Alberta's research priorities to advance organ donation and transplantation: an ecosystem-based and consensus-driven approach to strategic research planning.

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Abstract

The Alberta Transplant Institute designed a strategic research planning initiative to address the unique research needs of organ and tissue donation and transplantation in Alberta. Bringing together the broad Alberta donation and transplantation ecosystem, this initiative created an effective mechanism to link a region's research expertise with system-identified and patient, family, and donor-identified challenges to create a unified, prioritized body of key research needs. Patient, family, and donor partners were integrated into every stage of this initiative. We applied the Nominal Group Technique methodology to create consensus priorities, divided into five topic areas spanning the full spectrum of organ donation and transplantation science, policy, and practice. The consensus-building process involved a survey, 10 virtual working group sessions, and a hybrid community consultation event. Fifteen research priorities emerged and were consolidated into a strategic research roadmap for the Alberta Transplant Institute. This work aims to ensure that the Institute's research activities remain focused on addressing the most pressing challenges. The process and findings are a valuable resource for researchers, policymakers, and healthcare practitioners in Alberta and beyond who are committed to a consensus-based approach to producing new knowledge, practices, and policies.

Citation

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Acknowledgements

Status

Peer reviewed. Submitted: 15 JAN 2024. Published: 7 MAR 2024.

Introduction

Organ and tissue donation and transplantation (OTDT) is a critical and life-saving medical intervention that has transformed the lives of millions of patients worldwide. However, despite significant global advances in the science, technology, policy, and practice of donation and transplantation, significant challenges remain in many regions of the world, including Canada. These challenges include donation culture and practices, organ shortages, inequitable access to transplantation, and suboptimal long-term graft survival and patient outcomes, including quality of life and psychosocial concerns. A unique set of challenges in OTDT are faced by the province of Alberta. As the central referral centre for transplantation of all non-renal organs in the Prairies and Northwest Territories, and for certain transplants from British Columbia and Manitoba, Alberta's health system must meet diverse patient needs in a large geographic area. For deceased donation, the remote and rural nature of many communities in Alberta's catchment area presents challenges, including the lack of local intensive care units, inadequate transportation infrastructure, and a limited capacity of transplant teams to travel to remote areas for organ recovery. However, with recent advances in legislation[1], a single integrated health care system[2], and exceptional research capacity in transplantation[3–21], Alberta is well-positioned to address these issues.

The Alberta Transplant Institute (ATI) was established in 2011 with a vision to lead the Alberta donation and transplantation ecosystem to excellence in research, education, and advocacy. The ATI aims to increase the quality and availability of donated organs, cells, and tissues, improve transplant patient and family outcomes, and enhance the experiences of donor families and living donors by supporting excellence in donation and transplantation research, training the next generation of donation and transplantation specialists, and supporting patients, families, and donor-led engagement and empowerment.

In pursuit of these goals, ATI recognized the importance of setting long-term research priorities that not only reflect the leading edge of investigator-driven science and innovation, but also the needs of patients, families, donors (PFDs), and healthcare providers. We therefore designed a method to identify research priorities that will guide ATI's research activities over the next decade. We undertook a structured process of consultation and engagement with researchers, clinicians, organizational stakeholders, and PFDs from across the province, using the Nominal Group Technique to identify, define, and prioritize research topics and projects. Across five broad topic areas, fifteen research priorities emerged, providing a roadmap for the ATI to focus its research efforts for maximum impact.

Methods

Setting principles and five thematic Working Groups

This strategic research consultation was led by the ATI Research Committee (members listed in Appendix 1), which met in September 2022 to define the scope of the consultation, set the terms of reference, and establish the principles to guide the development of the research priorities (Table 1). The Research Committee recommended a scope of five Working Groups: (1) Advance the culture and practice of living donation; (2) Advance the culture and practice of deceased donation; (3) Optimize graft use and quality; (4) Improve immunologic health for transplant patients; (5) Improve long-term wellness for transplant patients. The committee proposed an Academic Lead and a Patient, Family or Donor (PFD) Partner Lead for each Working Group based on their expertise and experience, and recruited Working Group participants. The PFD Partner Leads were recruited through existing relationships with the ATI and its network across Alberta. The PFD Leads and Working Group members were encouraged to express their personal and professional experiences and expertise with OTDT to ensure that the language, content, and intent of the research priority recommendations reflected issues that were important to them. Each Working Group was mandated to select a maximum of three priorities, allowing the consultation to bring forward a maximum of 15 research foci. Priorities related to individual patient care or that directed changes to clinical practice and programs were considered out of scope. This process did not involve new research, therefore ethics approval was neither required nor sought. No funding was received from for-profit entities for this initiative; funding was provided by the University of Alberta Faculty of Medicine & Dentistry. Janet A. W. Elliott holds a Canada Research Chair in Thermodynamics.

Table 1. Principles guiding the development of ATI research priorities.

Initial survey

- Support the areas of existing research strength in Alberta
- Prioritize research areas that have the greatest need for new funding
- Ensure the inclusion of discovery, translational, and social science and humanities research
- Ensure the inclusion of specific needs in donation research, both living and deceased, for solid organs and tissue
- Address common challenges across transplant-related fields and organ and tissue specialties
- Include a focus on patient, family, and donor priorities
- Ensure that the research priorities address the needs and challenge of the clinical programs, both from physicians and allied health perspectives

To generate preliminary ideas for research priorities and to identify additional Working Group participants, we developed a survey that was sent to the ATI mailing list (n=695) and promoted by partners in October 2022. The survey asked participants to identify and prioritize key research priorities that link expertise across the Alberta donation and transplantation ecosystem (see Table 2 for example survey questions). The survey also included demographic questions to understand the roles, research interests, genders, and ethnicities of the respondents. The demographics were not linked to individual survey responses and were only used to ensure a broad representation of the survey results. We received 64 responses (9.2% response rate). Survey respondent profiles were as follows: 32.8% clinicians, 37.5% researchers, 21.9% patients, family, or donors, and the remainder with other roles, including trainees, administrators, staff from charitable organizations, and allied health personnel. Ethnicity representation was as follows: 68.8% identified as White, 7.8% East Asian, <5 individuals identified as each of Southeast Asian, Latino, Middle Eastern, Black, and South Asian, and 3.1% preferring not to answer. In terms of gender, 45.3% identified as cis-gender male, 51.6% as cis-gender female, and 3.1% preferred not to answer. For interests in donation and transplantation, participants were allowed to select multiple options. Respondents reflected a broad range of interests across donation and transplantation: 50% of participants indicated primary interests in deceased donation, 39.1% in living donation, and 46.9% in transplantation, with 31.3% specifically interested in liver, 26.6% in kidney, 28.1% in heart, 18.8% in lung, 23.4% in islet/pancreas, 10.9% in small bowel, 15.6% in tissues, 4.7% in vascularized composite allografts, 9.4% in infectious disease, and 9.4% in other non-organ specific fields of transplantation such as pharmacy.

Table 2: Example survey questions to determine ATI research priorities.

Which of these 5 research areas does your research or interest in donation and transplantation fit into (select all that apply)
- Advance the culture and practice of living donation.
- Advance the culture and practice of deceased donation.
- Optimize graft use and quality.
- Improving immunological health for transplant patients.
- Improve long-term wellness for transplant patients.
- None of the above.

If you selected "**none of the above**," please explain why your research and/or interests do not fit into these 5 Areas.

Is there a **research area** that you feel is missing from this list? Please explain.

For the **research areas described above** that your research and/or interests align with:
- Describe one or two research *priorities* or *outcomes* for this area that will advance donation and/or transplantation in Alberta over the next 5-10 years.
- Describe examples of *activities*, *collaborative projects*, or *initiatives* that the ATI could support if there was funding in place today that would advance and transform donation and transplantation research in this area.
- List the *people* and *organizations* in Alberta who could contribute to this work and/or indicate if there is a critical need for *recruitment* in this specific area.
- Please provide any *final general comments* or *feedback* regarding the future ATI Research Priorities

Identifying working group members

Forty-six Working Group participants (including the academic and PFD leads) were recruited based on their experience, expertise, or role in the OTDT ecosystem across Alberta, including healthcare administrators, healthcare professionals with no research roles, and patient support and advocacy groups (see Appendix 1 for a full list of Working Group members). We sought diverse representation based on professional roles, geography, career stage, research discipline, lived experience, and personal diversity. The range of professional expertise included physicians, surgeons, allied health, basic science (including areas such as immunology, cryobiology, stem cells and vascular biology), social science, representatives of health charities and leaders of organ donation organizations. Participants received no financial compensation for their participation.

Refinement of questions

The Working Group leads were responsible for reviewing the survey results, facilitating discussions, and developing the research priorities recommended by each Working Group. A modified version of the Nominal Group Technique (NGT) was used to discuss, prioritize, and rank ideas for each Working Group. NGT is a structured approach to facilitate problem identification, solution generation and decision-making[22]. NGT has been used extensively in healthcare[23] to identify priorities, support guideline development[24], and explore the views of health professionals and people with lived experience[25–27]. The four key steps of NGT are summarized in Figure 1. We modified the NGT to enable an entirely virtual format, with the steps divided between the survey and two Working Group meetings. We held an orientation and coaching session for each of the five Working Group leaders on how to conduct the NGT to encourage open and balanced group discussion, promote efficient identification of areas of agreement and persistent disagreement, and produce a ranked list of research priorities.

Figure 1. Key steps of the Nominal Group Technique to establish the research priorities in organ donation and transplantation in Alberta.
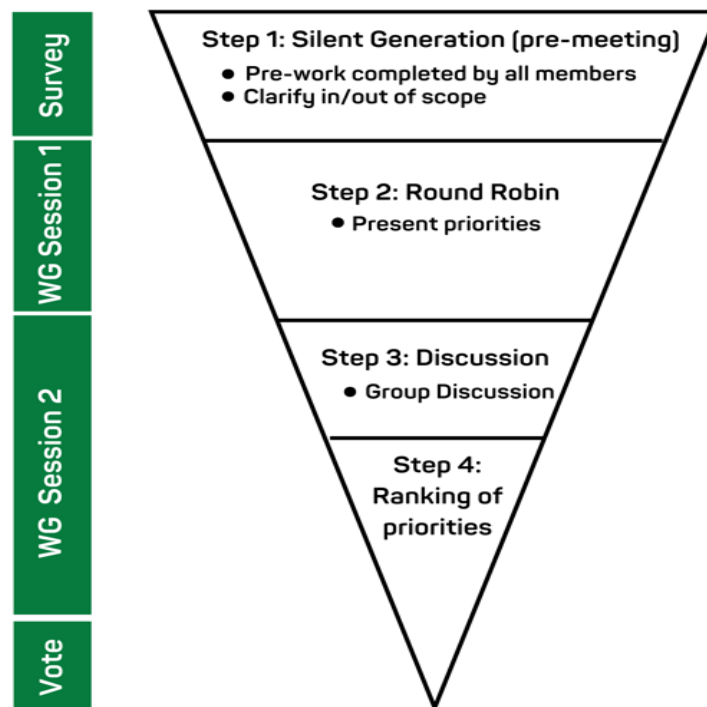
Interim prioritization

The Working Group Leads each chaired two virtual sessions between November and December 2022 to generate, discuss, and consolidate research priorities relevant to their topic. PFD partners were involved in all Working Group discussions. The ideas from the survey were presented in Session 1 and Working Group members were encouraged to add additional ideas. All Working Group members had the opportunity to present their ideas, and only clarifying questions were allowed in Session 1 (all debate and discussion were reserved for Session 2). In the days between Session 1 and Session 2, the Working Group Leads reviewed each of the priorities identified in Session 1 and attempted to group and consolidate similar, overlapping, and recurring priorities. The Leads also eliminated priorities that were considered out of scope or clearly not in line with the guiding principles (Table 1).

Final Prioritization

During Session 2, the Leads reviewed the suggested research priorities with the Working Group members and facilitated a discussion on each. The Leads asked Working Group members to determine whether each of the proposed priorities was S.M.A.R.T. (Specific, Measurable, Achievable, Realistic and Timely)[28,29], and helped the Working Group members to clarify, improve, amalgamate, and eliminate priorities. By the end of Session 2, if no consensus was reached on the top three research priorities in each group, Working Group members were asked to rank their top three priorities using an anonymous virtual poll. Following the Working Group sessions, the Leads (with the help of some Working Group members) collated and expanded the description and rationale for their priorities. The final fifteen recommended research priorities were presented to the ATI Executive in March 2023.

Results

We describe below the research priorities determined by each Working Group, their rationale, and potential projects that could support addressing each priority in Alberta.

Working Group 1: Advance the Culture of Donation and Donation Practices – Living Donation

1. Interventions to improve timely awareness of living donation

A lack of education for patients and a lack of public awareness about living donor transplantation is a major barrier in Alberta. There is a need to better inform potential organ transplant recipients, early in their transplant journey, about the benefits of living donation and the processes involved with identifying and screening potential living donors. To improve awareness of living donation, it is important to understand where potential donors are learning about living donation and what interventions are currently seeing success in getting patients to inquire about living donation in the province. This research priority aims to increase awareness of living donation amongst potential organ donors, recipients, and the public at large in Alberta.

Examples of potential projects include:

- Surveys of those who contact the living donor programs to determine where they are first learning about living donation (e.g., from the intended recipient, social media or educational websites, or family physicians). A better understanding of where current potential donors currently receive their information could inform future strategies that are likely to have the most impact and identify gaps that could present opportunities.

- Evaluation of projects aimed at increasing education and awareness in the Alberta educational curriculum, family physician offices, and through social media.

- Interventions that introduce the topic of living donor organ transplantation early in the care of organ failure patients. While directed living donors are not worked up until a patient is accepted as a transplant candidate, patients express the need for them and their families/friends to be well informed before they reach end-stage organ failure and are waitlisted. Interventions could be designed to increase the rate of contacts and inquiries to

the living donor programs and increase the number of completed living donor evaluations and assessments, ultimately leading to increased living donor transplants.

2. Understanding the long-term outcomes of living donors

Overall, there are minimal risks to living organ donors; however, much of the information about potential short- and long-term complications that are quoted to prospective potential donors are extrapolated from studies occurring outside of the province or country[30,31]. Although one previous retrospective cohort study of 604 living kidney donors in Alberta from 2002 to 2016 reported a stable and expected decline in kidney function over time relative to non-donor controls in the first decade following unilateral nephrectomy (estimated glomerular filtration rate, eGFR[32]), two subsequent studies from Norway and the United States reported that living kidney donors have an increased relative risk of kidney failure compared to matched healthy, non-donor controls, although the absolute risk for most donors is low (<1% over 15 years)[33–35]. There is a need to develop a better understanding of the short- and long-term risks to living donors in Alberta, including the risk of kidney and liver failure.

Examples of potential projects include:

- Evaluating the risks of living kidney donors in Alberta eventually developing kidney failure after the development of a secondary hit, such as hypertension or diabetes mellitus[36,37], and determining what interventions are most effective in maintaining long-term kidney health.

- Studying the risk of additional adverse events following living donation, including organ failure, chronic comorbidities and multi-morbidities, pregnancy complications, and diminished quality of life.

3. Strategies to improve, increase, and standardize donor follow-up care across Alberta

Currently, there is no national or provincial standard in Alberta for the follow-up care of living donors. One Alberta study found that only 25% of kidney donors had all three markers of care (physician visit, serum creatinine, albuminuria measurement) in each year of follow-up over a median follow-up of 7 years (maximum 13 years)[38]. This suggests a significant gap in care across Alberta relative to the recommended best practices. It is currently unknown what proportion of living liver donors complete this follow-up testing on an annual basis and what impact this has on long-term patient care in Alberta. Standardized follow-up care may lead to opportunities to mitigate long-term risks, promote good health and wellness, and update past donors on new and ongoing research in the field of living donation. If potential living donors are reassured that there is a dedicated medical follow-up clinic, this may result in increased rates of living organ donation.

Examples of potential projects include:

- Establishing a baseline measure of current practices and adherence to the follow-up care of living donors, with the goal of establishing a standardized protocol across Alberta.

- Evaluating the impact of standardized short- and long-term follow-up care of living donors offered by donor programs.

- Creating a provincial registry of living donors to allow for accurate identification of donors, reporting of outcomes with minimal additional resources required, and help implementing interventions that could improve the health and well-being of living donors in Alberta. Alberta is unique in its recent implementation of one pan-provincial electronic medical record that could facilitate the creation of this registry across hospitals and transplant programs and report consistently on outcomes for living donors.

Working Group 2: Advance the Culture of Donation and Donation Practices – Deceased Donation

1. Factors influencing consent decisions

The consent rate for organ donation in Alberta is relatively low, especially when compared against the findings of public opinion polls supporting donation[39,40]. Reasons for this discrepancy are not well understood, and potential solutions or

systemic improvements to address this gap are therefore not clear. A previous Alberta-wide study revealed that the annual rate of identified and approached potential death by neurological criteria (DNC) donors in whom consent is not given for organ donation exceeds 10 donors per million population[41]. In comparison, the number of missed potential DNC organ donors was only 4.5 donors per million population[41]. The consent rate is even lower for donation after circulatory death (DCD) than it is following DNC[42]. The consent rate for tissue donation in Edmonton is 32% in 2023[43]. Increasing the consent rate could have a large impact on deceased organ and tissue donation and transplantation rates in Alberta.

Examples of potential projects include:

- Determining the reasons why patients and alternate decision-makers did not give consent to deceased organ donation. This could be assessed with prospective surveys of consecutive alternate decision-makers that are approached in the intensive care unit for donation conversations.

- Qualitative research through interviews and/or focus groups with the same alternate decision makers at a later time would provide additional rich information regarding factors that affecting the donor family experience and influencing the consent decision.

- Interventional studies that modify the way consent conversations occur, primarily aiming to improve the experience of potential donors' families and possibly also increase the consent rate. For example, if surveys and interviews revealed that the refusal of consent was based on certain consistent themes (e.g., clarity of information provided, the modality of written/verbal communication, training/background of the professionals doing the family approach), these could be strategically addressed in future consent conversations or even assessed in cluster-design randomized controlled trials.

2. Public understanding of donation in Alberta

A general lack of understanding, misunderstandings, or lack of trust in organ and tissue donation processes may be a barrier to normalizing donation and achieving a "culture of donation" across Alberta. Decisions to donate are most often made under emotionally stressful and time-bound conditions. Little is known about the degree to which Albertans understand the process of deceased organ and tissue donation, or the potential benefits or risks associated (e.g., that organs offered may be offered but not accepted for transplant and the secondary loss that can accompany such a situation). This may be a factor contributing to the discrepancy between the large proportion of Albertans who support organ donation in surveys compared with the smaller number who have registered an intent to donate, and ultimately consent rates[39,40]. The goal of this research priority would be to instill a deeper public understanding of what to expect during the acute decision-making period of organ and tissue donation to improve the quality of decisions.

Examples of potential projects include:

- Exploring the views of religious and ethnic groups that have historically been less accepting of donation, using surveys and focus groups.

- Evaluating interventions aimed at improving the public's understanding of donation.

- Developing school curricula for education regarding organ and tissue donation, which could have a large impact on public understanding over time. The impact and effectiveness of such interventions could be explored using "before and after" assessment of students' knowledge.

3. Evaluation of Alberta's Bill 205 and the SEND Program

Bill 205 is an amendment to the Alberta Human Tissue and Organ Donation Act, passed unanimously by the Legislative Assembly of Alberta in May 2022[1] and which came into effect on April 1, 2023. One component of this legislation is the requirement for mandatory referral of patients dying within the healthcare system to the provincial organ and tissue donation program, to assess registration status and eligibility for donation. Bill 205 also mandates the monitoring and measuring of information about organ and tissue donation, the training of the health care community, education of the public, support, and encouragement of the use of the online registry use, and the creation of an annual report to the

Minister of Health that includes any recommendations to increase the efficacy and effectiveness of the organ and tissue donation system in Alberta.

Alberta also introduced the "Specialist in End-of-Life Care, Neuroprognostication, and Donation" (SEND) Program with support from the Government of Alberta, initiated by Alberta Health Services in July 2021[44]. National guidelines recommend increasing the placement of "donation specialist physicians" into all hospitals that care for organ donors to improve the culture of donation in hospitals[45]. Compared with donation specialist physicians from other Canadian regions, the Alberta SEND Program expands the scope of responsibilities to target excellence in all realms of critical care medicine that are related to organ donation and end-of-life care.

The introduction of these two initiatives in Alberta provides an opportunity to assess their impact and potentially identify opportunities for improvement.

Examples of potential projects include:

- Evaluating the impact of the two initiatives using metrics that are already routinely collected (e.g., referral rate, missed donation opportunities, conversion rate, etc.).

- Interrupted time series analysis could be used to assess the impact quantitatively, such as the LEADDR study in Nova Scotia that is measuring the impact of their legislation on deemed consent legislation[45,46]

- Qualitative assessments of the impact of both initiatives on patients, healthcare professionals, and hospital administrators could be achieved with surveys and focus groups.

Working Group 3: Optimizing Graft Use and Quality

1. Ex situ graft preservation and improvement between recovery and transplant

With the limited number of donors and the large geographical area covered by the Alberta transplant programs (> 6 million km^2), it is both a challenge and an opportunity to extend the viability of grafts before transplant. It is widely recognized that improving the physiology and prolonging the timeframe of organ and tissue preservation during procurement, storage, and transport would enable replacement of organs and tissues "on demand", could save or improve millions of lives each year globally, and would create public health benefits on par with curing cancer[47]. The goals of this priority are to extend the preservation timeframe and improve the graft *ex situ*.

To advance *ex situ* graft preservation, research should be aimed at enabling cells, tissues, or organ grafts to be maintained as close as possible to their incoming state, including sterility, viability, and function, for storage periods of hours, days, weeks, months, or years. The ultimate goal for graft storage is cryopreservation (storage at temperatures as low as -196 °C), which would allow storage times of years. Cryopreservation is currently used for most cells, a few tissues, but not organs. When cells, tissues, or organs cannot be adequately cryopreserved, the goal should be to refine strategies to allow the longest maintenance of sterility, viability, and function, typically hypothermic storage just above 0 °C for hours, days, or weeks.

Examples of potential projects in *ex situ* graft preservation include:

- Developing new cryopreservation protocols to expand banking to include new cell types and tissues or to improve graft quality of cells and tissues currently banked and transplanted.

- Leveraging advances in supercooled and partial freezing technologies to extend the storage time of organs.

- Creating programs to cryopreserve osteochondral allografts by vitrification and have them stored long-term and delivered on demand for orthopedic surgeries.

- Developing processes to increase the processing of fresh (hypothermically stored) osteochondral allografts, and processes to cryopreserve vascular grafts.

To advance *ex situ* graft improvement, research should focus on ways in which the cells, tissues, and organs can be treated to improve them from their incoming state, and *ex situ* engineering of new grafts. There is a need for expanded development and application of *ex vivo* perfusion as support for organs to allow assessment, modification, and repair of organs for transplant, including organs donated after circulatory death.

Examples of potential projects in *ex situ* graft improvement include:

- Studying the additives to *ex vivo* perfusion circuits to condition grafts to enhance their function post-transplant and provide a means to 'resuscitate' organs procured from extended criteria donors.

- Improving donor engraftment in the host and reducing off-target drug side-effects by providing localized intra-graft drug delivery (e.g., nano- and microparticles).

- Genetic engineering of cells and organs to be hypoimmunogenic (e.g., CRISPR knockdown of MHCI/II, humanized xenografts, autologous tissues).

- Providing an optimal transplant microenvironment using tissue engineering and functionalized biomaterials (e.g., angiogenic eluting scaffolds, hypoxic resistant lab growth cartilage).

2. Optimizing allocation–making the best possible use of a scarce resource

One of the ways to improve graft utilization is to focus on optimizing allocation, pairing each donor with the most suitable recipient with respect to their need and probability of survival. In practical terms, this means identifying the most important matching factors between donors and recipients, including variables such as organ size and weight, donor and recipient sex and age, immune system features like human leukocyte antigens (HLA) and anti-HLA antibodies–and using this information to take a precious resource and best distribute it to the people who need it.

It is important to systematically capture all donor and recipient data, to facilitate both a landscape view of how allocation is currently done and how it can be improved. Complex modelling and machine learning algorithms could identify alternative, optimized allocation strategies to facilitate the best transplant outcomes. Prioritizing this research would allow clinicians to potentially widen the donor pool: if individual variables that currently serve to exclude a particular donor or donor organ from use are associated with no or acceptable risk, many more transplants can be performed and fewer donor organs will be declined for transplant.

Another important aspect of allocation research is the ethics, transparency, and distributive justice of allocation strategies. Organ allocation is often the result of individual clinicians or teams of clinicians making the best decision they can, but as with any other human decision, these are vulnerable to bias and anecdotal experiences. It is essential for this research to engage patient, family, and donor partners to provide additional transparency to the allocation process.

Examples of potential projects include:

- Analyzing donor and recipient data to quantify the relative associations of factors such as ABO blood group, HLA sensitization, histocompatibility, size matching, age, and sex and gender matching, among many others, on recipient outcomes.

- Analyzing allocation based on future graft function, to determine which allocation strategies are associated with optimal utility (the most organ function for the longest period for the greatest number of people).

- Modelling new, innovative allocation strategies.

- Assessing the risk of individual immune mismatches and pre-formed donor-specific antibodies on graft function and recipient survival.

- Investigating Alberta's current allocation system for efficiencies, disparities, and biases.

- Implementing interventions and novel strategies to move closer to a system where all candidates have an equitable opportunity to access transplantation as a therapy.

3. Improving transplant outcomes by optimizing perioperative management and treating graft rejection and failure

The goal of transplantation should be to ensure that the recipient and their transplanted organ have the longest and best quality of life possible. Because organ donation rates in Alberta are currently lower than national averages, it is important to ensure that donation and transplantation opportunities have the maximum potential benefit and optimal long-term outcomes.

To advance this priority, it is essential to optimize the care and conduct of the transplant surgery, the early post-operative period, and long-term post-transplant care for the patient on their journey towards a healthy, independent life. Although transplants have been performed for more than 70 years, understanding rejection and other mechanisms that cause a transplanted organ to fail remains a major priority. Much of transplant medicine is directed at preventing or treating rejection and graft failure or managing complications of the therapies designed to prevent rejection. To improve transplant outcomes for patients in Alberta, it is essential to be able to track and study the current health and graft function of Albertans living with a transplant.

Examples of potential projects include:

- Studying the effects of preconditioning through physical rehabilitation of patients with end-stage organ failure, who have frequently lost strength, muscle mass, bone integrity, and global function, on their disease process.

- Comparing surgical techniques to determine which are most likely to produce a functional organ and result in the lowest chance of surgical complications.

- Studying the use of induction immunosuppression strategies that have the ideal balance between preventing acute rejection of the transplant while minimizing the risk of infection and other medication toxicities.

- Studying post-transplant rehabilitation interventions to help patients regain the function lost to their (now resolved) chronic disease while recovering from major surgery on a complex new medication regimen.

- Studying the use of molecular diagnostics to understand rejection and graft failure and to make tests and treatments safer and less invasive.

- Developing new therapeutics to treat rejection through investigator-initiated trials of drugs, devices, and diagnostics.

- Conducting research to reduce chronic allograft dysfunction in lung transplant recipients and cardiac allograft vasculopathy in heart transplant recipients.

Working Group 4: Improving Immunologic Health for Transplant Patients

1. Identify opportunities to personalize immunosuppression

Achieving optimal immunologic health after solid organ transplantation is a challenging endeavour. Graft rejection by the recipient's immune system due to histocompatibility antigens of the donor is one of the most feared post-transplant complications. Generally, treatment protocols for transplant patients to prevent and treat rejection follow a "one size fits all" strategy, aiming for the least aggressive medication regimen needed to prevent rejection. However, each donor-recipient pair is unique, and strategies that may be optimal for one transplant recipient may be insufficient in another or may be overly aggressive. There is a strong need for personalized or precision medicine to tailor treatment strategies to the need of the individual patient and their individual graft.

Personalizing immunosuppression is challenging due to the limited knowledge of the immunological profile of transplant patients in various stages of 'maturation' (e.g., young vs. old) and the influence of their sex and gender (e.g., the effect of sex hormones or lack thereof, the influence of gender-based behaviour patterns), underlying diseases, and body processes, such as metabolism. In addition, validated methods to define the status of the immune system delicately and dynamically are lacking, and clinical outcomes and interventions are often based on the after-effects of tipping the scale

(e.g., rejection or infection). Rapidly evolving technical advances in genomics, transcriptomics, proteomics, metabolomics and microbiomics, along with bioinformatics has led to the emergence of precision medicine strategies in the fields of immuno-oncology, autoimmunity, infectious immunity, and transplant immunology.

Examples of potential projects include:

- Leveraging the resources and expertise in 'multi-omics' available in Alberta to understand the immune health of our transplant recipients and apply the principles and practicalities of precision medicine.

- Improving diagnosis of immune health in relation to sex and maturation of our transplant recipients using state-of-the-art molecular and proteomic technologies.

- Studying relevant liver metabolism pathways prior to transplantation so appropriate drug doses can be used for the "high" vs. "low" metabolizing patients at the time of transplantation, avoiding a window of over- or under-immunosuppression in the early post-transplant period; and implementation of non-invasive cell-free DNA testing to enable early detection of graft injury.

2. Improving long-term graft survival through improved HLA-matching and risk stratification based on 'eplet' typing

In general, solid organ allocation in Alberta does not take HLA matching into consideration except avoiding HLA antigens to which the recipient has produced HLA antibodies. Even for this aspect, different approaches are common as to what transplant programs consider acceptable or unacceptable due to the nature, complexity, availability, and urgency of the transplant.

Recently, the focus of HLA matching has shifted from compatibility at the antigen level to the 'eplet' level. It has been speculated that HLA eplet matching might be a better approach than antigen matching to improve patient outcomes. Growing evidence suggests that HLA eplet mismatch load can predict outcomes and provide guidance for risk stratification and matching. Although allocation of organs based on eplet matching is attractive, this approach is still in its infancy due to the lack of sufficient data and limited knowledge regarding the immunogenicity of different eplets. In addition, many studies rely on HLA imputation to identify eplets due to the lack of high-resolution HLA typing, which could lead to misinterpretation of data. Since Alberta is home to multiple large transplant programs with dedicated support of two histocompatibility and immunogenetics laboratories, the ATI is well positioned to contribute to addressing the gaps in knowledge regarding eplet matching.

Examples of potential projects include:

- Implementing high-resolution HLA typing of all solid organ transplant patients and donors to be able to define mismatches at eplet level accurately and correlate this data to clinical outcomes of transplant recipients.

- Participating in (and leading) Alberta components of a national eplet matching program through collaboration with the Genome Canada Transplant Consortium to test effectiveness and efficacy of a new allocation system.

- Understanding immunogenicity of different eplets to find the best approach for eplet matching and risk stratification through collaboration with the International HLA & Immunogenetics Workshop programs.

3. Exploiting the expertise in basic chemistry of ABO and glycan structures and glyco-immunology to expand matching possibilities

ABO-incompatible (ABOi) transplantation expands the individual donor pool for patients in crucial need of transplants. To enhance risk assessment of ABOi transplantation, accurate measurement of ABO antibodies is crucial. However, the current hemagglutination assay, with its low specificity and reproducibility, has many well-recognized limitations. Through collaborations with carbohydrate chemists and the Canadian Glycomics Network (GlycoNet), ATI researchers are revolutionizing the analysis of ABO antibodies by employing a Luminex bead-based approach. This method, globally recognized as the 'gold standard' in HLA antibody testing, has demonstrated its potential suitability for clinical use following validation in an international multi-centre proficiency study involving healthy controls. By improving the

characterization of ABO antibodies, including accurate determination of isotypes and subtype specificities, this innovative assay will contribute substantially to reliable ABOi transplant risk assessment.

Moreover, recent advances in ABO genotyping have revealed a higher incidence of ABO-A2 subgroup individuals (approximately 20%) in the population compared to previous estimates[48]. This finding is important as kidney transplants from ABO-A2 donors have been shown to be safe for patients who have low levels of anti-A antibodies[49–51]. Increased identification of ABO-A2 individuals as potential donors will expand access to transplantation and enhance equity especially for blood group B patients awaiting transplant, who traditionally face much longer waiting times due to demographic factors in distribution of ABO blood groups. With the expertise and novel detection tools being developed by ATI investigators, Alberta is uniquely positioned to play a crucial role in improving the risk assessment of ABO-A2 ABOi transplantation not only locally but globally, ultimately benefiting patients and improving outcomes.

Examples of potential projects include:

- Studying the differences between the hemagglutination assay and the levels of allograft-specific ABO antibodies using the novel Luminex bead-based assay created at University of Alberta.

- Studying the impact that current desensitization strategies undertaken to remove HLA antibodies have on ABO antibodies, with the goal of increasing access to transplantation for patients with the most difficult histocompatibility risks.

- Through national collaborations, evaluating the use of an ABO-adjusted cPRA calculator to address ABO inequity in Canadian transplant recipients.

Working Group 5: Improve Long-term Wellness for Transplant Patients

1. Strategies and interventions to empower patients to make transplanted organs last as long as possible

To improve graft and patient survival, there is a need for accessible and customizable programs to address modifiable factors (e.g., optimizing metabolic risk factors, stopping smoking, minimizing immunosuppression, and protecting renal function)[52]. It is important to empower patients with knowledge and self-management practices that they could use to optimize long-term outcomes (e.g., physical activity, support for medication adherence, and community support groups). Future research could ideally not only personalize which strategies would be the most relevant at the individual patient level but also identify what support would be needed to successfully promote long-term behaviour change.

Transplantation is not a cure: ensuring the longevity of the transplant also requires the patient to strictly adhere to many guidelines including medication, exercise, frequent check-ups/procedures to monitor rejection, medication side-effects and a support system. Many people are not set up for this extreme life change after transplant, whether it be obtaining proper insurance, organizing time off work for medical and laboratory appointments, or developing an effective support system to assist in coping with physical/mental health barriers both pre- and post-transplant. Mental, physical, and social empowerment is necessary for successful outcomes as most patients were not prepared for how difficult the transplant process (both before and after) would be, not only for the recipient, but also for the caregivers. Every patient should have easy and automatic access to psychology and mental health services, as well as the ability to connect with other patients in the transplant community with similar stories. Access to physical rehabilitation specialists and services both pre- and post-transplant was also highly recommended.

Examples of potential projects include:

- Exploring interventions to study effective supports and long-term follow-up care strategies for patients/caregivers and assess the impact on outcomes and quality of life.

- Evaluating the retrospective and prospective data for graft and patient survival to identify modifiable factors, targeting those with prospective interventions and evaluating long-term impacts on graft and patient outcomes.

2. Mental, physical and social empowerment at pre- and post-transplant transitions of care

Mental health, physical health, and social empowerment in solid organ transplantation are particularly important during transitions of care, between the pre- and post-transplant state and between pediatric to adult transplant programs. The American Society of Transplantation (AST) has recognized the importance and impact of pediatric-to-adult transitions in solid organ transplantation, detailing in 2015 several important recommendations including guidelines for the pediatric transplant team, challenges for the adult transplant team, strategies for integration into adult care programs, and addressing system issues[53].

Palliative care has an evolving role in the transplant process. It no longer applies only to "end-of-life" compassionate or hospice care, but also to care that begins as early as the time of diagnosis of a chronic medical condition. There is evidence to support integration of palliative care in solid organ transplantation with the goals of supporting care coordination, symptom management, and advance care planning[54]. Models for delivery have involved integrated care with both specialists and palliative care team members co-managing patients[54]. Although the studies to date have been small, solid organ transplant palliative care interventions have led to improvements in patients' symptom burden and quality of life. To reflect the valuable involvement of palliative care teams in transplantation, re-naming of this care should be considered (e.g., chronic supportive care team).

Examples of potential projects include:

- Studies to examine and address high rates of depression and anxiety across all solid organ transplant groups, directed both at patients undergoing transplantation as well as caregivers, a group with tremendous challenges in maintaining wellness[55].

- Studies looking at physical frailty and recovery of physical function, including evaluation of strategies to optimize recovery of physical function by undertaking pre-habilitation and post-habilitation interventions that address potentially modifiable factors such as poor nutritional intake and sedentary behaviour.

- Trials of pre-habilitation or post-habilitation interventions with virtual or hybrid delivery that could support patients in both rural and urban areas.

- Evaluation of the effectiveness of pediatric to adult transition programs.

- Evaluation of the impact of palliative care initiatives across the transplant continuum.

- Evaluation of mental health interventions for patients undergoing transplantation and for their caregivers.

3. Systemic data collection to guide decision-making and predict outcomes

The collection of standardized data at common timepoints across the continuum from pre- through post-transplant periods is a key priority to predict transplant outcomes, guide transplant decision-making, and guide conversations with patients regarding anticipated outcomes. Priority outcome measures extend beyond graft and patient survival data, including measured tests (e.g., Fried frailty testing[56], clinician-reported measures (e.g., Karnofsky performance score[57]), patient-reported outcomes (e.g., depression and anxiety screens, health-related quality of life), medical record data, and biological samples (e.g., biobanking, admissions/discharges, infections). It is important for different organ transplant groups to agree on a minimal dataset of harmonized measures that could be used across clinical trials, electronic health records and patient registries; this standardized minimal dataset of common measures would allow for comparisons across data in these platforms. Given that Alberta's entire provincial health care system will be using the electronic health record system EPIC (Connect Care) across acute care and some outpatient sites, there is incredible potential to develop a transplant outcome registry in this system. Patients should be able to answer surveys directly within the EPIC platform or within a secure research database[58].

Examples of potential projects include:

- Partnership with transplant centres in other provinces and countries to harmonize data collection using open-access registries and databases to compare with patient outcomes in Alberta.

- Development of artificial intelligence (AI)-based studies to test organ allocation and donor-recipient pairing algorithms and to test real-time immunosuppression regimens to improve patient and graft outcomes.

- Evaluation of variations in outcomes based on ethnicity, socioeconomic status, sex, and gender, as well as rural vs. urban locale. This could highlight differences in access to transplantation, to follow-up care, and to medications.

- Collaboration with health economists to determine the economic costs and benefits associated with transplantation and transplant care.

Discussion

The purpose of this strategic planning exercise was to establish an effective mechanism to identify and prioritize key research needs within the Alberta donation and transplantation ecosystem. The primary goal was to establish an effective framework that would not only connect research expertise with patient, family, donor, and health system needs, but also foster collaboration. The next steps for the ATI are to develop a comprehensive strategy to resource and initiate projects within the identified research priorities, including exploring potential funding sources, building collaborations, establishing plans for measuring impact.

A unique aspect of this work is the inclusion of the full spectrum of topics linked to organ donation and transplantation from a wide range of perspectives. Working Group 1 focused on living donation, integrating the perspectives of living donors and recipients alongside discussion of clinical processes. Working Group 2 focused on the deceased donation system, ranging from family experiences, the influence of culture, religion, and ethnicity, and the process for consent conversations with families making decisions at an extraordinarily difficult time. Working Group 3 emphasized understanding the current health and graft function of Albertans who have undergone transplantation, as this knowledge plays a critical role in improving transplant outcomes across the province. Working Group 4 advocated for implementation of an HLA (and ABO) typing strategy and highlighted the need for a comprehensive transplant outcomes data system to measure the impact of changes to the allocation system. Finally, Working Group 5 prioritized standardized collection of data at several key timepoints, from pre- through post-transplantation from a perspective of empowering patients and their families. This data would be an invaluable tool for predicting transplant outcomes, guiding decision-making processes, and facilitating informed discussions with patients.

A common idea raised by each of the Working Groups was the importance of systematically collecting and analyzing long-term outcome data on patients (both living donors and transplant recipients) to improve decision-making and patient outcomes. Each group discussed developing a comprehensive and long-term patient-tracking (and graft-tracking) strategy to support potential projects. The theme of systemic data infrastructure extended to Working Group 2, which discussed establishing a provincial living-donor registry that would serve multiple purposes, such as facilitating accurate donor identification, efficiently reporting outcomes, and supporting the implementation of interventions aimed at improving the health and well-being of living donors in Alberta. Alberta is in a unique position to capture long-term patient outcome data and use this to inform research and decisions with the recent implementation of the Alberta ConnectCare system[2]. This system provides a harmonized province-wide electronic medical record that could be used to extract standardized data elements entered for the purposes of clinical care.

As a provincial initiative, this work aimed to mobilize stakeholders from different institutions and organizations across Alberta, fostering a collaborative environment to collectively address identified priorities. The ATI recognizes the importance of engaging the broad community, including experts from various disciplines who were not part of this process, to support and collaborate with ATI researchers to take this work forward. While this strategic plan is specific to Alberta and tailored to the research expertise and needs present in the province, it is worth noting that the priorities identified are broadly consistent with those of other transplant programs[59–63]. Alignment of these priorities with other jurisdictions may provide opportunities to advance research through national and international collaborations, allowing the impactful research conducted in Alberta to extend its reach and positively impact donors, patients, and families worldwide.

Appendix 1.

Working Group (WG) Leads and members.

Name	Role	Title	Affiliation/location
WG1: Advance the culture and practice of living donation			
Ngan Lam	Academic Lead	Transplant nephrologist	University of Calgary
Anne Halpin	PFD Lead	Living kidney donor/Assistant clinical professor	University of Alberta
Michelle Skogstad	Group member	Living donor coordinator (Liver/lung)	Alberta Health Services, Edmonton
Wenjie Wang	Group member	Medical lead/living donor kidney program	University of Calgary
Sita Gourishankar	Group member	Medical lead/living donor kidney program	University of Alberta
Uchenna Ibelo	Group member	Living donor kidney coordinator	Alberta Health Services, Calgary
Jana Costa	Group member	Living donor kidney coordinator	Alberta Health Services, Calgary
Flavia Robles	Group member	Executive Director	Kidney Foundation, Northern Alberta& Territories
Kathy Yetzer	Group member	Associate Director, Living Donation & Transplantation	Canadian Blood Services
Darlene Jagusic	Group member	Living Donation & Transplantation Manager	Canadian Blood Services
WG2: Advance the culture and practice of deceased donation			
Andreas Kramer	Academic Lead	Clinical associate professor, SEND physician	University of Calgary
Jennifer Woolfsmith	PFD Lead	Mother of a deceased donor	Calgary
Toby Boulet	PFD Lead	Father of a deceased donor	Lethbridge
Bernie Boulet	PFD Lead	Mother of a deceased donor	Lethbridge
Linda Powell	Group member	President	Alberta ORGANization Group
Laura Grantham	Group member	Project manager	Alberta Organ and Tissue Donation Agency, Government of Alberta
Rachel Wilkins	Group member	Administrative support for SEND program	Alberta Health Services, Calgary
Deanna Paulson	Group member	Director of Donation/Transplant Services	Alberta Health Services, Edmonton
Dennis Djogovic	Group member	Clinical professor, SEND physician	University of Alberta
Meagan Mahoney	Group member	Pediatric intensivist, SEND physician	Alberta Health Services, Calgary
Kerry Holliday	Group member	Project manager for SEND program	Alberta Health Services, Calgary
Sean Spence	Group member	SEND physician	Alberta Health Services, Lethbridge
Candice Bohonis	Group member	Senior tissue specialist	Alberta Health Services, Edmonton

Manuel Escoto	Group member	Kidney transplant recipient	Edmonton

WG3: Optimize graft use and quality

Kieran Halloran	Academic Lead	Lung transplant specialist	University of Alberta
Murray Wilson	PFD Lead	Liver transplant recipient	Calgary
Braulio A. Marfil-Garza	Group member	Clinical fellow/pancreatic islet transplantation	University of Alberta
Andrew Pepper	Group member	Assistant professor, islet research	University of Alberta
Janet A. W. Elliott	Group member	Professor/cryobiology research	University of Alberta
Jason Acker	Group member	Professor, cryobiology research	University of Alberta
Tumelo Mokoena	Group member	Quality assurance/tissue transplant	Alberta Health Services, Edmonton

WG4: Improving immunological health for transplant patients

Esme Dijke	Academic Lead	Assistant professor	University of Alberta
Sean Delaney	PFD Lead	Kidney transplant recipient	Edmonton
Andrew Masoud	Group member	Postdoctoral fellow	University of Alberta
Gina Rayat	Group member	Professor	University of Alberta
Lori West	Group member	Professor/Director of Alberta Transplant Institute	University of Alberta
Alim Hirji	Group member	Respirologist	University of Alberta
Simon Urschel	Group member	Pediatric cardiac transplant	University of Alberta
Ben Adam	Group member	Anatomical pathologist	University of Alberta
Braulio A. Marfil-Garza	Group member	Clinical fellow/pancreatic islet transplantation	University of Alberta

WG5: Improve long-term wellness for transplant patients

Puneeta Tandon	Academic Lead	Transplant hepatologist	University of Alberta
Lindsey Kemp	PFD Lead	Mother of a two-time heart transplant recipient	Edmonton
Deb Isaac	Group member	Cardiologist	University of Calgary
Kari Furnell	Group member	Regional manager	Canadian Liver Foundation, Alberta Chapter
Jennifer Conway	Group member	Pediatric cardiologist	University of Alberta
Nicholas Mitchell	Group member	Psychiatrist	Alberta Health Services, Edmonton
Carlos Cervera Alvarez	Group member	Infectious disease specialist	University of Alberta

Emily Christie	Group member	Transplant nephrologist	University of Alberta
Diana Mager	Group member	Professor	University of Alberta
Cori Knowles	Group member	Lead medical advisor	Paladin Labs

Members of the ATI Research Committee in September 2022

Name	Title	Affiliation
Andrew Masoud	Postdoctoral fellow	University of Alberta
Gina Rayat	Professor	University of Alberta
Jason Acker	Professor	University of Alberta
Michael Khoury	Assistant professor	University of Alberta
Kieran Halloran	Associate professor	University of Alberta
Esme Dijke	Assistant professor	University of Alberta
Allan Murray	Professor	University of Alberta
Braulio Marfil Garza	Clinical fellow/pancreatic islet transplantation	University of Alberta
Carlos Cervera Alvarez	Associate professor	University of Alberta
Lindsey Kemp	Mother of a two-time heart transplant recipient	Alberta Transplant Institute

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