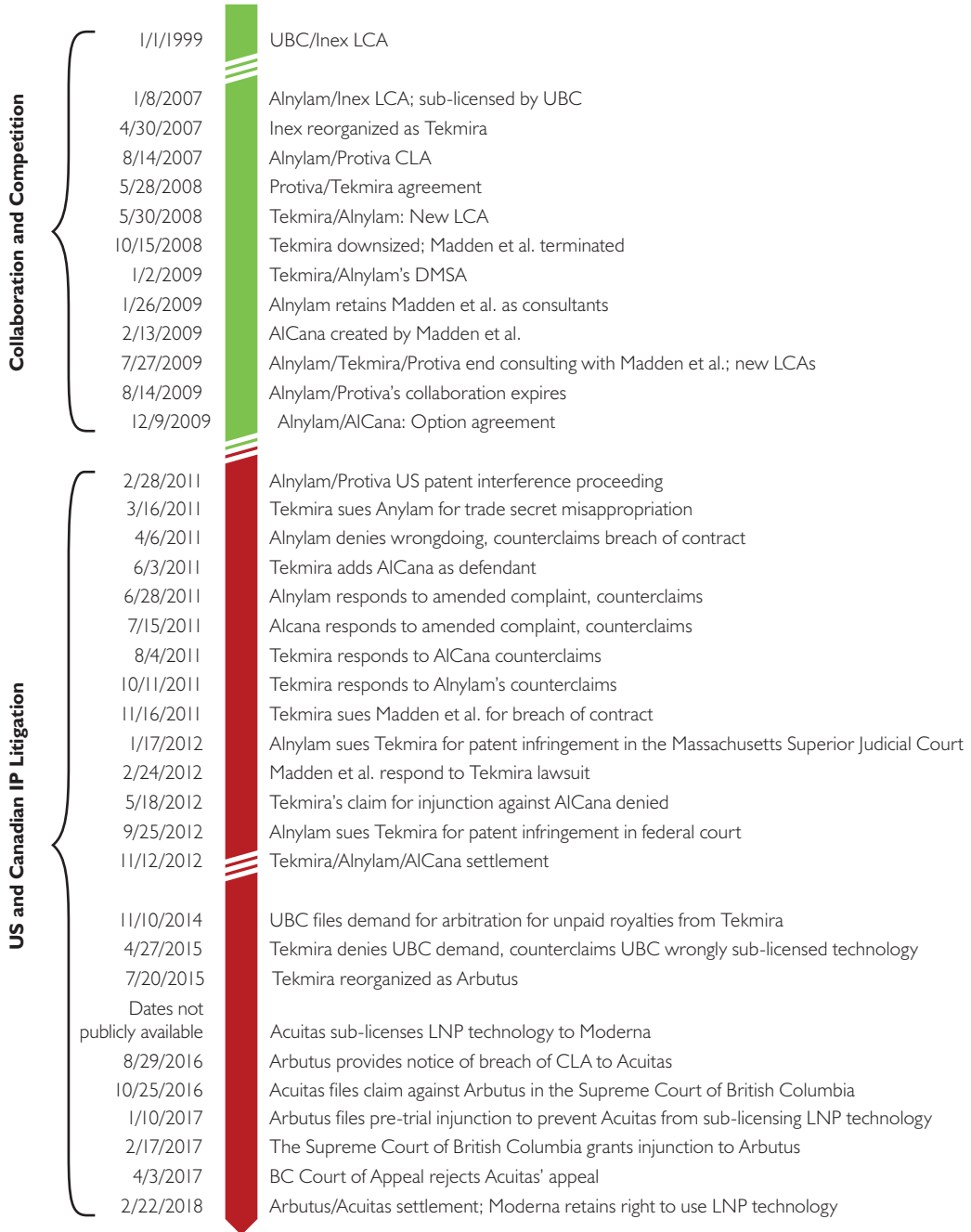
The LNP delivery system emerged from decades of research in the area of lipids led in significant part by UBC's Pieter Cullis (Dolgin 2021). Throughout the process, Cullis raised millions in federal government funding to support his research while also founding a number of companies to commercialize his findings, including Inex Pharmaceuticals (later becoming Tekmira and known today as Arbutus Biopharma) as well as Acuitas, which worked with Pfizer/BioNTech in developing its COVID-19 vaccine (Box 1). Along the way, dozens of patents were filed by UBC, Arbutus, Acuitas and a host of other entities pertaining to the LNP technology (Gaviria and Kilic 2021). Consistent with the assumption that IP spurs commercialization, IP licensing agreements between Arbutus, Acuitas and other companies in the field that Cullis did not help form, such as the US-based Alnylam, also fuelled a number of research partnerships (Leung et al. 2019).

However, a significant amount of litigation also attended these efforts to commercialize the LNP technology (Box 1). According to an investigation by *Forbes* magazine, Cullis, Madden and MacLachlan – all of whom once worked together at Inex – became embroiled in a series of lawsuits among Arbutus, Acuitas and Alnylam, alleging misappropriation of trade secrets and/or patent infringement (Vardi 2021). Arbutus (the holder of several LNP patents) is still in the midst of a patent dispute with Moderna (Brennan 2021; Gaviria and Kilic 2021; “Moderna Loses Key Patent” 2020). New products incorporating the LNP technology, including but not limited to COVID-19 vaccines, have since entered the market (Wan et al. 2014). Yet it is far from clear whether this complicated web of patent rights, contractual agreements, spin-off companies, corporate reorganizations and litigation ultimately hastened or complicated the development of products using LNP technology (Figure 1).

It is equally unclear whether UBC's 2007 Global Access Principles had any effect on how the university managed the patents it filed related to the LNP technology, much less the IP-mediated agreements that UBC, Arbutus (which through its previously owned subsidiary Protiva filed several LNP patents starting in 2008) or Acuitas (which enjoyed a licence to use those patent rights between 2012 and 2018 and evidently still possesses relevant knowledge) struck to develop a range of products, including the agreements with Pfizer/BioNTech and Moderna for the purposes of developing COVID-19 vaccines.

Throughout the pandemic, UBC has emphasized its commitment to “mobilize COVID-19 related technology through time-limited, non-exclusive royalty-free licences, in

FIGURE 1. Collaboration, competition and litigation related to LNP technology



CLA = cross-license agreement; DMSA = development, manufacturing, supply agreement.; LCA = license and collaboration agreement; Option agreement = an agreement that confers upon one or more parties the right to renew an existing agreement.
 A number of the companies mentioned in this figure underwent corporate reorganizations during the time-frame depicted: Inex was reorganized as Tekmira and then later as Arbutus; Protiva was a subsidiary of Tekmira; and AlCana subsequently became Acuitas.
 All of the information depicted in this figure was derived from publicly available information on the website of the US Securities and Exchange Commission (<https://www.sec.gov/>).

exchange for the licensee's commitment to rapidly make and broadly distribute products and services to prevent, diagnose, treat and contain COVID-19" (UBC University–Industry Liaison Office n.d.). But it has clearly taken a hands-off approach to how UBC-founded companies manage the IP generated after they are spun off from the university, even when UBC-affiliated scientists help run those companies and when the IP is critically important to global health. There is no indication that provisions designed to allow the use of the technology in LMICs or share the underlying know-how in order to address a public health emergency were integrated into any of the IP-related agreements among UBC, Arbutus, Acuitas, Alnylam, Pfizer/BioNTech, Moderna, CureVac (a German biopharmaceutical company) and others (Gaviria and Kilic 2021). Whether LMIC-based vaccine manufacturers have the freedom to utilize the LNP technology without risk of liability for patent infringement is also unclear in the absence of greater transparency about where the various actors involved have sought patent protection.

Systemic Barriers to Realizing Global Access Commitments

The fact that UBC's stated commitment to global health has not been realized vis-à-vis the LNP technology is not its fault alone. There are multiple interconnected barriers to systemic change.

To begin with, enforcement of measures such as UBC's Global Access Principles is challenging. Those principles will only extend to sub-licences and corporate subsidiaries if UBC remains actively engaged in monitoring and enforcing compliance in subsequent commercial transactions. Universities are not always well positioned (in terms of resources) or willing (for fear of discouraging other industrial partners) to actually enforce their agreements, especially in the face of a complex array of private – demonstrably litigious and well-resourced – actors, as in the case of the LNP technology.

Achieving global access also requires overcoming multiple layers of IP protection. Even if UBC's principles had been enforced by UBC or followed by the companies connected to the university, licensing the LNP delivery system in line with the goal of improving access in LMICs would not, by itself, have resulted in the availability of an mRNA vaccine made by, or for, LMIC-based manufacturers. Access to the knowledge related to the LNP technology (in addition to those both Arbutus and Acuitas possess) and the manufacturing processes used to make COVID-19 vaccines is also essential to scaling up the production of vaccines (Erfani et al. 2021). But that know-how is treated as proprietary information and kept confidential by a range of actors, including national regulatory agencies, such that outsiders cannot discern what precise LNP formulation is in use or whether the LNP technology within the Pfizer/BioNTech and NIH/Moderna vaccines is one and the same (Vardi 2021).

Fundamentally, there exists a deep-seated deference to market actors regarding which product leads to pursue and how best to manage biopharmaceutical IP. Research funding bodies typically do not assert any interest in IP generated with public funds. The massive

amounts of public funding allocated toward research and development of COVID-19 health products provided an important opportunity to reset expectations. Yet no strings were attached to any of those public dollars to ensure that the resulting products (and/or associated IP) are available to people around the world despite the need (Herder 2021). Notwithstanding the “vaccine apartheid” (Brown 2021) that has segregated LMICs from the rest of the world during the COVID-19 pandemic, efforts to establish an “IP waiver,” whereby countries loosening IP requirements over vaccines and other COVID-19 health products can do so without fear of trade sanctions, have so far failed (Krishtel and Malpani 2021).

While it may not alter the course of the current pandemic, policy action is needed to alter these deep-seated norms around biopharmaceutical innovation. University technology transfer practices offer a logical starting point, given that most health products originate in publicly funded science. Yet the COVID-19 pandemic has taught us that voluntary approaches, such as UBC’s Global Access Principles, are inadequate for the task of ensuring equitable access to promising technologies such as the LNP delivery system.

Policy Actions to Improve Global Access to Publicly Funded Research

To improve access to university-developed health products in LMICs, the Canadian government can and should, at a minimum, undertake three policy actions:

- The federal government should articulate a set of standardized terms and conditions that must be included in any and all IP agreements that flow from federally funded research. This will serve to ensure that the resulting knowledge and products can be accessed in LMICs without the prior consent of other parties to IP agreements. Precedents for such “equitable access licensing” terms and conditions already exist (Kapczynski et al. 2005), which could be readily expanded to include not only patents but also proprietary knowledge and adapted into policies for research funding bodies. UBC has, for instance, recently attracted over \$18 million in federal funding to establish a “Nanomedicines Innovation Network” (<https://www.nanomedicines.ca/>). This funding should come with commitments to ensure equitable access to follow-on LNP technologies that emerge from the network’s research.
- The government should ensure the transparency of IP agreements arising from publicly funded research. This requirement has two components:
 - o Firstly, all university-based research funded by the federal government should require – as a condition of funding – that a copy of all IP agreements (defined broadly to include patent licences, non-disclosure agreements, collaboration agreements, etc.) be provided without redaction to an independent body charged with auditing these agreements for compliance with the above-mentioned standardized

terms and conditions designed to enhance equitable access. Provided it is equipped with the necessary resources and expertise (e.g., legal scholars, ethicists, etc.) to review such IP agreements, this body could be housed within an existing (e.g., the Secretariat on the Responsible Conduct of Research) or newly created organization in the federal government. But it is imperative that it operates at an arm's length from government research funding bodies, university administrations, academic researchers who have industry funding and/or who are commercializing a product and the industry itself – all of whom may have an interest in preserving the status quo. Agreements between government laboratories and private partners should similarly be shared with that same body for auditing. This requirement should apply immediately – not at the end of the funding period.

- o Secondly, a copy of those agreements redacted only for pricing information and disclosing the IP previously held by the private party ought to be publicly released within a reasonable – yet short – period after signing to enable independent review and analysis.
- To counter the entrenched, IP-focused approach to biomedical research, the government should support open science approaches to drug and vaccine development (Gold 2021). This should take at least two forms:
 - o Firstly, the government should create specific funding programs aimed at those agreeing to abide by open science principles – open data, open materials, open tools, open publications and the absence of IP rights, which restrict others from using those data, materials and tools or building new products.
 - o Secondly, governments should create incentives for firms to engage in open science, such as new regulatory incentives that give priority to sharing. In return for placing key knowledge such as the LNP delivery system in the public domain, developers of therapies, vaccines and other products would be rewarded with a carefully crafted time-limited period of market exclusivity under the *Food and Drug Regulations* (2022).

Relying on current voluntary university and government technology transfer practices has left a hole in the global effort to combat COVID-19 and future health crises by failing to ensure equitable access to knowledge by LMICs. These problems are not new, and despite past calls, universities have failed to meet their stated commitment to global health. The actions we propose are a start on efforts necessary to redress this failure and realign university technology transfer with the public good.

Conflict of Interest

Herder reported being a member of the Patented Medicine Prices Review Board, Canada's national drug price regulator, and receiving honoraria from the Board for his service.

Murthy's institution receives support from the Health Research Foundation and Innovative Medicines Canada through a research chair in pandemic preparedness research. He receives research support from the Canadian Institutes of Health Research (CIHR).

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Commentary: University Technology Transfer Has Made a Significant Contribution to Fighting COVID-19 while Ensuring Global Access

Commentaire : Le transfert de technologie universitaire a apporté une importante contribution à la lutte contre la COVID-19 tout en garantissant l'accès universel

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Abstract

This paper reviews the response by public sector research organizations and their technology transfer offices to the COVID-19 pandemic. It shows that leading universities and technology transfer associations quickly enacted licensing principles for the duration of the pandemic to maximize availability and minimize delays in translating public sector research institutes' (PSRIs') COVID-19 inventions to the public – in both the developed and the developing world – while waiving payment of royalties. It discusses examples of vaccines, drugs, diagnostics and personal protective equipment that were developed in PSRIs and swiftly deployed throughout the world on socially responsible terms. It reviews the case cited by Herder et al. (2022) and concludes that their proposed mandates are unnecessary and may inhibit the free flow of healthcare innovation from bench to bedside.

Résumé

Cet article passe en revue la réaction à la pandémie de la COVID-19 de la part des organismes de recherche du secteur public et de leurs bureaux de transfert de technologie. Il montre que les principales universités et associations de transfert de technologie ont rapidement adopté des principes d'octroi de licences pour la durée de la pandémie afin de maximiser la disponibilité et de minimiser les retards dans la transposition des inventions des instituts de recherche publics (IRP) vers les populations – dans les pays développés comme dans ceux en développement – tout en renonçant au paiement des redevances. Il présente des exemples de

vaccins, de médicaments, de tests diagnostiques et d'équipements de protection individuelle qui ont été développés dans des IRP et rapidement déployés dans le monde, et ce, dans des conditions socialement responsables. Il passe en revue le cas cité par Herder et al. (2022) et conclut que les mandats qu'ils proposent sont inutiles et pourraient entraver la libre circulation des innovations en soins de santé du laboratoire au chevet du patient.

Background

Herder and colleagues' (2022) article "University Technology Transfer Has Failed to Improve Access to Global Health Products during the COVID-19 Pandemic" is a severe indictment of academic technology transfer, and one would hope that the authors base their conclusion on a comprehensive survey and detailed analysis of academia's response to the pandemic. It appears that this is not the case. The authors do not seem to have surveyed the landscape of the responses to the pandemic by universities in Canada, the UK and the US – thereby failing to identify numerous cases and examples that contradict their thesis – and seem to have reached their conclusion by extrapolating from a single, complex technology development effort. This effort, which centred on lipid nanoparticle delivery (LNP) technology, spanned over 20 years and moved back and forth between companies and universities, has been characterized by Herder et al. (2022) as having been "developed in and around the University of British Columbia in Vancouver, BC, and incorporated into the Pfizer/BioNTech COVID-19 vaccine" (p. 16). Finally, they recommend "remedies" that would very likely inhibit the free flow of academic healthcare technologies to the bedside.

Response to the Pandemic by the Academic Technology Transfer Community

Contrary to Herder and colleagues' (2022) assertion, the response of universities in both North America and Europe to the pandemic has been both heroic and exemplary. By April 7, 2020, less than a month after the pandemic started to spread in the US, Harvard, MIT and Stanford universities published (Stanford Office of Technology Licensing n.d.) a "COVID-19 Technology Access Framework" in which they pledged to license any COVID-19-related technologies "quickly, non-exclusively and royalty-free for the duration of the pandemic and for a short period thereafter." Twenty additional institutions also signed on to this framework. Ten days later, on April 17, AUTM (formerly the Association of University Technology Managers), the leading association for technology transfer professionals globally, released its "COVID-19 Licensing Guidelines" (AUTM n.d.), which were essentially identical to the Harvard/MIT/Stanford framework. Ninety-five institutions (some of which also signed the Harvard/MIT/Stanford framework) have signed the AUTM guidelines, including some outside the US, specifically including McGill University with which E. Richard Gold is affiliated, and the University of British Columbia (UBC), with which Srinivas Murthy is affiliated.

The generic drug industry has shown that the key to making drugs accessible is to have multiple suppliers competing (Stevens and Effort 2008), instead of a single company whose sales are protected by patents. So by licensing technology non-exclusively and royalty-free,

signatories of these pledges are ensuring affordable access in both the developed and the developing world. Making technologies available royalty-free lowers production costs and increases affordability.

These are voluntary licensing approaches. By contrast, the World Trade Organization has been debating a proposal to waive patent rights on COVID-19 vaccines, which has been proposed by India and South Africa (World Trade Organization 2020) since early in the pandemic and has got nowhere (Farge 2021). International treaties are slow and cumbersome to change; licensing decisions are business decisions and can be made overnight. Later, I show how a voluntary licensing decision has obviated Herder and colleagues' (2022) complaint about UBC.

Some Specific Academic Contributions to Fighting the Pandemic

Turning to specific academic technologies to fight the pandemic, one of the major contributions has been the AstraZeneca vaccine, which was created by the University of Oxford and co-developed by Oxford and AstraZeneca. According to the *Wall Street Journal* (Strasburg and Woo 2020), after contentious negotiations involving Oxford and a university spin out, Vaccitech – which co-invented the technology with Oxford and will receive around 24% of Oxford's revenues from the vaccine (see Vaccitech S-1 prospectus filed with SEC, April 9, 2021, page 16: <https://www.sec.gov/edgar/searchedgar/companysearch.html>) – AstraZeneca agreed to pay Oxford \$10 million upfront and another \$80 million in regulatory and sales milestone payments. Oxford agreed to suspend all royalties for the duration of the pandemic and a royalty rate of 6% in the developed world thereafter, and insisted on stringent protections for the developing world with regard to the licence, requiring AstraZeneca to make the vaccine available to low- and middle-income countries (LMICs) at no profit *in perpetuity*. Although not approved in the US, Vaxzevria is one of the most important vaccines globally. AstraZeneca was the first company to start shipping doses of the COVID-19 vaccine to COVAX, the non-profit set up to co-ordinate the supply of COVID-19 vaccines to some 142 lower income countries (AstraZeneca 2021). As of December 2021, 65% of the COVID-19 vaccine doses supplied via COVAX had come from AstraZeneca, and over half a billion doses of the Oxford–AstraZeneca vaccine have been delivered at a non-profit price globally, with two-thirds going to LMICs (British High Commission Dhaka 2021). AstraZeneca has contracted with Serum Institute of India to manufacture Vaxzevria. It is also being jointly produced under licence in Latin America by Argentina's mAbxience, which reproduces the active pharmaceutical ingredient, and Mexico's Laboratorios Liomont, which formulates, fills and finishes the product for distribution. The Latin American product has received WHO Emergency Use Authorization (PAHO 2021).

Baylor College of Medicine (BCM) and Texas Children's Hospital Center for Vaccine Development developed a protein subunit vaccine called CORBEVAX based on unpatentable, older "tried and true" vaccine technology (Hotez and Bottazzi 2021). The resulting

vaccine is stable and does not require storage under low-temperature conditions. BCM is non-exclusively licensing the vaccine to vaccine manufacturers in the developing world. They have targeted manufacturers in countries where the vaccine can have the most impact:

- India through a licence to Biological E Ltd.;
- Indonesia through a licence to Bio Farma;
- Bangladesh through a licence to Incepta Pharmaceuticals; and
- Africa through a licence to ImmunityBio.

Emory University, a powerhouse in antiviral research, originally discovered Lagevrio (molnupiravir), one of the two orally administered small molecules that have been shown to be effective in treating COVID-19, as a potential treatment for influenza. Emory licensed molnupiravir to DRIVE, a limited liability company specialized in drug development wholly owned by Emory and funded by the royalties from Emory's earlier successes in discovering effective antiretrovirals to treat HIV. At the outset of the pandemic, DRIVE recognized molnupiravir's potential to treat COVID-19, developed it to the point of submitting an Investigational New Drug Application and licensed it to Ridgeback Therapeutics, which had been set up to treat Ebola. Ridgeback got molnupiravir into Phase 1 and was very quickly able to strike a partnership with Merck to co-develop molnupiravir. Emory – which has a well-established set of global health principles (Emory University Office of Technology Transfer n.d.) – Merck and Ridgeback granted a licence to the Medicines Patent Pool (MPP), which has already granted non-exclusive licences to manufacturers for around a hundred LMICs. The licences will be royalty-free for the duration of the pandemic (Merck 2021). Thirty generic drug companies have already signed on to obtain licences (Guarascio 2022).

Pfizer, which both discovered and developed the second oral small molecule shown to be effective against COVID-19 – Paxlovid (ritonavir-boosted nirmatrelvir) – has also licensed it to the MPP. MPP can license Paxlovid to multiple licensees to supply LMICs, again illustrating sensitivity to global health needs during the pandemic in the corporate sector as well as in academia (Pfizer 2021).

Academic institutions were also very active in developing COVID-19 tests.

The University of California, Berkeley, which started incorporating global health provisions in its licence agreements as early as 2003 (Mimura et al. 2011) to facilitate affordable access to its innovations in LMICs, discovered a new implementation of CRISPR (the gene editing technology), involving the enzyme Cas12 and licensed it including global health protection terms to Mammoth Biosciences – a company co-founded by CRISPR Nobel Laureate Jennifer Doudna. As part of a National Institutes of Health (NIH n.d.) program called Rapid Acceleration of Diagnostics, Mammoth used the technology to develop a high throughput COVID-19 test called DETECTR BOOST (WebWire 2020), which received

a United States Food and Drug Administration (FDA) Emergency Use Authorization in January 2022 (Hale 2022). Mammoth is continuing to develop the use of the DETECTR assay in different diagnostic formats for different uses, including under the Department of Defense's Defense Advanced Research Projects Agency program, "Detect It with Gene Editing Technologies" (WebWire 2021).

Yale University and the National Basketball Association (Poitras 2020) developed the SalivaDirect COVID test. The test received Emergency Use Authorization from the FDA in August 2020 and has been deployed to hundreds of labs in dozens of states, provinces and countries free of charge, with weekly webinars that share experiences and improvements with the user community (Yale School of Public Health n.d.).

Academic institutions even started making and testing COVID-19 supplies in the very early days of the pandemic. Herder's institution, Dalhousie University, tested personal protective equipment supplies being imported into Canada (Layne and Palmetter 2020). Columbia University used various 3D printing machines and, eventually, contract manufacturing facilities to turn out first thousands and then millions of face shields in the earliest days of the pandemic (Evarts 2020). The University of Calgary started manufacturing ventilators (Platt 2020).

AUTM has collected other examples of technologies developed to fight the pandemic at universities (AUTM n.d.).

The University of British Columbia and Lipid Nanoparticles

As noted, Herder and colleagues' (2022) entire indictment of academic technology transfer rests on the case of UBC and the LNP delivery technology used by both the Moderna and Pfizer COVID-19 vaccines. The authors document the complex history of the technology and the extensive litigation, which they state appears to have been driven by intercompany rivalries between Arbutus, UBC's spin-off company, and its predecessors and Acuitas.

UBC was a pioneer in developing liposome technology starting in the early 1980s and had spun out several companies in the space prior to the LNP technology, including Northern Lipids, The Canadian Liposome Company and Lipex.

Using the BioScience Advisors database (<https://www.biosciadvisors.com/>), I was able to identify that UBC signed a licence with Tekmira, which became Arbutus, effective July 1, 1998, that was amended effective July 11, 2006, and amended again effective January 8, 2007. I was not able to access a copy of this licence. This licence and its amendments are the only vehicles through which UBC could have exerted any influence on the development of the LNP technology and the financial terms for its use in LMICs. All of the subsequent technology development appears to have been done in these companies: Acuitas, Arbutus and its predecessors and Alnylam.

Blaming UBC for not including global health provisions in the licence is inappropriate on multiple levels:

- UBC could potentially have exerted an influence on the LNP technology development when it negotiated the licence with Tekmira in July 1998. As Herder et al. (2022) acknowledge, the global health implications of academic licences were not on anybody's radar screen until the Yale/Zerit case in 2001 (Michaelson 2002). UBC would have had additional opportunities to include global health provisions in the renegotiations in 2006 and 2007, but generally speaking, only minor changes are usually made to the original deal terms in later amendments. Even in 2007, the mechanisms to include global health protections in academic licences were only just beginning to be identified, formulated and adopted.
- The LNP technology is only a delivery technology and by itself does not enable an mRNA vaccine. Even had the UBC licence included global health protections, it is most unlikely that UBC would have been able to negotiate provisions that would have required companies licensing the LNP technology to include their downstream vaccine know-how in the global health provisions. Even if UBC had included onerous reach-through provisions, companies may have sought an alternative formulation technology.
- Any UBC patents and the associated licence would have expired by the time that the LNP's importance in delivering an mRNA COVID-19 vaccine had become apparent, and I am informed that neither the Pfizer nor the Moderna vaccines are royalty-bearing to UBC.
- Arbutus sued Moderna for infringing its LNP patents on February 28, 2022. In the complaint (*Arbutus Biopharma Corporation and Genevant Sciences GmbH, Plaintiffs v. Moderna, Inc. and Modernatx, Inc., Defendants* 2022), the patents Arbutus asserts are wholly owned either by Protiva, a company Arbutus acquired in 2008, or by Arbutus itself. The complaint's account of the development of the LNP technology nowhere mentions UBC.

Interestingly, BioNTech has just announced that it will establish mobile manufacturing units that will make Comirnaty (the trade name for its COVID vaccine) for sale at no profit (Pancevski 2022) in LMICs. The first three units will be located in the African countries of Ghana, Rwanda and Senegal.

In addition, early in the pandemic, Moderna announced it would not assert its COVID-19 vaccine patents during the pandemic (Sagonowsky 2020), and on March 8, 2022, it announced that it is permanently waiving its COVID-19 vaccine-related patents in the 92 countries that are members of COVAX (Cullinan 2022).

In other words, *voluntary* licensing decisions by BioNTech and Moderna have achieved what Herder et al. (2022) criticize UBC for not achieving, while the World Trade Organization has made no progress on a proposal to allow patent waivers, which would not have included the necessary knowledge for making a finished vaccine.

Herder and Colleagues' Proposed Remedies

Herder et al. (2022) use the LNP technology case to justify a series of public policy responses that the Canadian government should implement.

Mandatory Licensing Provisions

They propose that the Canadian government develop a set of standardized terms and conditions that *must* be included in any and all intellectual property (IP) agreements that flow from federally funded research and propose as a model those developed by Kapczynski et al. (2005). Kapczynski's proposed model was developed in response to the Yale/South Africa/d4T access issue, an episode in which Kapczynski, at the time a Yale undergraduate, was a prime actor (Kapczynski et al. 2005).

Academic technology transfer itself was active in response to this episode. Ten US universities and the Association of American Medical Colleges developed tech transfer's ethical guidelines, the *Nine Points to Consider*, of which point nine states:

Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics and agricultural technologies for the developing world (*"In the Public Interest: Nine Points"* 2007: 8)

However, the *Nine Points* document did not provide specific licensing mechanisms to achieve this.

Stevens and Effort (2008) filled this gap by identifying a number of different licensing mechanisms and corresponding implementing language that would protect global health needs in academic licences. AUTM subsequently incorporated these in a *Statement of Principles and Strategies for the Equitable Dissemination of Medical Technologies* ("Statement of Principles and Strategies" 2004). A number of universities signed on to these principles and have included them in their standard forms of licence agreement ("Boston University EZ Start" 2012).

Such voluntary approaches are very different from a mandatory approach. Licence negotiations *always* involve a give and take and the changing of language. Were there a single, legally mandated mechanism, any language change that a prospective licensee insisted on would have to be agreed to by the government, inevitably delaying, and thereby threatening, the completion of the licence. Nor can we be sure that the Canadian government would come up with a practical or acceptable approach. Canada is notable for being the only country to have established a compulsory licensing mechanism in response to Paragraph 6 of the *Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)* and on July 17, 2007, authorized Apotex to export to Rwanda a fixed-dose combination AIDS medication, TriAvir (lamivudine+nevirapine+zidovudine), without licences from the patent holders

(World Trade Organization 2007). The procedure for receiving authorization was so complex that no other company has applied for a Paragraph 6 authorization since (Cotter 2008).

Agreement Transparency

Herder et al. (2022) propose that an unredacted copy of all agreements granting rights to the results of federally funded research be provided to a government body, whereby legal scholars and ethicists would be charged with ensuring compliance with the above-mentioned mandate, and that copies redacted for pricing information and IP previously held by the private party be placed in the public domain.

In the US, the Securities and Exchange Commission (SEC) requires that publicly traded companies and companies filing to go public file copies of all their material agreements, including their licence agreements. These are publicly accessible through the EDGAR system. Commercially sensitive information can be redacted, but the redaction is only available for five years. Database companies, such as the earlier referenced BioScience Advisors, are adept at filing *Freedom of Information Act* (US Securities and Exchange Commission 2021) requests for the unredacted versions at the end of the five-year process and would undoubtedly welcome the additional availability of additional transactions from this source. The Canadian Securities Commission has a requirement similar to the SEC.

The problem would come from the first part of the proposal: the review of the agreements by legal scholars and ethicists and its potential to delay and deter deal completion.

Support IP-Free Open Science

The authors propose that the Canadian government provide incentives for open science approaches to drug and vaccine development. While it is not clear how attractive such programs would be to scientists, the current IP-based approach that facilitates the transfer of rights from researchers to companies that wish to develop the technology has been extraordinarily successful in getting academic healthcare discoveries into the hands of the public (Stevens et al. 2011). Governments should be extremely cautious about changing it without evidence that any alternative system would be as successful.

McGill Research and Innovation (n.d.) and UBC (University–Industry Liaison Office n.d) have both adopted Global Access Principles that appear to be very similar to the open science approach that Herder et al. (2022) advocate. It is important to note, however, that open science is not synonymous with no-IP science, as Herder et al. (2022) seem to think.

Conflict of Interest

Ashley J. Stevens discloses the following relationships with the entities mentioned in his response:

1. He has provided assistance to 10X Genomics in a legal dispute with Harvard University and OneCell Bio, Inc., for which he was compensated.

2. He is a past president of AUTM and has previously received compensation for consulting services from it.
3. He is an alumnus of Oxford University and is a past president of the Oxford and Cambridge Society of New England.
4. He has provided assistance to AstraZeneca in a legal dispute with Her Majesty's Commissioners of Revenue, for which he was compensated.
5. He has provided assistance to MedImmune, a subsidiary of AstraZeneca, in a legal dispute with the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Board of Trustees of the University of Massachusetts and Third Sector New England, Inc., for which he was compensated.
6. He has provided assistance to Emory University in a legal dispute with Glaxo, Inc. and BioChem Pharma, for which he was compensated.
7. He has provided assistance to Pfizer in a legal dispute with Brigham Young University and Daniel L. Simmonds, for which he was compensated.
8. He has provided assistance to Caribou Biosciences, Inc., a company working in CRISPR founded by Jennifer Doudna in a legal dispute with Intellia Therapeutics, for which he was compensated.

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Commentary: Fulfilling the Promise of Global Access Licensing Principles to Enable Equitable Access

Commentaire : Tenir la promesse du principe d'accès universel dans l'octroi des licences pour permettre un accès équitable

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Abstract

In their piece, Herder and colleagues (2022) reveal the university origins of a key technology used in COVID-19 mRNA vaccines. They note that despite federal funding support and the university adopting “Global Access Principles,” equitable, global access remains a challenge – in part due to the university’s technology transfer practices. While for the past two decades university students have been successful in engaging institutional technology transfer offices in adopting similar access principles, implementation of these principles has been limited. This rejoinder points to the need for greater federal oversight and regulation to incentivize university action that enables equitable, global access.

Résumé

Dans leur article, Herder et ses collègues (2022) révèlent les origines universitaires d’une technologie clé utilisée dans les vaccins à ARNm contre la COVID-19. Ils notent qu’en dépit du soutien financier fédéral et de l’adoption par l’université des principes d’accès universel, l’accès équitable demeure un défi, en partie en raison des pratiques de transfert de

technologie de l'université. Bien qu'au cours des deux dernières décennies les étudiants universitaires aient réussi à inciter les bureaux de transfert de technologie à adopter des principes d'accès similaires, leur mise en œuvre a été limitée. Cette réplique souligne la nécessité d'une plus grande surveillance et une meilleure réglementation de la part du fédéral pour encourager une action universitaire qui permette un accès universel équitable.

Introduction

In their original and timely analysis, Herder and colleagues (2022) reveal the origins of the lipid nanoparticle (LNP) delivery technology – a critical component of COVID-19 mRNA vaccines – at the University of British Columbia (UBC). Through significant financial support from the federal government, researchers at UBC developed the LNP delivery system, filing patents and licensing this technology to various entities including spin-off companies founded by these researchers, as well as COVID-19 mRNA vaccine manufacturers.

The authors (Herder et al. 2022) call particular attention to UBC's adoption of "Global Access Principles," including more recent commitments related to COVID-19 technologies meant to "ensure fair access" to university innovations (University–Industry Liaison Office n.d.a.; University–Industry Liaison Office n.d.b.). However, they question whether this had any impact on how the university managed its own and other licensed intellectual property (IP) toward enabling global access to COVID-19 mRNA vaccines utilizing this technology, especially in low- and middle-income countries (LMICs).

Today, just one in six people in low-income countries have received the first dose of any COVID-19 vaccine (UNDP n.d.). Access to COVID-19 mRNA vaccines utilizing the LNP delivery system has been even scarcer in LMICs. As of September 2021, nearly 80% and 85% of Moderna and Pfizer/BioNTech COVID-19 mRNA vaccines, respectively, had been delivered to high-income countries, while only 2% and 11.8% had been delivered to LMICs (Mikulic 2021a, 2021b). Low-income countries fared even worse, receiving only 0.1% of deliveries from Pfizer/BioNTech and none from Moderna (Mikulic 2021a, 2021b).

Universities Have Largely Failed to Implement Global Access Principles in Licensing Agreements

These findings highlight the pervasive failure of universities in implementing their public pledges to use licensing strategies that prioritize global access to technologies developed on their campuses even with significant federal funding support. Nevertheless, students have played an instrumental role in holding universities accountable. Following their success in urging Yale University and Bristol Myers Squibb to no longer impede the production of an affordable generic alternative to the HIV/AIDS treatment stavudine (d4T) in 2001, students founded the global non-profit organization, Universities Allied for Essential Medicines (UAEM), to close the gap between research and access across academic institutions (Chokshi 2006; Contreras 2021).

Initial UAEM advocacy efforts focused on individual universities and were effective in urging technology transfer offices to publicly adopt principles outlined within UAEM's Global Access Licensing framework, which called for licensing agreements to "[protect] access to the final end product needed by patients" (UAEM 2010: 1). In 2007, students at the UBC chapter of UAEM successfully endeavoured to position UBC to become the first Canadian university to publicly commit to these principles (Wasan et al. 2009). Since then, other Canadian academic institutions, including McGill University, have also openly acknowledged their commitment to implement such principles in future licensing agreements (Thurston 2019).

Recognizing that the adoption of these principles alone would not be sufficient to enable global access without additional oversight and enforcement measures to ensure implementation, UAEM has partnered with other non-profit organizations and experts to call on specific universities to use such strategies for critical treatments of limited access in LMICs. In 2017, following a multi-year campaign led by UAEM in collaboration with the Médecins Sans Frontières' Access Campaign (<https://msfaccess.org/>), Treatment Action Group (<https://www.treatmentactiongroup.org/>), the Global Tuberculosis Community Advisory Board (<https://www.tbonline.info/>), Public Citizen (<https://www.citizen.org/>) and Johns Hopkins University signed an agreement licensing the drug sutezolid for multi-drug resistant tuberculosis to the Medicines Patent Pool, thereby enabling multiple manufacturers to research and develop new drug combinations containing sutezolid (Andrews 2016; MSF Access Campaign 2017).

Universities Have Narrowed Efforts to Enable Global Access to Publicly Funded Research despite Public Commitments

To be sure, such institutional campaigns focused on enabling global access to individual drugs can be a precedent for other universities to endeavour to do the same for other health technologies. Even so, such a drug-by-drug accountability approach has had several limitations. Notably, universities began to select for a narrower subset of drugs, diseases and countries to implement the adopted global access licensing principles. For example, shortly after its much-lauded decision to not enforce any patents on d4T in LMICs, Yale University exclusively licensed a similar HIV/AIDS treatment, ethynylstavudine, to the Japanese manufacturer Oncolys BioPharma (Check 2006). In response to public outcry surrounding this licensing decision, Yale took modest steps to allow for greater global access, including public commitments to not enforce patents in low-income countries and to not grant licences to manufacturers wishing to market the drug within these countries.

Other institutions that have taken a seemingly broader approach have also opted to narrowly apply espoused global access licensing principles. In 2003, the University of California, Berkeley, launched the Socially Responsible Licensing Program (SRLP) to promote "affordability and accessibility of drugs, therapies, diagnostics, crops and vaccines to the developing

world” (Mimura 2007: 296). The SRLP allows the university to use various mechanisms including, but not limited to, royalty-free licensing, humanitarian reservation of IP rights, mandatory sub-licensing to achieve lower prices or address unmet needs and prohibition of patent filing outside a few select high-income countries (Mimura 2018). However, the University of California, Berkeley, has not publicly acknowledged the use of SRLP provisions outside of a handful of licences negotiated in the early years of the program and predominantly for health technologies indicated for neglected tropical diseases that are more prevalent in LMICs (IPIRA n.d.). Notably, researchers at the University of California, Berkeley, have been developing novel gene therapies, but it is unclear if any SRLP provisions have been used in licensing agreements for these promising technologies as they continue to remain largely inaccessible for much of the developing world (Leuty 2019; “Gene Therapies Should Be” 2021).

Case Study: How the University of California Health System Has Hindered Global Access to Enzalutamide (Xtandi)

Another example demonstrative of the selective implementation of global access licensing principles by universities is that of enzalutamide (Xtandi), a prostate cancer treatment drug developed with public funding support from the National Institutes of Health (NIH) and the US Department of Defense at the University of California, Los Angeles (UCLA) (Knowledge Ecology International 2022). In 2012, following a multi-year campaign led by UAEM students, the University of California system adopted global access licensing principles, including recommendations for alternative licensing strategies to allow third-party manufacturers to produce and distribute generic or other alternative, affordable options at “low or no cost” in developing countries (Chen et al. 2010; UCOP 2012).

Yet, just a few years later in 2016, the Board of Regents for the University of California filed a patent claim on enzalutamide with the Indian Patent Office as local manufacturers were attempting to make available a generic option more affordable than the US\$179-per-day version marketed to Indian patients by Astellas Pharma, one of the manufacturers to which UCLA had initially licensed their patents (Ress 2017). Shortly after the Indian Patent Office denied the University of California’s patent claim, the Board of Regents filed a petition with the Delhi High Court, again barring availability of a generic treatment option for Indian patients with prostate cancer (Rosenbluth 2020). In response, UAEM students at UCLA launched a campaign urging the university to uphold its global access licensing principles adopted over a decade earlier and to withdraw its patent claim in India (Verma 2021). Looking beyond enzalutamide, the UAEM UCLA chapter has also been working collaboratively with the technology transfer office in collaboration with the Medicines Patent Pool to establish the Affordable Access Plan, which begins to operationalize global access licensing principles and has been utilized in licensing agreements as of July 2020 (UCLA Technology Development Group 2022).

Using Transparency of University COVID-19 Licensing Practices for Accountability

COVID-19 has further amplified the divergence between university commitments to global access licensing and the lack of university action to enable more equitable access. In May 2020, UAEM released the Public Medicines for COVID-19 database, mapping the locations of publicly funded research and development initiatives for COVID-19 vaccines, diagnostics and therapeutics (UAEM 2021b). As of April 2021, 600 publicly funded COVID-19 research projects were in North America, including many based at academic institutions.

However, UAEM's separate examination of the top 60 US-based research universities by NIH and the National Science Foundation funding found that half had made no commitments to use equitable licensing practices for COVID-19 technologies, only 12% had adopted licensing provisions that would enable generic production of university-developed treatments for use in low-income countries and just over one-fifth had committed to any specific global access licensing strategies (UAEM 2021a). Moreover, none had adopted the Open COVID Pledge or the World Health Organization's COVID-19 Technology Access Pool (Open COVID Pledge n.d.; WHO 2020). Instead, most opted to endorse time-limited and weaker commitments for ensuring global access to urgently needed health technologies, such as the COVID-19 Technology Access Framework developed by the universities of Harvard and Stanford and the Massachusetts Institute of Technology, or the COVID-19 Licensing Guidelines developed by AUTM (AUTM n.d.; Stanford Office of Technology Licensing n.d.).

Moving Forward: The Role of Federal Governments

In response to these institutional limitations, Herder and colleagues (2022) outline upstream accountability approaches for the Canadian government to pursue, including mandating a standard set of terms and conditions be included within all IP agreements stemming from publicly funded research; requiring universities to disclose all IP agreements for publicly funded technologies for external, independent government review; and supporting open science approaches to drug and vaccine development. However, to ensure the success of these mechanisms, governments must also condition research funding support to academic institutions based on their compliance in enacting these access-oriented licensing strategies and transparency measures. Regardless, such oversight and accountability measures of university licensing practices are long overdue to fulfil the forgotten promises of enabling equitable global access to life-saving health technologies.

Conflict of Interest

Reshma Ramachandran sits on the board of directors of the Universities Allied for Essential Medicines, North America, the global non-profit organization referenced in this article, as well as the American Medical Student Association Foundation. Both positions are unpaid. She also serves on the Affordability Task Force for the Innovative Genomics Institute at the

University of California, Berkeley, and University of California, San Francisco. No other disclosures were reported. While Ramachandran is an employee of the Veterans Health Administration, the views expressed in this article are those of the author and do not necessarily reflect those of the US Department of Veteran Affairs or the US government.

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Fulfilling the Promise of Global Access Licensing Principles to Enable Equitable Access

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Authors' Response – A Status Quo of Failure: Time to Fix University Technology Transfer to Address Global Health

Réponse des auteurs – Un statu quo d'échec : il est temps de corriger les pratiques de transfert de technologie des universités pour aborder la santé mondiale

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Abstract

Ramachandran (2022) and Stevens (2022) provide careful responses to our article (Herder et al. 2022) about universities' failure to enhance access to innovations in the Global South. Ramachandran's (2022) reply underscores our concerns with the process, and Stevens (2022) brings an industry perspective to contest our conclusions.

Résumé

Ramachandran (2022) et Stevens (2022) apportent des réponses prudentes à notre article (Herder et al. 2022) sur l'échec des universités à améliorer l'accès aux innovations dans les

pays de la limite Sud. La réponse de Ramachandran (2022) souligne nos préoccupations concernant le processus et Stevens (2022) apporte le point de vue de l'industrie pour contester nos conclusions.

Introduction

Both Ramachandran (2022) and Stevens (2022) provide careful responses to our article about universities' failure (Herder et al. 2022) to enhance access to innovations in the Global South. Whereas Ramachandran's (2022) reply underscores our concerns, Stevens (2022) brings an industry perspective to contest our conclusions. Stevens (2022) raises three main arguments: (1) universities contribute substantially to global health, (2) the evidence we rely upon does not support our thesis and (3) our policy proposals will prove ineffective.

Discussion

On the first, we agree that university-based scientists have contributed significantly to the fight against COVID-19. But contributing to the science is not equivalent to contributing to global health, given the inequitable access to vaccines and drugs. Only 11% of those in low-income countries have received two vaccine doses. Stevens (2022) cites the example of Emory University's licence to the United Nations' Medicines Patent Pool for the antiviral molnupiravir. Close scrutiny reveals major shortcomings, including the fact that it shuts out key middle-income countries, such as Brazil with strong manufacturing capacity (Abinader 2021), despite those countries accounting for 50% of all infections in low- and middle-income countries (Doctors Without Borders/Médecins Sans Frontières 2021).

Second, while Stevens (2022) is correct that a single case study does not itself prove that there is a problem in university technology transfer, there is a growing body of evidence illustrating how the patent-and-license-it strategy in university biomedical innovation carries significant trade-offs in terms of access to the resulting knowledge and products (Gotham et al. 2021; Herder et al. 2020; Padmanabhan et al. 2010). While a comprehensive investigation of the topic would be welcome, it would require universities to fully disclose their arrangements with respect to their licensing, something that they have been unwilling to do. Improving transparency to enable a comprehensive evaluation of universities' contributions to global health is, therefore, one of our key policy recommendations.

Third, Stevens (2022) argues that the voluntary measures adopted by universities to facilitate equitable access are sufficient. Ramachandran (2022) points to evidence that this is incorrect. She cites, for example, the role of University of California, Los Angeles (UCLA), in the development of the prostate cancer treatment drug, enzalutamide (Xtandi). Four years after UCLA adopted global access principles, the university filed a patent on the drug with the Indian Patent Office in order to block local manufacturers from producing a cheaper version of the drug. Ramachandran (2022) similarly notes that in the context of the current pandemic, half of the top 60 research universities still made "no commitments to use equitable licensing practices for COVID-19 technologies" (p. 41) and "only 12% had adopted

licensing provisions that would enable generic production of university-developed treatments for use in low-income countries ... (p. 41).”

Conclusion

Stevens (2022) gives a vigorous defence of the status quo, warning that “[g]overnments should be extremely cautious about changing it without evidence that any alternative system would be as successful (p. 33).” In light of an ongoing health crisis in which too much of the world is shut out of access to vaccines and drugs – many developed at universities – those arguing for the status quo properly bear the burden of evidence.

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Propelled by the Pandemic: Responses and Shifts in Primary Healthcare Models for Indigenous Peoples

Propulsé par la pandémie : réponses et changements dans les modèles de soins de santé primaires pour les peuples autochtones



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Abstract

The COVID-19 pandemic posed a significant risk to the health and well-being of First Nations and Métis communities in Alberta. Communities' self-determined and integrated responses with embedded cultural supports – in collaboration with governments, organizations and providers – were key to minimizing morbidity and mortality. Maintaining and building these relationships in the continued pandemic response, broadening approaches to healthcare delivery and continuing to include culture will support attainment of the Indigenous primary healthcare model while addressing logistical challenges in transforming and sustaining healthcare systems in the background of ongoing inequities in the social determinants of health.

Résumé

La pandémie de la COVID-19 a posé un risque important pour la santé et le bien-être des communautés des Premières Nations et des Métis en Alberta. La réaction autodéterminée et intégrée des communautés avec le soutien culturel intégré – en collaboration avec les gouvernements, les organisations et les prestataires – a été essentielle pour minimiser la morbidité et la mortalité. L'établissement et le maintien de ces relations dans la réaction face à la pandémie, l'élargissement des approches pour la prestation des soins de santé et l'inclusion des éléments culturels permettront d'atteindre un modèle autochtone en matière de soins de santé primaires, tout en relevant les défis logistiques liés à la transformation et au maintien des systèmes de santé dans le contexte des inégalités qui persistent dans les déterminants sociaux de la santé.

Introduction

The statement in the final report of the Truth and Reconciliation Commission of Canada (2015), “Best practices for Aboriginal wellness involve a range of service from mainstream health care to traditional practices and medicines, all under community leadership and control” (p. 163), speaks to a broader consideration of what the scope of primary healthcare should be in Indigenous communities, with Indigenous culture and self-determination being focal in changing the narrative of existing health outcomes. Indeed, Harfield and colleagues' (2018) systematic review of characteristics of successful Indigenous primary healthcare service delivery models highlights the centrality of culture to these systems while also promoting accessibility, community participation, continuous quality improvement, a culturally skilled workforce and flexible and holistic approaches to health with self-determination and empowerment. These aspects have been consistently demonstrated through the COVID-19 pandemic response in two Indigenous communities in Alberta, which we share here as evidence of emerging systems transformation and as an anchor for primary healthcare delivery and policy through the ongoing pandemic recovery phase.

COVID-19 Pandemic Response in Indigenous Communities in Alberta

As of July 14, 2021, Alberta First Nations communities had 8,961 confirmed cases of COVID-19 infection, accounting for 27.5% of all on-reserve cases in Canada (Government of Canada 2021) despite representing just 14% of the total population (Statistics Canada 2017). At that time, there had been 166 deaths in both on- and off-reserve First Nations residents, accounting for 7.2% of COVID-19–related deaths in Alberta (AFNIGC 2021). Case and mortality data for the Alberta Métis and Inuit populations are not known. As expected through the experience of other modern-day public health crises, additional strains occur in under-resourced communities facing structural racism, inequities in physical environments and poor access to quality health services. Management of past infectious pandemics, such as the H1N1 influenza pandemic, was fraught with inadequate surveillance and delayed provision of necessary supplies and healthcare worker supports to Indigenous communities, and characterized as having poor federal government leadership, communication and coordination (National Collaborating Centre for Aboriginal Health 2016). Fragmented or “siloe” healthcare and social care systems are exposed when challenged with adapting to crises that require an urgent and collaborative response (International Foundation for Integrated Care 2020; Montesanti et al. 2022; Valentijn et al. 2013).

However, with the COVID-19 pandemic, the sovereignty, leadership and knowledge of Indigenous communities proved to be an essential foundation for the public health response. Supported by respectful relationships and coordinated efforts between federal, provincial and on-reserve governments that have developed over the many recent public health crises (the 2013 floods in southern Alberta, the 2016 wildfires in northern Alberta and the opioid epidemic), we observed an innovative and creative mobilization of resources beyond health services alone in a self-determined response in two communities. A focus on maintaining cultural approaches and activities to support wellness was equally critical to the response, supporting community members and leaders in the uncertainty of the overwhelming situation with ongoing inequities through the social determinants of health.

How Did Indigenous Communities in Alberta Mobilize to Facilitate the First Phase of the COVID-19 Pandemic Response?

The Siksika Nation includes approximately 7,000 Blackfoot members and is located one hour southeast of Calgary. Siksika is an example of a First Nations community that has developed robust governance emergency response systems (Montesanti et al. 2019) and was able to swiftly mobilize health supports throughout the Nation to maintain critical operations. Health services leadership rapidly assembled a response team consisting of representatives from health, education, band council and both federal and provincial government agencies. Public health experts were engaged to develop protocols and processes for testing – including the mobile COVID-19 Response Unit and drive-through testing sites – obtain personal protective equipment and establish infection prevention and control

procedures within the Nation's facilities and congregate living sites. Communication was effective with call lines for COVID-19 concerns, including Blackfoot translation services and the COVID-19 "chatbot" providing information via social media. A taskforce specifically ensured that the Nation's Elders and persons with disabilities could access information and resources. Strengthened relationships between Alberta First Nations communities and Indigenous Services Canada, which respected Indigenous self-determination, facilitated the pandemic response. A structural change two years ago to dissolve Indigenous and Northern Affairs Canada and transfer the First Nations and Inuit Health Branch from Health Canada to form Indigenous Services Canada streamlined points of contact for the health centres and the bands. Communication directly with the Regional Office representatives through video conferencing, bulletins and individual discussions facilitated information sharing and rapid identification of community needs that could be supported, such as housing for those requiring isolation. Federally employed public health providers utilized centralized computerized contact tracing in real time, and public health officials liaised directly with primary care providers both on reserve and in surrounding communities. Thus, the federal resources were directed to what the communities requested, and were accessible. While the mechanistic public health and health system responses support aspects of diagnosis, treatment and transmission prevention, culture supports mental, spiritual and emotional wellness while coping with pandemic restrictions and losses. As pandemic responses commenced in Siksika, their Nation's Elders were a source of support and strength, providing guidance to health leadership. Sharing and service to community were evident, with volunteers and redeployed staff delivering food hampers to Elders and isolated Nation members.

The Métis Nation of Alberta represents the interests of approximately 47,000 Métis peoples province wide; it does not receive direct supports from Indigenous Services Canada, and its citizenship accesses health services through the provincial health authority. Thus, rather than needing to mobilize direct health supports, the organization initiated its own community-based response by distributing financial support through the provincial office, with regional offices tailoring supports to local realities. A robust communication strategy included translation of COVID-19 information into Michif and Cree and distribution of resources in both written and oral formats. The youth of the Métis Nation of Alberta developed online programming and assembled mail-out kits that included cultural activities, mental health resources and traditional medicinal plant guides. Educational programs could be continued through the distribution of donated technology via the Rupertsland Institute (<https://www.rupertsland.org/>). Métis Nation's citizens volunteered to teach cultural traditions such as beading, dancing and music through online sessions. Elders shared stories that were recorded for online viewing. Ceremonies and celebrations such as the annual Métis Fest were adapted to the online platform.

These two leading examples demonstrate an integrated response in supporting determinants of health for Indigenous communities throughout the pandemic. Public health

measures and pivoting health services were not the sole focus; the health directorates also ensured access to education, housing, financial and cultural supports. This approach should be upheld within the primary healthcare system during pandemic recovery.

What Are the Anticipated Indigenous Primary Healthcare Needs in the Post-Pandemic Recovery Phase?

Health systems are beginning to contemplate the needs for the pandemic recovery period. Healthcare utilization patterns rapidly changed throughout primary healthcare domains, with physical distancing protocols, redeployment of service providers and the redirection of health infrastructure to support the COVID-19 response particularly impacting ambulatory care services provided through primary healthcare and public health. There will now be a need to address health concerns that were deferred. As a reflection of the historic difficulties in access to high-quality primary healthcare leading to deferral of care (Blanchard et al. 2003; Browne et al. 2011), Indigenous populations, especially in the north of the province, rely on emergency departments as the entry point to the health system (Dell et al. 2016; Ospina et al. 2016). Thus, the 50% decline in emergency department use seen in the total population (CIHI 2020) likely has had substantial impacts on Indigenous people's access to healthcare services. Services including preventive initiatives, such as vaccination programs, were placed on hold to redistribute the available workforce to support COVID-19 testing and contact tracing and will need to catch up. Many patients require reassessment of chronic medical conditions and diagnosis and management of new acute concerns, including new mental health threats. It will be necessary for health surveillance teams to monitor and report on excess deaths and consequences of later disease presentation. This will require that the issue of Indigenous identification in health data be addressed (Carroll et al. 2021). Most jurisdictions do not have the appropriate processes needed to safeguard the ownership and stewardship of Indigenous persons' identifiers, limiting the availability of Indigenous-specific data needed to inform an evidence-based response (Smylie and Firestone 2015).

How Can Indigenous Primary Healthcare Models Enacted during the Pandemic Be Sustained to Respond to These Needs?

Sharing examples of sustainable innovations in Indigenous primary healthcare is a first step toward inspiring change in policy and service delivery (Henderson et al. 2018). Successful approaches for Indigenous primary healthcare during a public health crisis must be anchored in the principles of self-determination for Indigenous peoples as articulated in the 2007 United Nations Declaration on the Rights of Indigenous People (United Nations 2007). The demonstrations of self-determined actions in the examples illustrated – which prioritized culture and collaboration in integrated responses across determinants of health during the COVID-19 pandemic – were instrumental to healing and promoting health for Indigenous communities.

Human resources in healthcare will be needed to respond to the anticipated healthcare needs listed earlier, and thus the post-pandemic recovery phase presents an opportunity for community-based employment. The training of Indigenous health practitioners will help reduce the reliance on out-of-community health practitioners providing services to Indigenous communities and, more importantly, address surge workforce planning in Indigenous and rural communities in anticipation of future outbreaks of COVID-19 and the associated mental health and social impacts. While some may say virtual healthcare – which has rapidly been established as a critical activity to maintain health services while minimizing in-person contact where appropriate – may fill these gaps, there are anticipated limitations. There are logistical factors to resolve, such as how communication portals can be put in place for all Indigenous community residents, especially if in a location with tenuous telecommunication service (Graves et al. 2021) or with limited accessibility related to income. We must also consider how virtual care will impact patient experience (Donelan et al. 2019) as limited evidence on acceptability of telemedicine by Indigenous patients is available (Roberts et al. 2015). Relationship building and engaging culture as a facilitator to care is a critical element of care delivery in Indigenous communities and with Indigenous patients (Crowshoe et al. 2019). There is a risk that shifting to remote provider models alone will result in reduced provider knowledge of a community’s culture, making it difficult to utilize this care facilitator in practice.

Conclusion

Enactment of the principle of primary healthcare in self-determined service delivery and the incorporation of Indigenous culture have facilitated a strong COVID-19 response in diverse Indigenous communities. This provides policy direction for health service delivery recovery in the post-pandemic period, with ongoing collaboration between providers and ensured cultural safety for patients in the delivery of sustainable, effective and acceptable Indigenous primary healthcare.

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A row of several green, teardrop-shaped pills is arranged on a reflective surface. The background is a blurred, warm-toned image of what appears to be a row of pencils or pens. The overall aesthetic is clean and professional.

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Commentary: Developing Relationships through Trust in Indigenous Health Research

Commentaire : Développer des relations grâce à la confiance dans la recherche en santé autochtone

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Abstract

Developing strong relationships between researchers and Indigenous partners and communities is crucial for mutually beneficial and appropriate Indigenous health research. However, explanations on the need for strong relationships and how they may be achieved are not often found within the research literature. Given the history of mistrust, exploitation and even unethical research practices with Indigenous populations, collaborative research partnerships necessitate good relationships. For our long-standing community-based participatory research partnership, trust in our relationships has been foundational. Several key elements are central to developing this trust, including coming together in ceremony, practising humility and becoming personally and emotionally invested in each other's lives. We also prioritize time, effort and flexibility to actively work on our relationships. To make effective and beneficial change within Indigenous health research compels reframing western perspectives and overcoming long-standing institutional barriers, such that enduring and trusting relationships are the focus and not a means to an end.

Résumé

L'établissement de relations solides entre les chercheurs et les partenaires autochtones est essentiel pour une recherche en santé autochtone mutuellement bénéfique et appropriée. Cependant, les explications sur la nécessité d'établir de telles relations et sur la manière d'y

arriver ne sont pas souvent données dans la littérature scientifique. Compte tenu de l'historique de méfiance, d'exploitation et même de pratiques de recherche contraires à l'éthique avec les populations autochtones, les partenariats de recherche collaborative nécessitent de bonnes relations. Dans le cas de notre partenariat de recherche participative communautaire de longue date, la confiance dans nos relations a été fondamentale. Plusieurs éléments clés sont essentiels pour développer cette confiance, notamment se réunir lors de cérémonies, pratiquer l'humilité et s'investir personnellement et émotionnellement dans la vie de l'autre. Nous privilégions également le temps, les efforts et la flexibilité pour travailler activement sur ces relations. Pour apporter des changements efficaces et bénéfiques au sein de la recherche sur la santé autochtone, il faut recadrer les perspectives occidentales et surmonter les barrières institutionnelles de longue date, de sorte que des relations durables et de confiance soient au centre des préoccupations et non un moyen d'atteindre une fin.

We feel that it is important to begin with who we are and where we come from.

Richard Oster: My ceremonial name is Wâpastim (white horse). I come from mixed European descent, including Danish, Scottish, German, Austrian and Ukrainian ancestries. Since birth, I have called Treaty Six Territory and Métis Region Four in Alberta, home. My family has lived in this area for four generations, and I continue to live here with my fiancée (who is of Cantonese Han Chinese descent) to raise my two children.

Patrick Lightning: My name is Wapî-maskwa (white bear). I come from the Buffalo Child family (Albert Lightning) and the Bear Hills people of Maskwacis, in Treaty Six Territory. My wife, Inez Lightning (yellow bird woman), is Anishinaabe. I have 10 children, 37 grandchildren and 10 great-grandchildren. I am Nêhiyaw (Cree) and live my life accordingly. I am a third-generation residential school survivor.

Introduction

Examples from two distinct Indigenous communities in the province of Alberta demonstrate that autonomy, self-determination and ownership in applying ways of knowing and expertise are key to strong community responses toward public health crises, such as the COVID-19 pandemic (Barnabe et al. 2022). This should not come as a surprise, as Indigenous peoples and communities are experts on the issues they face. The examples from Siksika Nation and the Métis Nation of Alberta are positive accounts of community-led efforts to support the well-being of community members during a global pandemic and the need to be heard. Strengths-based and community-driven stories that centre on Indigenous ways of knowing abound, yet the literature and media around Indigenous health remain overwhelmingly deficit focused, which can perpetuate inaccurate stereotypes and rhetoric (Bryant et al. 2021). Responsive, empowering, decolonizing and positive solutions to health issues are needed to move communities forward and ultimately reframe the issues so that they shame the underlying causes (such as the impacts of colonization and westernization, historical and intergenerational trauma and inequities in the social determinants of health), rather than shaming Indigenous peoples (Bryant et al. 2021; Snelgrove et al. 2014).

Barnabe et al. (2022) support upholding an approach of “self-determined service delivery and the incorporation of Indigenous culture” (p. 53) and indicate that it should be supported

by respectful relationships and collaboration. We agree, and the literature is clear on the need to develop collaborative relationships for Indigenous health research, healthcare innovation, policy advancement and societal reconciliation (Anderson 2019; Drawson et al. 2017). That said, in their article, Barnabe et al. (2022) provide little insight into *why* the development of strong relationships is needed or *how* this may be achieved. Herein, we seek to extend the discussion initiated in their paper, briefly discuss the necessity of relationship building in Indigenous health transformation and research and provide insights from our own relationship built through trust.

Relationships Are the Blueprint for Successful Research Partnerships

We will not discuss the health and social inequities faced by many Indigenous populations as this story is too often told in research literature (Bryant et al. 2021). Suffice it to say that there are marked disparities (King et al. 2009), such as life expectancy (Government of Alberta 2021), that are widening throughout Alberta. Transformational Indigenous health research is critical. However, the word “research” is often viewed negatively in many Indigenous communities as there has been a lengthy history of mistrust, exploitation and even unethical research practices (Hyett et al. 2018). Moreover, there are many examples of well-intentioned research studies with unintended consequences, such as “helicopter research,” which has benefited the careers of researchers and western science as a whole but brought no tangible benefit to communities (Campbell 2014; Dudgeon et al. 2010). External observation of Indigenous subjects is another damaging pattern, which results in limited community input or control and top-down authoritarian prescriptions of what communities should be doing. Practices of this nature are not historical, but continue in the present day (Campbell 2014; Dudgeon et al. 2010; Hyett et al. 2018). These approaches are generally devoid of any vested, emotional concern for the Indigenous peoples and communities involved and are developed from a reality and perspective that is completely separate from and ignorant of those being researched.

Given the history of Indigenous health research – coupled with the ongoing impacts of colonization – new research practices founded on genuine relationships are needed. In Canada, most university ethics boards are now in line with the following: the chapter “Research Involving the First Nations, Inuit and Métis Peoples of Canada” of the *Tri-Council Policy Statement Ethical Conduct for Research Involving Humans* (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council 2018: 107–12); the principles of Ownership, Control, Access and Possession (The First Nations Information Governance Centre 2014); the Principles of Ethical Métis Research (NAHO n.d.); and the National Inuit Strategy on Research (Inuit Tapiriit Kanatami 2018). These research protocols situate control of research with Indigenous communities and partners and prioritize engagement, relationship building and collaboration. Recently, there has been a surge of collaborative and community-based participatory research (CBPR), as well as supporting

literature, to establish considerate, culturally sensitive, relevant and equitable research partnerships that lead to community-owned health strategies and viable benefits to Indigenous communities (Dadich et al. 2019; Kyoon-Achan et al. 2018; Wallerstein and Duran 2006). Such partnerships necessitate good relationships and can help to reverse stereotypes, racism and imbalances of power or privilege; produce knowledge that is meaningful and beneficial to community; enhance self-determination and autonomy; and increase community capacity (Jernigan 2010; Wallerstein and Duran 2010).

Developing Trust Is Key to Developing Good Relationships

In the Nêhiyaw Nations of Maskwacîs, we have been working together for over 10 years as part of a CBPR partnership aimed at improving maternal, child and family well-being (Anand et al. 2018; Oster et al. 2016, 2018, 2021). The goal has always been to attain community-led and entrusted control over research, such that it leads to tangible community benefits. Since the inception of our collaboration, all activities are underpinned by good relationships built upon trust. We acknowledge that every community is unique – as is every project – and thus there is a spectrum of engagement and community involvement. Good relationships will look different for every research project, and pan-Indigenous approaches to relationship building that generalize rather than acknowledge the cultural, linguistic and historical distinctions between Indigenous communities are not appropriate. However, we feel that there are examples from our experience that can be useful for others seeking to collaborate from a place of trusting and respectful relationships.

In our CBPR partnership, hundreds of individuals have been involved over the years. Although the principle of trusting relationships has been front and centre, each relationship is distinct. Here, we briefly describe several key elements that have proven crucial to developing trust between the two of us – researcher and Elder – who, for over a decade, have worked closely together. Once we came together in ceremony, we were able to trust each other fully. Our ceremonial interactions were appropriate for Maskwacîs and our family, and followed the ways of knowing of this territory. The details remain private – suffice to say ceremony is spiritual, healing and connecting. Ceremony permeates all aspects of our research now, and we often come together in this way, specifically to ground ourselves in the spirit, intent and commitment of trusting relationships. In ceremony, our relationship flourishes as we meet in a deeper way by creating a spiritual connection that transcends the western concept of relationship and embraces and imbeds mutual respect, personal vulnerability, compassion and kindness, humbleness, humanness, openness and a responsibility to one another. In ceremony, our relationship becomes more, connecting our hearts rather than our minds. Finally, coming together in ceremony paves the way for ceremonial-based thinking, where we can work together “outside the box” and feel anything is possible.

In order to have a strong relationship, we need to practise humility. Therefore, we consciously decide to come together not as “settler” and “Indigenous,” nor as “researcher” and “Elder,” but as people in equal partnership. During our time together, we make space

to acknowledge, explore and reconcile the fact that we come from different backgrounds, systems of learning and ways of knowing. We deliberately open up to each other's perspectives and willingly accept that our intrinsic ways of viewing the world are not the only way or the right way. When working together, we move away from an approach to "save the Indigenous person," which seeks to impose western systems and beliefs. Rather, we seek mutual understanding, two-way learning (and sometimes unlearning), equal power dynamics and opportunities to live with and understand each other's experiences. For our relationship, humility ensues when we are our genuine selves, rather than trying to be someone more or different than who we are.

Often, when speaking together publicly, we are asked: "What do trustworthy and respectful relationships look like?" For us, the depth of a meaningful relationship is akin to family. Our families have adopted one another, not from a western or legal sense, but in a real way such that we are and always will be family. We spend time together outside of work to enjoy each other's company, we help and support one another, we see each other at our worst and are still there afterward, we gift each other our favourite things and we do not give up on one another. In short, we are personally and emotionally invested in each other's lives through a relationship that extends beyond the life cycle of a research partnership. Western academia may consider it a risk, but our relationship is our strength and sustains our purpose – research that benefits communities.

Finally, relationships and trust take time. In our experience, trust was not established within the first month, or even year, of our relationship. Now, our entire research framework is centred on relationships. We have learned to go at the pace of the community and individuals involved, allowing them time to navigate their priorities and capacity. We have also learned that relationships cannot be forced into a preconceived and prescribed timeline. Our grant proposals and budgets have been restructured over time to focus on relationships rather than meeting a one-off "checkbox" of activity or as a means to an end. Relationships and trust also take effort, not only to develop, but to maintain and nurture. The effort we put into our relationships extends beyond a standard western working week and requires both flexibility and dedication. It also includes reflection, as well as understanding and acknowledging the value of the knowledge that is being shared.

Conclusion

The cornerstone of effective Indigenous health transformation is, and will continue to be, community-led initiatives based on mutual collaboration as Barnabe et al. (2022) clearly identify. When it comes to transformational Indigenous health research, it is simply not enough to conduct research in a "culturally sensitive way." Researchers must engage in Indigenous methodology where practice is practical, localized and invested, and the focus is on relationships that are emotionally, spiritually, physically and mentally reciprocated. This requires reframing western perspectives and overhauling long-standing institutional barriers such that relationships and trust are at the core of frameworks, processes and programs.

Pan-Indigenous approaches are not the answer as what works in one community may not work elsewhere. Since all communities and projects are unique, we believe that this further reinforces the need to develop good relationships, understand one another and contextualize the research appropriately.

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Regulating the Safety of Health-Related Artificial Intelligence

Réglementer la sécurité de l'intelligence artificielle dans les soins de santé



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Abstract

This article analyzes whether Canada's present approach to regulating health-related artificial intelligence (AI) can address relevant safety-related challenges. Focusing primarily on Health Canada's regulation of medical devices with AI, it examines whether the existing regulatory approach can adequately address general safety concerns, as well as those related to algorithmic bias and challenges posed by the intersections of these concerns with privacy and security interests. It identifies several issues and proposes reforms that aim to ensure that Canadians can access beneficial AI while keeping unsafe products off Canadian markets and motivating safe, effective use of AI products for appropriate purposes and populations.

Résumé

Cet article cherche à savoir si l'approche actuelle du Canada en matière de réglementation de l'intelligence artificielle (IA) dans les soins de santé permet de relever les défis pertinents en matière de sécurité. Se concentrant principalement sur la réglementation de Santé Canada pour les dispositifs médicaux qui intègre l'IA, l'article cherche à savoir si l'approche réglementaire en place peut répondre adéquatement aux préoccupations générales en matière de sécurité, ainsi qu'à celles liées aux biais algorithmiques et aux défis sous-jacents en matière de confidentialité et de sécurité. L'article repère plusieurs problèmes et propose des réformes qui visent à garantir l'accès à une IA bénéfique tout en gardant les produits dangereux hors des marchés canadiens et en motivant une utilisation sûre et efficace des produits d'IA pour les groupes appropriés.

Introduction

Artificial intelligence (AI) refers to machines (including software) that perform functions that normally require human cognition without direct human aid (WHO 2021). The use of AI in healthcare settings engenders fierce debates as to its benefits and risks. Health-related AI offers possibilities of more accurate diagnoses, more finely tailored treatment plans, shorter wait times, and greater patient involvement in directing care (CIFAR 2020, 2021; CMA 2020; Reznick et al. 2020). Yet, at the same time, health-related AI raises concerns, for example, about how to ensure that an AI product is both itself safe and used safely by healthcare professionals; how to apportion liability for harm as between manufacturers, professionals, and institutions; what informed consent should entail in AI settings; the threat of algorithmic bias/discrimination; and potential AI-related privacy and security breaches (Blasimme and Vayena 2020; Flood and Régis 2021; Gerke et al. 2020; Murphy et al. 2021). The great challenge, then, concerns how to ensure the benefits of AI while eliminating (or at least limiting) any adverse outcomes of AI use. To meet this challenge, we need sophisticated decision making by humans, particularly with respect to choices as to how to regulate health-related AI.

There are layers of uncoordinated laws that will (often indirectly) impact how AI is used in the Canadian healthcare system (or systems, given provincial legal variations). Regulations include “hard” laws – such as provincial laws regulating hospitals and the operation of safety committees therein, privacy laws and anti-discrimination laws – and “soft” laws – such as hospital accreditation standards, as well as clinical guidelines and educational standards set by professional colleges. There are also incentives flowing from tort law and contract law; over time, judges will develop a body of case law that will help guide how to apportion liability should a patient be harmed as a result of the use (or non-use) of health-related AI (Flood and Régis 2021).

In this paper, we consider one location of regulation of health-related AI, namely, Health Canada. We look at Health Canada's role in approving medical devices as sufficiently safe for sale within Canadian markets. We take this approach as regulation at the federal level

impacts healthcare systems, healthcare providers, patients and AI innovators across Canada: reform here offers an important window of opportunity for national rules/policies. Health Canada also recently adopted a new regulatory pathway to better permit the licensing of health-related AI, including adaptive machine learning (explained further later). As it is presently seeking some input on how best to operationalize this new regulatory pathway (Health Canada 2021, e-mail communication, June 21, 2021), we hope our analysis can inform that process. Likewise, while health-related AI implicates a broad range of important legal concerns, here we focus on product safety – i.e., safety of a given health-related AI tool. However, product safety is entwined with the problem of algorithmic bias and, more indirectly, by privacy/data access issues, so we include these issues within our analysis.

Thus, in what follows, we outline three safety-related concerns (general safety, algorithmic bias and privacy/security) specific to Health Canada’s regulation of medical devices. For each, we discuss how existing regulation may address the issue and offer recommendations regarding regulatory reform as needed.

(General) Safety of Health-Related AI

The concern(s)

Existing evidence from research settings suggests that many health-related AI tools outperform their human counterparts (Topol 2019a, 2019b). However, AI will make mistakes. For instance, IBM Watson for Oncology was not trained on real patient data and made erroneous treatment recommendations (Gerke et al. 2020: 302–03). Errors were identified before it was implemented in clinical practice, but developers did not disclose the problems for over a year (Gerke et al. 2020). More recently, the Epic Sepsis Model designed to predict sepsis cases based on electronic health records was found to miss two-thirds of cases (Wong et al. 2021). One hopes that such examples will be rare. But for AI to spark a seismic shift toward improved safety of healthcare, professionals, patients and the public must be able to trust that regulatory systems will weed out unsafe AI.

The last decade saw a rapid expansion of machine learning (ML), a subfield of AI that now powers most AI applications across industry. ML models learn from data and are designed to improve their performance over time from new data without being explicitly (re-)programmed. Adaptive ML that can evolve and continuously learn from real-world health data, as opposed to remaining static, is a potential game changer in terms of safety. It offers a major advantage over other technologies, such as a drug or a hard medical device that does not improve itself over time. Unlike other tools, ML might realize its errors and correct its performance issues. But, at the same time, this aspect of ML creates real challenges: if an ML tool is “approved” as safe prior to entry to the market but then evolves, how can a regulator guarantee that it remains safe for use as it evolves?

Presently, regulation of medical devices assumes that AI software is of lower risk if there is a “human in the loop”; that is, if a healthcare professional oversees the use of AI.

However, many scholars raise concerns that algorithms are “black boxes”: healthcare professionals cannot know how a particular diagnosis or treatment recommendation has been reached (Pasquale 2015; Price 2018). Some of these concerns may be overstated given the status quo. Physicians may not, for example, fully understand different clinical interventions (e.g., common medications such as acetaminophen, for which the mechanism of action is not entirely clear [Gerriets et al. 2021]), but they are trained to understand their mechanisms in a general sense and are alert for potential problems. Such general understanding may be all that we should require with respect to AI. Regulators could, in turn, seek transparency on ML decision making; there is an increased emphasis by some on the need for “explainability” tools (e.g., Lundberg et al. 2020; Yap et al. 2021). However, easy fixes in this regard are unlikely. For instance, recent research suggests that this potential technical “fix” can backfire when people put too much trust in “interpretable” models and do not correct their mistakes (Poursabzi-Sangdeh et al. 2021).

Other safety issues relate to how healthcare providers interact with AI tools. There are two sides to this problem: underutilization and overreliance. With respect to underutilization, providers who are uncertain about how AI works may be reluctant to trust and unwilling to adopt AI that could reduce medical errors, which results in an estimated 20,000 Canadian deaths per annum (Baker et al. 2004; Risk Analytica 2017). With respect to overreliance, there are risks if providers rely reflexively on an AI tool without deliberating on, for example, whether it has been trained on unrepresentative data; in such cases, the tool’s advice/diagnosis for a particular patient may not be correct (CIFAR 2020). Some experts worry that physicians may even feel compelled to rely on AI against their professional judgment if AI use becomes the standard of care and not using AI results in liability (Froomkin et al. 2019). There are also deeper safety issues inherent in any human–computer interface related to human factors engineering, including how the algorithm presents information and if it does so in a way that minimizes the chance of human error in application.

Existing regulations

Our focus here is, again, on Health Canada, which regulates medical devices, including those with AI, via a licensing regime. This regime is authorized and established under the *Food and Drugs Act* (1985) and *Medical Devices Regulations* (1998). Software that meets the definition of “medical device” under the *Food and Drugs Act* (1985) and *Medical Devices Regulations* (1998) falls under this licensing regime even if it is not part of a hard physical device (Health Canada 2019). Once Health Canada approves a medical device, it is deemed safe for general distribution and sale in Canada and may be adopted into public health plans or sold privately.

There are gaps in this federal regulatory framework (as detailed further in Da Silva et al. 2022). One is that Health Canada’s “pre-market” licensing scheme for medical devices only requires that higher-risk devices provide explicit evidence (from studies) of product safety and efficacy. Lower-risk devices can be approved for distribution and sale without providing even

a summary of studies on which safety claims are made. Companies initially self-select the risk category and thus the degree of regulatory oversight. There are no public records as to the extent to which Health Canada reviews this selection process.

A further gap is found in Health Canada's guidance documents interpreting the *Food and Drugs Act's* (1985) and *Medical Devices Regulations'* (1998) application to software. Current guidance largely excludes AI software from licensing requirements if it is "not intended to acquire, process, or analyze a medical image or signal," "intended to display, analyze, or print medical information," "only intended to support" provider decision making, and "not intended to replace ... clinical judgment" (Health Canada 2019). While these criteria are not meant to be "determinative" of whether software falls under the *Medical Devices Regulations* (1998), it is again primarily up to innovators themselves to apply these criteria and select their own licensing category. The rationale behind this regulatory carve-out is, presumably, that having a human in the loop can ensure the safety of a given AI tool. But no such exception is made for prescription drugs (i.e., having a physician prescribe the drug does not negate rigorous requirements for testing in the pre-market stage), and it seems unlikely that most healthcare professionals would be able to sufficiently assess any hidden safety issues in AI alone. Furthermore, such an approach would result in underuse of AI by risk-averse physicians, who could not rely on the fact that the product has been cleared as safe by the regulator.

Apart from concerns about gaps in regulatory oversight, ML applications will require ongoing regulatory oversight of a different nature and quality as they evolve over time. Under section 21 of the *Medical Devices Regulations* (1998), all software must be "validated" before entering Canadian markets. This effectively prohibits approval of "adaptive" ML algorithms that learn from new data and change how they operate based on their own real-world performance without human intervention. Under the existing law, this kind of algorithmic change would mean that the application would have to be repeatedly re-licensed. To respond to this, Health Canada is developing a new regulatory pathway for the approval of medical devices with adaptive ML (Health Canada, e-mail communication, June 21, 2021). Yet details on this pathway remain to be seen apart from principles and statements regarding Health Canada plans to work closely with industry partners and "innovate" in the "regulatory sandbox" (Vural et al. 2021).

Recommendations

Health Canada must meet the challenge of how to regulate health-related AI, particularly ML, as safe for use in Canadian markets. To support this task, we offer five brief recommendations.

- a. *Transparency*: First, Health Canada will need to be transparent about its plans to regulate and report regularly on performance to garner the trust of patients, healthcare

professionals, the public and even innovators themselves. For example, if AI tools continue to be regulated based on the category of risk that they pose, we suggest that there needs to be transparency in how innovators' choice of licensing category is reviewed. Information should be publicly available on how these choices are audited, how often innovators are required to resubmit to a higher licensing category, and which innovators are required to resubmit. Similarly, as Health Canada develops a new regulatory pathway for ML tools (in the so-called "regulatory sandbox"), it must be transparent regarding what evidence is being relied upon to assess safety prior to market entry and what safety standards will be applied in the post-market stage.

- b. *Human in the loop*: Health Canada's current exemption for licensing of health-related AI in some circumstances where there is a healthcare provider "in the loop" should be removed. Providers are not yet trained to assess the risks of health-related AI (Reznick et al. 2020). For the same reason, the mere presence of a human in the loop also should not necessarily trigger lesser scrutiny or a lower risk classification.
- c. *Post-market surveillance*: Health Canada should ensure effective post-market surveillance of and transparent reporting on the safety and quality of AI in/as medical devices, particularly for ML. When it comes to post-market surveillance, where risk criteria are set at the pre-market stage, Health Canada should require regular reporting (indexed to risk) within those parameters. Regular random audits by the regulator to ensure that tools are working as intended will be key to successful regulation.
- d. *Strong pre-market and post-market oversight*: There may be pressure from some innovators to follow in the footsteps of the US Food and Drug Administration's pilot project, under which "excellent" companies could receive "pre-certification" of new software technologies in exchange for post-market surveillance (US FDA 2020). However, while post-market surveillance is critical for ML tools, this should not be at the expense of appropriate pre-market review. A focus on the track record of the innovator, rather than the product, may be appealing to innovators in terms of having, at least at first blush, a lighter regulatory impact. However, this kind of regulatory oversight could backfire by disadvantaging smaller start-ups without a significant track record but with an excellent product.

Furthermore, as we discuss below with respect to the problem of algorithmic bias, the initial design of the ML device is critical to how it will perform over time, and appropriate pre-market licensing requirements can ensure that high standards are met in terms of design. Where one unsafe AI tool could produce significant public pushback (Terry 2018), innovators too should support pre-market review – addressing traditional safety concerns and algorithmic bias and cybersecurity issues discussed below – to weed out bad products before they come to market and cause harm to patients.

- e. *Regulatory burden assessment*: While it is vital for Health Canada to appropriately regulate the safety of health-related AI, they must also evaluate the regulatory burden that falls upon AI innovators, particularly for start-ups and small companies, so that they are not deterred from bringing excellent products to the market. Constant attention must be

paid to achieving the goal of patient safety while minimizing unnecessary regulatory barriers. After all, unduly keeping otherwise safe health-related AI with huge potential for improving health outcomes off the market will not improve patient safety.

Algorithmic Bias and Safety Worries

The concern(s)

Health-related AI is designed by humans, who have explicit and implicit biases. The algorithms that humans develop could accordingly be inadvertently biased against marginalized groups/patients. AI innovators make many design choices that may increase or decrease algorithmic bias risks, such as decisions about whether or not to pursue and build upon data sets that are more representative but may be more costly or otherwise difficult to obtain. Even representative data sets may prove problematic if, for example, the data were originally collected in ways that encode researchers' bias or are input into an algorithm that itself encodes biases and accordingly has differential impacts (Cirillo et al. 2020).

Beyond the biases/limitations of the programmers/developers themselves, there is the question of whether data sets are themselves representative. There is already discrimination against different groups (e.g., women, racialized populations, sexual and gender minorities) in healthcare (Ayhan et al. 2020; Ben et al. 2017; Dusenbery 2018). Health-related AI might help by providing recommendations that could cause providers to "check" their inherent biases/judgments. Yet AI trained on data that themselves systematically under-represent groups because of discrimination already within the system may not cure, but replicate, existing discrimination problems, resulting in AI recommendations that are subpar for patients from marginalized populations (McCadden et al. 2020; Obermeyer et al. 2019). This could entrench or exacerbate existing inequalities. Consider, for example, the well-known under-inclusion of pregnant women in psychiatric trials (Cirillo et al. 2020; WHO 2009) or the under-treatment of both women and black individuals for cardiovascular disease (Vaccarino et al. 2005). Not all recorded differences in the data are bad biases. Where there are clinical differences scientifically grounded in gender, sex, age or race, this specificity is welcome for it leads to better diagnoses, treatment plans and ultimately health outcomes. But the risks of wrongful bias demand regulatory attention.

Existing regulations

Present medical device regulations in Canada do not specifically address the problem of algorithmic bias. One could look to federal and provincial human rights laws to combat discrimination that results from undesirable algorithmic bias in healthcare settings. However, unlike upstream device regulations, human rights laws will only have impact after discriminatory action occurs, and it will be difficult for individual patients to show causation between upstream decisions made in AI innovation and the harms that they experience (Henderson et al. 2022).

The scope of human rights laws presents further limits. Canada's supreme human rights law, the constitutional *Canadian Charter of Rights and Freedoms* (1982), only applies to governmental action so its protections cannot directly apply to developers or (normally) healthcare professionals. Provincial human rights laws, like the Saskatchewan Human Rights Code (<https://saskatchewanhumanrights.ca/your-rights/saskatchewan-human-rights-code/>), do apply to private actors and prohibit discrimination on grounds such as race and gender. So, at least theoretically, an AI tool that is not trained on an appropriately representative database may violate the provincial laws. But claimants would face steep evidentiary burdens (Henderson et al. 2022), and we have yet to see judgments requiring collection of "representative" data or, otherwise, clearly protecting against algorithmic bias (Krishnamurthy 2021).

Recommendations

Health Canada alone likely cannot eliminate the threat of algorithmic bias stemming from health-related AI, but we have recommendations on how the federal government can use its powers to at least minimize the algorithmic bias-based risks most likely to have an impact on patient safety.

- a. *Assess risk of algorithmic bias in pre-market review:* Health Canada should assess the risk of algorithmic bias as part of safety review. Health Canada should, for instance, require that developers of all health-related AI applications, regardless of risk classification, take all reasonable steps to collect and use training data that are representative of the populations for whom an AI tool will be used. It should also carefully review its present expedited processes for adoption of devices approved by regulators in foreign jurisdictions to ensure that this does not mean that adoption of health-related AI is inapt for Canadian needs. This is particularly so if international regulators try to speed up or lighten regulatory oversight to "support" their own local AI innovators. For Canadian innovators, Health Canada could assess which other mechanisms exist to spur better data inclusiveness, such as whether the Tri-Council (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council 2018) guidelines on research ethics sufficiently speak to this issue.

In some cases, using representative data may not be feasible, given the unavailability or prohibitive cost of acquiring it. Race-specific data are not even collected in some jurisdictions, preventing some biases from being assessed. The salience of, for example, race or gender to diagnosis or treatment may vary by clinical context, and risks posed by algorithmic bias may vary accordingly. It is thus essential that in every circumstance, significant effort is put into understanding for whom this algorithm will work by properly characterizing the population on which it was trained and thus providing information as to its limitations for use in clinical settings. While Health Canada may already attend

to these issues (and representatives suggest that this is the case), an explicit and transparent requirement is needed to engender trust on the part of healthcare professionals and patients.

- b. *Assess algorithmic bias as part of post-market review:* Beyond the initial point of licensure, Health Canada should also monitor the extent to which AI tools may be perpetuating or exacerbating existing inequalities via life-cycle surveillance of AI in the real world (e.g., examining if any adverse errors disproportionately impact those underrepresented in training data sets).
- c. *The federal government should fund data set development:* As we discuss further in the context of privacy issues, Health Canada should also spearhead with other federal departments and agencies the building and liberalization of representative data sets to support the development of health-related AI.

Safety, Privacy and Security

The concern(s)

Many worry that “big data” collection by governments or multinational corporations (e.g., Google, IBM, Facebook) will inevitably produce privacy violations. Users worry that their personal health data might be used to, for example, deny insurance or risk-rate premiums or adversely affect employment opportunities. High-profile personal information breaches, such as an agreement between Google DeepMind and the National Health Service that gave Google 1.5 million patients’ records in 2015, which Google sought to bring to the US, underscore these concerns (BBC News 2021). The UK Privacy Commission found that there were insufficient privacy protections in that case, which is now the subject of a class action suit (BBC News 2021). However, large, representative data sets remain necessary to build safe, effective AI and to mitigate risks of algorithmic bias.

Privacy concerns are further complicated by related cybersecurity issues. Even where data holders and users acquire data in a justified manner, they must ensure that they have sufficient security safeguards to protect the data from falling into the hands of persons without legitimate claims to access them. Canada’s healthcare systems are, in practice, operated by a plethora of different actors and entities (non-profit hospitals, private clinics, small general practices, large pharmacy chains) with varying capacity to ensure secure systems.

From a safety lens, privacy concerns may make it more difficult for AI innovations to be built from aggregate data that are representative of populations they will serve. Members of Indigenous, Black and other communities that have been marginalized may oppose sharing data because of historical and present-day abuses of their data by governments and private actors. Yet there is a risk of error in diagnosis and treatment if data are not included from such populations. Data “de-identification,” in which identifying information is stripped away, reduces privacy risks but is not always possible. There is a risk too, with large data sets involved in most health-related AI projects, of “re-identification” and misuse by less

scrupulous actors (Cohen and Mello 2018). International actors and other jurisdictions are developing best practice standards for protecting data used in AI, and even basic cybersecurity standards can help minimize these risks. But the risks remain. Innovators may also face challenges acquiring representative data from excessive privacy restrictions and/or the multiple layers of restrictions operating at federal, provincial and sub-provincial (e.g., hospital) levels.

Existing regulations

Across Canada, there is a lattice of federal and provincial law relating to privacy of health information. At the heart of federal and provincial privacy protections are requirements that Canadians normally must give consent to the disclosure and sharing of their personal health information. Access to data is, however, difficult across Canada, and given the large data sets needed to create AI tools, it is more likely that AI will seek out extant data sets, even if not sourced in Canada. This is almost always viewed as more feasible than building data sets themselves, avoiding the need to obtain patient consent. Indeed, many AI tools rely on the same data sets from foreign jurisdictions, like US-based MIMIC data sets (Nagaraj et al. 2020).

Canadian privacy laws also do not generally require consent for the use of de-identified data, but triangulation of data and AI could be used to re-identify persons. Recent amendments to Ontario's *Personal Health Information Protection Act (PHIPA)* (2004), prohibit re-identification of health information and penalize rule-breakers, and *PHIPA* sets some minimal cybersecurity standards that different types of medical tools must meet. But these kinds of protections are not uniform across Canada.

Recommendations

Health Canada also cannot address issues regarding safety, privacy and security on its own, but there are at least three ways that the federal government, likely including Health Canada, can minimize related concerns.

- a. *International security standards*: First, as part of pre-market clearance and ongoing post-market surveillance of ML applications, Health Canada should require compliance with international cybersecurity standards, similar to what regulators have proposed in Germany (FIDMD 2021). For instance, it could require completion of a checklist by the applicant "on data protection, information security and quality," including whether the manufacturer has met international (specifically ISO) and domestic standards with respect to information security and management (FIDMD 2021). These kinds of basic requirements are, of course, not a panacea. Yet they will minimize the chances of at least some kinds of privacy violations, which is a good outcome on its own and should help foster the development of more inclusive data sets.

- b. *Punishment for re-identification:* Second, to deliver on the promise of safer healthcare for groups who have been marginalized by society, AI requires large representative data sets, and yet the same historically marginalized groups who may benefit from AI built on more representative data do not necessarily trust our governance systems. To address this problem, the federal government of Canada should assess whether existing federal and provincial laws adequately prevent sharing of identifiable information and reconstituting of previously de-identified information and work with others to ensure an adequate framework exists. Importantly, particularly as the technological capacity of re-identification becomes more feasible with ML, there must be a review of whether penalties for re-identification are sufficient to deter bad actors. Presently, there are many ethical AI innovators who cannot access the data they need because of re-identification concerns. All else being equal, it would seem better to heavily punish bad actors as opposed to inhibiting access to data for all.

This broader problem is likely one beyond Health Canada's jurisdiction and points to broader systemic concerns – hence the move away from our specific focus and discussion regarding “the federal government,” rather than Health Canada, in the preceding paragraphs – but Health Canada should consider whether it can require as part of both pre-market and post-market oversight that patients' and users' privacy is sufficiently protected, given the connections among robust privacy protections, data representativeness and safety. These issues may simply stem from a more general failure to protect data outside Health Canada's jurisdiction, but that should not stop Health Canada from examining if/how they can contribute to better protections. Insofar as Health Canada is not enabled to address these issues, in turn, the federal government may consider providing it with the authority to consider them within safety analyses. Regardless of what one thinks of that proposal, it is clear that the federal government must ensure that someone is attending to these important concerns.

- c. *A pan-Canadian strategy on data creation and protection:* Finally, we agree with the Public Health Agency of Canada (2021) Expert Advisory Group on the Pan-Canadian Health Data Strategy's recent statement on the need to enable safe, national pooling of representative data sets. This will require the federal government to use its convening power to lead all provinces and territories into common standards for data sharing and support Indigenous governments and communities that have been marginalized in data sharing (Black Health Equity Working Group 2021).

Once again, Health Canada may not be able to resolve these issues alone, but the federal government could support and fund Indigenous peoples, Black and other visible minority groups for “better data collection to ensure fair and inclusive AI in medicine” (Pasquale 2020: 39). Health Canada could consider funding partnerships between AI innovators and marginalized groups – provided it is more than a tokenistic exercise – to foster data inclusivity.

Conclusion

AI promises a safer future for Canadian patients, overall, but to realize that future, legal governance of health-related AI must support safe innovations and weed out poor products and unethical innovators. In other words, Health Canada as the regulator must have as its primary goal protection of patient safety and with it a fundamental commitment to transparency, particularly as it experiments with different kinds of regulatory approaches and standards of evidence for AI products that evolve over time.

The regulatory challenge here is significant for health-related AI (particularly ML) is not static: Health Canada as the regulator must be nimble but, at the same time, relentlessly transparent with its successes and failures to garner trust in the safety of health-related AI. Of course, the goal should be to ensure that the regulatory touch consistent with patient safety does not bury innovations in red tape, which will not help Canadian patients. However, this should not be an excuse to aim for minimal or ineffective regulation in a bid to foster Canadian innovation and support Canadian innovators. Furthering innovation consistent with protecting patient safety, Health Canada's primary goal, requires that Health Canada conduct both pre- and post-market review of medical devices with AI that attends to the safety-related risks, including those relating to algorithmic bias, privacy and cybersecurity. Health Canada's resources will need to be bolstered to achieve these goals, so that the resulting regulatory framework ensures that the safety and quality of health-related AI products are maintained over time. This will help foster trust on the part of all stakeholders and the use of beneficial health-related AI that rightly makes it onto Canadian markets.

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