


Changing Paradigms in the Management of Rejection in Kidney Transplantation: Evolving From Protocol-Based Care to the Era of P4 Medicine

Canadian Journal of Kidney Health and Disease
Volume 4, 2017: 1–12
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sagepub.com/journalsPermissions.nav
DOI: 10.1177/2054358116688227
journals.sagepub.com/home/cjk


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Abstract

Purpose of review: P4 medicine denotes an evolving field of medicine encompassing predictive, preventive, personalized, and participatory medicine. Using the example of kidney allograft rejection because of donor-recipient incompatibility in human leukocyte antigens, this review outlines P4 medicine's relevance to the various stages of the kidney transplant cycle.

Sources of information: A search for English articles was conducted in Medline via OvidSP (up to August 18, 2016) using a combination of subject headings (MeSH) and free text in titles, abstracts, and author keywords for the concepts kidney transplantation and P4 medicine. The electronic database search was expanded further on particular subject headings.

Findings: Available histocompatibility methods exemplify current applications of the predictive and preventive domains of P4 medicine in kidney transplant recipients' care. Pharmacogenomics are discussed as means to facilitate personalized immunosuppression regimens and promotion of active patient participation as a means to improve adherence.

Limitations: For simplicity, this review focuses on rejection. P4 medicine, however, should more broadly address health concerns in kidney transplant recipients, including competing outcomes such as infections, malignancies, and cardiovascular disease. This review highlights how biomarkers to evaluate these competing outcomes warrant validation and standardization prior to their incorporation into clinical practice.

Implications: Consideration of all 4 domains of the P4 medicine framework when caring for and/or studying kidney transplant recipients has the potential of increasing therapeutic efficiency, minimizing adverse effects, decreasing health care costs, and maximizing wellness. Technologies to gauge immune competency, immunosuppression requirements, and early/reversible immune-mediated injuries are required to optimize kidney transplant care.

Abrégé

Objectif de la revue: La médecine des 4P constitue une approche évolutive qui englobe la médecine prédictive, préventive, personnalisée et participative. En prenant l'exemple du rejet du greffon pour cause d'incompatibilité des antigènes HLA entre le donneur et le receveur en transplantation rénale, cette revue fait état de la pertinence de faire intervenir la médecine des 4P dans les différentes étapes du processus menant à la greffe.

Sources: Une recherche a été effectuée sur Medline via OvidSP pour répertorier les articles publiés en anglais avant le 18 août 2016 au sujet de la transplantation de rein et de la médecine des 4P. Les articles mentionnant ces concepts dans la rubrique des objectifs de l'étude, dans le titre, dans l'abrégé ou dans les mots-clés listés par les auteurs ont été retenus. La recherche sur la base de données électronique a été davantage élargie pour certains sujets de rubriques.

Constatations: Les méthodes d'histocompatibilité disponibles illustrent bien les applications actuelles des branches prédictive et préventive de la médecine des 4P du côté des soins prodigués au receveur de la greffe de rein. La pharmacogénomique est pressentie comme moyen de mieux personnaliser le protocole d'immunosuppression du receveur et de favoriser la participation active du patient pour améliorer son adhérence.

Limites: Pour simplifier la recherche, la revue s'est concentrée sur les rejets de greffon. La médecine des 4P devrait toutefois tenir compte des préoccupations de santé pour les receveurs de greffe de manière plus globale en prenant également en compte les risques concurrents tels que les infections, le développement de tumeurs malignes ou les maladies cardiovasculaires. Cette revue met en lumière la manière dont les biomarqueurs, pour évaluer ces risques, justifient une validation et de la standardisation avant leur intégration aux pratiques cliniques.



Conclusions: Le fait de tenir compte des 4 domaines de la médecine des 4P au moment de prodiguer des soins ou d'étudier le cas des receveurs de greffe de rein a le potentiel d'améliorer l'efficacité thérapeutique, de minimiser les effets indésirables, de réduire les coûts des soins de santé et de maximiser le bien-être des patients. Afin d'optimiser les soins en transplantation rénale, des méthodes permettant d'évaluer la compétence immune, les exigences en immunosuppression ainsi que les lésions à médiation immunitaire précoces ou réversibles sont nécessaires.

Keywords

pharmacogenomics, biomarkers, surveillance, immune competency, adherence

Received August 31, 2016. Accepted for publication November 17, 2016.

What was known before

The management of kidney transplant recipients (KTRs) is often determined by transplant center's protocols; however, this "one-size-fits-all" approach fails to proactively address individual KTRs' needs and may contribute to the lack of improvement in long-term outcomes. P4 medicine provides a comprehensive framework for individualized care in kidney transplantation.

What does this add

P4 medicine denotes an evolving field in medicine focused on disease prediction and prevention, personalization of care, and promotion of patient participation. Using the example of kidney allograft rejection, because of donor-recipient incompatibility in human leukocyte antigens, we demonstrate the roles of (1) immune sensitization and immune competency in *predicting* individual patient's risk of rejection, (2) minimization of donor-recipient incompatibility in *preventing* rejection, (3) pharmacogenomics in *personalizing* immunosuppression regimens, and (4) enhancing patient *participation* in improving adherence and wellness.

Implications for Future Research/Policy

The field is in need of technology to gauge individual KTRs' immune competency and immunosuppression requirements, noninvasive biomarkers for prediction and early diagnosis of subclinical rejection, and strategies to promote engagement of both patients and society at large. Large prospective multicenter studies are required to advance knowledge in this field and improve KTRs' care.

Introduction

Kidney transplantation is the preferred renal replacement therapy in patients with end-stage renal disease¹; however, allograft rejection remains a major barrier to successful transplantation. Although the incidence of acute rejection has decreased in recent years thanks to effective induction and maintenance immunosuppression therapies²⁻⁶ and advancements in histocompatibility methods,⁷ long-term allograft outcomes have not shown much improvement. This has been largely attributed to chronic rejection and nonadherence to immunosuppression.⁸

Following transplantation, kidney transplant recipients (KTRs) are prescribed standard induction and maintenance immunosuppression regimens governed by each transplant center's protocols. Yet this "one-size-fits-all" approach may, inadvertently, overlook the diversity of treatment effects observed across KTRs. This diversity is governed, among others, by each KTR's genome, comorbidities, lifestyle, and environment.

P4 medicine denotes an evolving field in medicine, which takes a systems approach to health and disease. This holistic and integrative framework includes 4 domains focused on disease prediction and prevention, personalization of care, and promotion of patient participation.⁹ This review illustrates applications of P4 medicine in kidney transplant care. For the sake of simplicity, this review is focused on kidney allograft rejection and the roles of (1) immune sensitization in predicting KTRs' risk of rejection, (2) minimization of donor-recipient incompatibility in preventing rejection, (3) pharmacogenomics in personalizing immunosuppression regimens, and (4) attention to KTRs' priorities, values, beliefs, and preferences for enhancing patient participation

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and adherence. Future directions and challenges identified to date are also discussed.

PI: Prediction of Kidney Transplant Rejection

Immune Sensitization and Organ Allocation

KTRs' susceptibility to rejection is determined by their degree of immune sensitization. Pregnancies, blood transfusions, and previous transplants can result in immune sensitization against "nonself" human leukocyte antigens (HLA). Immune sensitization is estimated in transplant candidates by panel reactive antibody (PRA) testing.¹⁰ Sensitive and specific solid-phase assays allow determination of specific HLA to which anti-HLA antibodies bind. Consequently, calculated PRA (cPRA) estimates the percentage of donors with unacceptable HLA for a given patient. A Canadian cPRA calculator, which considers molecular donor HLA typing at the HLA-A, HLA-B, HLA-C, DRB1, DRB3/4/5, DQB1, DQA1, DPA1, and DPB1 loci, is available to support the Canadian Blood Services Transplant Programs' and local transplant programs' organ allocation decisions.¹¹

Currently, organ allocation decisions are guided by virtual crossmatch results. Virtual crossmatches rely on knowledge of the proposed donor's HLA type and kidney transplant candidates' anti-HLA antibody specificities. By ensuring the absence of preformed donor-specific anti-HLA antibodies (DSA), virtual crossmatches have been deemed highly sensitive in *predicting* donor-recipient compatibility.¹² Virtual crossmatches, thus, increase transplantation success¹² and decrease costs associated with allograft rejection.¹³ Centers conducting transplantation across the DSA barrier, on the contrary, report a greater risk of antibody-mediated rejection (ABMR). This risk is more pronounced the greater the DSA level and when DSA results in a positive crossmatch,¹⁴ as determined by flow cytometry and complement-dependent cytotoxicity assays. Highly sensitized patients, who possess a wide selection of antibodies against HLA, are, therefore, less likely to undergo transplantation and more likely to die on the waiting list.^{15,16}

Desensitization

Shortages in organs available for transplantation lead some highly sensitized candidates who have incompatible living donors to consider transplantation in the presence of DSA. Transplantation across HLA-incompatible donor-recipient pairs, or in the presence of DSA, is made possible by desensitization. Although desensitization protocols may vary across centers, they typically include an alloantibody-depleting modality (eg, plasmapheresis/immunoabsorption), a B-cell-depleting therapy (eg, rituximab and bortezomib), and intravenous immunoglobulin (IVIg).¹⁷ Although desensitization has been shown to significantly improve survival among KTRs in comparison with remaining on dialysis,^{18,19}

it does not abrogate the risk of ABMR,²⁰ and the risk of allograft loss remains high.²¹⁻²⁵

Future Directions in Predictive Medicine

Immune competency. In addition to HLA incompatibility, the risk of experiencing rejection also depends on KTRs' immune competency. Immune competency is influenced by age, sex, genetic predisposition, and comorbidities. For example, immune competency is considered to decrease with age.^{26,27} This has been related to lower numbers of naive T cells and progenitor B cells in the elderly.²⁸ Despite their clinical relevance, however, no immune competency assays are readily available in clinical practice. This is because commercial immune assays, such as Immuknow, demonstrate poor sensitivity and modest specificity for detecting rejection.²⁹ Assays like enzyme-linked immunospot assay (ELISPOT) lack standardization and cutoff values.³⁰ Furthermore, noncommercial laboratory markers of immune function such as serum immunoglobulins, serum complement factors, and peripheral blood lymphocyte subpopulations also lack standardized cutoff values and do not provide information on the functionality of the humoral, complement, or cellular immune systems, respectively.³⁰ Thus, biomarkers for immune competency evaluation as *predictors* of the risk of experiencing rejection warrant further study.

P2: Prevention of Immune-Mediated Injuries

Donor-Recipient Compatibility

Although the risk of ABMR is decreased in the absence of preformed DSA, ABMR can only be *prevented* if "de novo" DSA (dnDSA) are also avoided. *Prevention* of dnDSA may be achieved through optimized donor-recipient matching across HLA loci (ie, class I [HLA-A, HLA-B, HLA-C] and class II [HLA-DR, HLA-DQ, HLA-DP]). With the advent of more effective induction and maintenance immunosuppression and focus on equitable access to transplantation, efforts to optimize donor-recipient HLA compatibility have lessened.³¹ Importantly, despite a growing appreciation of incompatibility at the level of HLA-DQ as a predictor of dnDSA,³²⁻³⁶ neither compatibility at the level of HLA-DQ nor at the level of HLA-DP is routinely considered by many organ allocation schemes.³⁷

Kidney Paired Donation

A unique opportunity to *prevent* immune-mediated injuries is made possible through kidney paired donation (KPD) programs. KPD enables kidney transplant candidates with willing yet incompatible living donors to join a registry of other incompatible pairs in order to find potentially compatible donors.³⁸ KPD programs represent a promising opportunity to improve transplant rates among highly sensitized patients,

maximize donor-recipient HLA compatibility, and minimize risks of immune-mediated injuries across *all* living donor KTRs as well as sensitized patients with high DSA levels, in whom desensitization failure is common.^{14,39-41} Indeed, as of December 2013, the Canadian KPD program facilitated 240 transplantations including 10% with cPRA \geq 97%. The unique characteristics of the Canadian interprovincial KPD program are summarized by Cole et al.⁴²

Highly Sensitized Patient Program

Another Canadian initiative set to facilitate access to transplantation among highly sensitized kidney transplant candidates, and at the same time minimize the risk of rejection, is the Highly Sensitized Patient (HSP) program. Through successful collaboration between the Canadian Blood Services, the Canadian health care systems, and individual transplant programs across Canada, the HSP program helps highly sensitized patients to be matched with compatible donors anywhere in Canada. Donor-recipient compatibility is determined by a virtual crossmatch and confirmed by a flow crossmatch. According to the Canadian Blood Services 2014-2015 annual report, by the end of March 2015, the HSP program had enabled 108 transplants, which would have otherwise been unlikely to occur.⁴³

Future Directions in Preventive Medicine

Minimizing mismatches at the epitope level. Although kidney transplantation in the absence of preformed DSA helps minimize the risk of rejection, a more refined strategy for *preventing* rejection is by minimizing mismatches at the epitope level. It is now accepted that HLA antibodies recognize a variety of epitopes on HLA molecules and that the identity of these epitopes can be determined from high-resolution allele-level HLA typing. Molecular determination of HLA compatibility at the allele level, hence, represents a more accurate, albeit more costly and time-consuming, approach to identifying compatible donors.⁴⁴ HLAMatchmaker is a computer algorithm capable of estimating incompatibility at the epitope level from high-resolution donor-recipient allele types.⁴⁵⁻⁴⁸ Minimizing structural incompatibility between donors and recipients has been proposed as a novel strategy to *prevent* dnDSA,⁴⁹ chronic antibody-mediated injury,⁵⁰ and allograft failure.^{51,52} To overcome the limited availability of high-resolution HLA typing, low-resolution to high-resolution prediction tools^{53,54} are often used to estimate donor-recipient compatibility at the allele level. These tools, however, were developed based on HLA frequencies in non-Canadian populations, and their performance warrants evaluation in Canadian donors/KTRs.

Pronounced polymorphisms in HLA, thus, make KTRs susceptible to rejection when exposure to immunosuppression is insufficient to abrogate alloimmune responses.

P3: Personalized Immunosuppression Regimens and Posttransplant Monitoring

Personalized Therapy

Immunosuppression regimens following kidney transplantation typically include induction and maintenance therapies.²⁻⁶ The type and dose of prescribed immunosuppression are usually determined by transplant centers' protocols. Changes to drug regimens often occur in reaction to adverse effects of immunosuppression or when drug levels (typically calcineurin inhibitors [CNI]) deviate from the recommended therapeutic range.

Trough drug levels are currently used to verify adequate exposure to immunosuppression. In children, physiological changes during growth give rise to increased variability in drug effects.⁵⁵ This warrants frequent monitoring of children to verify that their drug exposure remains within the therapeutic window. Pronounced fluctuations in trough CNI levels have been linked with clinical and subclinical immune-mediated allograft injuries.⁵⁶⁻⁵⁸

Future Directions in Personalized Therapy

In an effort to increase drug efficacy while minimizing toxicity, combinations of immunosuppression medications with different mechanisms of action and side effects are prescribed.⁵⁹ There are currently no tests to identify KTRs' likelihood to respond to a particular medication. A T-cell activity assay, which relies on *in vitro* stimulation of isolated peripheral blood mononuclear cells when exposed to immunosuppression, however, has been recently studied.⁶⁰ Polymorphisms in genes encoding for interferon gamma or tumor necrosis factor alpha are also being evaluated to taper immunosuppression regimens to each KTRs' needs.⁶¹⁻⁶⁵

Pharmacogenomics also offer a more proactive approach to immunosuppression choices. Pharmacogenomics encompass the genetic determinants of pharmacokinetics and pharmacodynamics.⁶⁶ Pharmacokinetics (ie, the bodily absorption, distribution, metabolism, and excretion of drugs) and pharmacodynamics (ie, the physiological effects caused by a specific drug concentration) differ among individuals, giving rise to variability in KTRs' responses to drugs.

The cytochrome P450 system is involved in the pharmacokinetic handling of tacrolimus,⁶⁷ and genetic polymorphisms affecting this system can explain variations in dosages required to achieve therapeutic levels. In a case series by Lampreabe et al., patients with CYP3A5*1 allele or the null allele in GSTM1 required higher doses to ensure a therapeutic effect. In addition to the intended drug effects, genetic polymorphisms can also lead to varied side effect profiles. KTRs carrying the CYP3A4*1/CYP3A5*1 or CYP3A4*1B/CYP3A5*1 genotypes, for example, are at

greater risk of experiencing tacrolimus-related nephrotoxicity than patients carrying the CYP3A4*1/CYP3A5*3 genotype.^{66,67}

Genetic polymorphisms can also affect the pharmacodynamics of immunosuppression medication. For example, *ABCB1* encodes the multidrug resistance protein 1, an efflux pump that removes CNI from intracellular compartments. The 3435C>T single-nucleotide polymorphism (SNP) in *ABCB1* alters interleukin 2 production by T cells, which can lead to more pronounced immunosuppression.⁶⁸ Pharmacogenomics can, therefore, inform KTRs' risk of under- and over-immunosuppression.^{58,69}

Personalized Surveillance

Allograft injury is typically identified by rising serum creatinine and proteinuria. These tools, however, are nonspecific and, consequently, cannot guide targeted treatment to address a specific disease.⁷⁰ The diagnosis of rejection relies on DSA and histopathological findings on allograft biopsies. Diagnoses are often assigned by pathologists based on the Banff scoring system⁷¹ using allograft biopsies that are conducted for cause (in the presence of allograft dysfunction) or for surveillance (to detect subclinical rejection).

Nowadays, dnDSA are also used for surveillance in KTRs. In 2013, consensus guidelines proposed DSA monitoring posttransplant to be stratified by baseline immune risk⁷² such that high-risk patients (ie, desensitized or DSA positive/crossmatch negative) undergo DSA screening and surveillance biopsies by 3 months posttransplant, intermediate-risk patients undergo DSA monitoring within the first month, and low-risk patients (nonsensitized) are screened for DSA at least once 3 to 12 months posttransplant. Identification of DSA in intermediate and low-risk patients should prompt a biopsy to confirm tissue injury. Although antibody titer,⁷³ subclass,⁷⁴ and complement binding capacity as determined by the C1q binding assay⁷⁵ may further refine risk prediction, the recommended monitoring schedule, effectiveness of available therapies, and cost-effectiveness of long-term DSA monitoring are a matter of ongoing debate.^{72,76,77}

The field is in need of monitoring schedules tailored to individual patients' risk. Closer monitoring is particularly important when there is concern of under-immunosuppression because of immunosuppression minimization or nonadherence.

Future Directions in Personalized Surveillance

Biopsies can be used for transcriptomics, which study the relationship between clinical phenotypes and gene expression. Halloran and colleagues developed a microarray-based messenger RNA assessment tool, which identifies, among others, molecular patterns representative of T-cell-mediated rejection (TCMR) and ABMR.⁷⁸ In a recent study of 164 indication biopsies, 3 ABMR subphenotypes have been

confirmed by this Molecular Microscope™ System, which include early peritubular capillaritis/glomerulitis-dominant (pg), late chronic glomerulopathy-dominant (cg), and combined pgcg phenotypes. In addition to timing posttransplant, each subphenotype differed in molecular features, accompanying TCMR, HLA antibody, and probability of nonadherence.⁷⁹ Transcriptomics have also been studied as predictors of histological and functional decline. In a recent multicenter prospective study (the Genomics of Chronic Allograft Rejection (GoCAR) Study), which included discovery (N = 159 biopsies) and validation (N = 45 biopsies) cohorts, messenger RNA levels of 13 genes in biopsies conducted 3 months posttransplant were predictive of allograft fibrosis and loss by 12 months posttransplant.⁸⁰

Transcriptomics, proteomics, and metabolomics are examples of biomarkers, which may be found in the peripheral blood and urine. Such biomarkers are appealing surveillance tools because they are less invasive than biopsies and they may predict rejection prior to any clinically evident and irreversible injury.⁸¹ Transcriptomics represented by overexpression of microRNA in peripheral blood mononuclear cells, for example, may distinguish patients with and without acute rejection.⁸²

Proteomics have also been proposed as diagnostic tools in KTRs. For example, urinary C-X-C motif chemokine ligand 9 (CXCL9) and CXCL10 have also been proposed for early detection of acute kidney allograft rejection.⁸³⁻⁸⁵ CXCL10 to creatinine ratios have been linked to microvascular inflammation and TCMR.^{83,86} Moreover, in a recent prospective multicenter study including 280 adult and pediatric KTRs, increased CXCL9 levels were detectable up to 30 days before clinical rejection.⁸⁷ These urinary biomarkers can be readily translated into clinical practice because they can be measured by a low-cost enzyme-linked immunosorbent assay (ELISA).^{86,87} Randomized controlled clinical trials are awaited, however, to confirm their utility in guiding therapy and improving kidney transplant outcomes.⁸⁵

Last, metabolomics, the study of high-throughput analysis of small-molecule metabolites, remains at its infancy in KTRs. Yet it is evolving into a promising tool to assess organs at risk of rejection and identify organs that have been damaged by immunosuppressive drugs.⁸⁸ The utility of urinary metabolomics for noninvasive diagnosis of TCMR was evaluated using 277 urine samples from 57 KTRs. A selection of 134 unique metabolites was assessed by quantitative mass spectrometry to detect a selection of metabolites capable of discriminating TCMR on surveillance and for-cause biopsies versus borderline rejection and no TCMR. A group of 10 metabolites (representing products of activated macrophages, Th1 cells, and metabolites involved in propagation of inflammatory signals) were found to be sensitive and specific noninvasive tools for TCMR.⁸⁹

Importantly, genomics, proteomics and metabolomics can be combined into a "cross-platform" signature.⁹⁰ A composite signature, including a combination of metabolomics

and transcriptomics developed using solely biopsy specimen-matched urine samples, predicted future acute cellular rejection when applied to pristine samples taken days to weeks before biopsy.⁹¹ Similarly, compared with gene expression profiles alone, cross-platform biomarkers have increased sensitivity and specificity when identifying operational tolerance.⁹⁰ Tolerance develops when the immune response to the “foreign” allograft or antigen wanes. This results in a generalized state of nonresponsiveness.⁹² A combination of transcriptional profiling with flow cytometry of peripheral blood to determine patients’ immunological tolerance of kidney allografts appears to be an appealing future strategy for monitoring KTRs.

P4: Participatory Medicine Catered to Individual KTRs

The final “P” of P4 medicine refers to “patient participation” or KTRs’ engagement in their care. Patient engagement has been defined as “the actions people take for their health and to benefit from health care.”^{93,94} Promotion of participatory medicine can only be achieved when acknowledging patients’ priorities, values, beliefs, and preferences.⁹⁵ Patient participation, in turn, is expected to promote greater adherence to immunosuppression regimens.

Adherence

Nonadherence to immunosuppression is the most common preventable cause of rejection, allograft failure, and patient mortality.^{8,96,97} Readmissions and graft failure, resulting in dialysis resumption or retransplantation, impose additional costs and burden on health care systems.⁹⁸ Nonadherence has been evaluated by patient self-reporting, electronic monitoring of pill bottles, prescription refill rates, and drug level monitoring. Each of these methods, however, has inherent flaws as discussed by Prendergast and Gaston.⁹⁶ The prevalence of nonadherence has, therefore, been difficult to estimate; yet prior reports estimate nonadherence to range from 22% to 33% of KTRs,⁹⁹⁻¹⁰¹ and despite high adherence during the first 6 months posttransplant (91.5%), it steadily tapers off over time (to 82.7% at 3 years posttransplant).¹⁰² Nonadherence is more frequently observed among adolescents than preadolescent children¹⁰³ and adults (24 to 44 years of age).¹⁰⁴

The culprits of nonadherence highlight the complexity of this phenomenon. The World Health Organization attributes nonadherence to 5 interacting dimensions: (1) patient-related factors such as health beliefs, self-efficacy, and health literacy; (b) social and economic factors such as social supports and affordability of medication; (c) therapy-related factors such as adverse effects, duration of treatment, and treatment complexity; (d) condition-related factors, including comorbidities or cognitive status; and (e) health care system-related and health care team-related factors.¹⁰⁵

Several interventions have been proposed to promote adherence when modifiable risk factors are at play. The type¹⁰⁶ and dosing frequency¹⁰⁷ of the immunosuppression, for example, can be modified to attenuate nonadherence. Furthermore, because forgetting is one of the most common causes for nonadherence among adolescents¹⁰⁸ (as well as the elderly¹⁰⁹), pillboxes can be implemented.¹⁰⁸ Social supports from family and community alike have also been deemed effective in promoting adherence.^{108,110} Several multicenter studies focused on adherence are underway.¹¹¹⁻¹¹² TAKE-IT evaluates the effectiveness of a clinic-based intervention, including educational, organizational, and behavioural components, in improving immunosuppressive medication adherence among adolescent and young adult kidney transplant recipients¹¹¹; POSITIVE-adherence evaluates health care system factors affecting treatment adherence (<https://clinicaltrials.gov/ct2/show/NCT02318030>); and MAGIC seeks to assess the effect of SystemCHANGE™ intervention, designed to improve medication adherence behaviors by identifying and shaping routines, involving supportive others in routines, and using medication taking feedback.¹¹²

Future Directions in Participatory Medicine

In addition to patient adherence, *participatory* medicine also seeks to measure KTRs’ wellness. There has been a growing interest in patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs), which can be evaluated by measurement instruments, or questionnaires, which are completed by patients. PROMs include various metrics capable of assessing health, illness, or health care benefits from the patient’s perspective. In contrast, PREMs capture information about the health care experience as perceived by patients.¹¹³ They can refer to issues such as information provision, timeliness of transport, and family members’ access to health professionals.^{113,114} Incorporation of PROMs and PREMs into routine clinical practice offers the potential for highlighting relevant symptoms and changes in symptoms, enhancing the understanding of patient experiences, promoting patient adherence to their treatment,^{94,96,113,115} and, in turn, result in improved patient outcomes.¹¹³

In addition to PROMs and PREMs, other ways of appreciating patient wellness and experience are through initiatives in which health staff learn from patients. In 2007, the British Columbia Ministry of Health founded the “Patients as Partners” initiative, which considers patients equally involved in the health care team as medical staff.¹¹⁶ This concept takes into account that patients suffering from chronic diseases develop “experiential knowledge,” which can complement clinicians’ scientific knowledge. This experiential knowledge has also been used for training health science students (Faculty of Medicine at the University of Montreal) and for peer-mentoring patients with chronic disease by patient trainers.^{116,117} In the case of research prioritization, prior prioritization methods primarily included expert panels, consensus conferences, voting surveys, focus groups, and interviews.

However, when setting research priorities, the perspective of patients, caregivers, and health care providers must also be considered.¹¹⁸ Surprisingly, a systematic review on patient engagement showed that only 4 out of 16 studies on research prioritization in kidney disease explicitly mentioned patient participation.¹¹⁸ Some challenges to patient participation in research include increased costs and time as well as the risk of “tokenistic engagement.”¹¹⁹

In addition to individual participation in their care, decisions with an impact on society as a whole must engage a larger community. Novel initiatives to engage and allow patients, caretakers, and communities to voice their preferences are underway (eg, <http://www.cntrp.ca/news/tag/patient-engagement>, <http://www.kidney.ca/Can-SOLVE-CKD>, and <http://songinitiative.org/song-tx/>). In relation to kidney allograft rejection, such forums may be consulted to identify patients’ preferences and priorities on decisions affecting organ allocation schemes and access to transplantation.

Challenges to Achieving P4 Medicine

P4 Medicine and Competing Complications Following Kidney Transplantation

P4 medicine is an attractive framework for KTR care because it intends to simultaneously account for competing complications. Rejection is often considered a consequence of under-immunosuppression. Over-immunosuppression, on the contrary, may give rise to complications such as infections, malignancies, and cardiovascular disease. Importantly, posttransplant incidence of these complications may be compounded by KTRs’ individual genetic predisposition. Recent genome-wide association studies, for example, implicate polymorphisms in genes responsible for innate and acquired immune human host defenses. HLA assumes a prominent role as a predictor of susceptibility to many infectious diseases.^{120,121} When considering cancer risk, nonmelanoma skin cancers (NMSC) occur at a greater frequency in KTRs than the general population. NMSC have been linked to immunosuppression-related (eg, glucocorticoid receptor polymorphisms¹²²) and immunosuppression-unrelated (eg, SNPs in glutathione S-transferases¹²³ and methylenetetrahydrofolate reductase¹²⁴) genetic predictors. Moreover, the pathogenesis of posttransplantation lymphoproliferative disorder (PTLD) has been linked both to polymorphisms in the Epstein-Barr virus genome, as well as translocations, various copy number variations, DNA mutations, and polymorphisms in KTR genome. These are described in detail in Morscio et al.¹²⁵

Despite significant efforts to study genetic biomarkers of cardiovascular disease in the general population,^{126,127} this field remains largely unstudied among KTRs. Although P4 medicine could better guide the care for KTRs, it is unlikely to eliminate all uncertainty related to competing complications following kidney transplantation. Population-level studies boasting large sample sizes and conducted in diverse

ethnicities are needed to evaluate the added role of genetic biomarkers in predicting the development of these complication over and above traditional risk factors.

Technologies to Enable P4 Medicine

Despite the potential advantages of biomarkers, there are inherent risks associated with their use as substitutes for clinical endpoints. Biomarkers, which have not been rigorously validated, may give rise to inaccurate estimates of clinical efficacy.¹²⁸ Reports of diagnostic characteristics (predictive values and likelihood ratios) for populations of varying immune and comorbidity risks are necessary to guide applications of particular biomarkers and risk scores in various KTR groups. Furthermore, subsequent to validation, biomarkers must be standardized to minimize intra-assay and inter-assay variability within, and across, centers.¹²⁹

With rapid advancement of bioinformatics, large amounts of data are available in publicly accessible repositories (“big data”). Extraction of useful information from data collected as part of the efforts to validate and standardize biomarkers, and their conversion into clinical utility, however, remains a challenge. Importantly, inappropriate analyses of these data may lead to inaccurate estimation of predictive accuracy.¹³⁰ Last, subsequent to validation and standardization of biomarkers of confirmed clinical utility, another challenge may arise, namely, prohibitive costs, which prevent their application in clinical practice (eg, as exemplified by high-resolution HLA typing).

Impact of P4 Medicine on Society

When planning to incorporate scientifically proven biomarker-derived risk scores into clinical practice, one must also consider inadvertent implications. For example, when minimizing epitope-level donor-recipient mismatches, one must simultaneously ensure that this does not hinder some candidates’ access to transplantation.¹³¹ This challenge was highlighted in semistructured interviews of 22 Quebec nephrologists where it was proposed that scientifically calculated risks should not be the sole determinant of patients’ access to transplantation.¹³¹ This example also illustrates potential tensions that could arise when contradictory recommendations arise from the different domains of P4 medicine (eg, predictive vs participatory). Thus, as predicted by Hood and Flores,⁹ in the process of implementing P4 medicine, we should be alert to “key ethical, social, legal, regulatory, and economic issues” that will surface and need to be addressed.

Conclusion

P4 medicine outlines a comprehensive framework for the management of KTRs (Figure 1). Changing paradigms from protocol-based peritransplant care to P4 medicine has the potential of increasing therapeutic efficiency, minimizing adverse effects, decreasing health care costs, and maximizing wellness and adherence of individual KTRs. Large

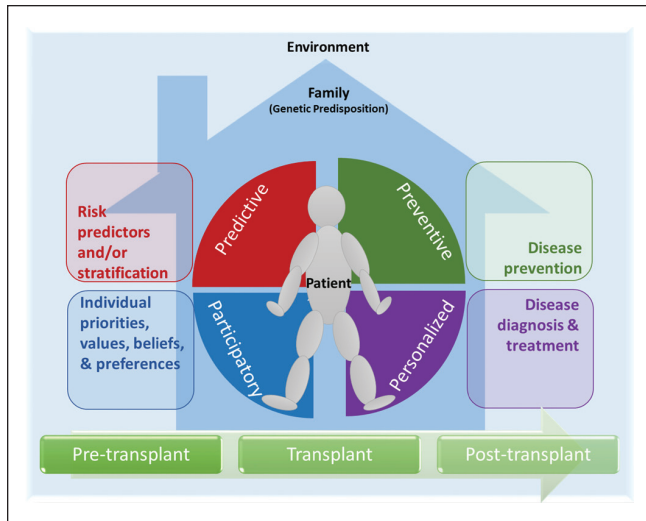


Figure 1. Applications of P4 medicine across the kidney transplant cycle.

Source. Adapted with permission from the Quebec Network for Personalized Health Care (QNPHC).

prospective multicenter studies and randomized controlled trials are required to validate and standardize novel technologies and biomarkers capable of estimating individual KTRs' immune competency and immunosuppression needs prior to the (noninvasive) detection of clinically relevant immune injuries. Simultaneous promotion of KTRs and societal engagement throughout this discovery, validation, and standardization process is necessary to realize the potential of P4 medicine, facilitate translation of the acquired knowledge into KTRs' clinical care, and evaluate the effect of P4 medicine on kidney transplant outcomes.

List of Abbreviations

ABMR, antibody-mediated rejection; CNI, calcineurin inhibitors; cPRA, calculated panel reactive antibodies; CXCL, chemokine (C-X-C motif) ligand; Cg, chronic glomerulopathy; DSA, donor-specific anti-HLA antibodies; dnDSA, de novo donor-specific anti-HLA antibodies; ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunospot assay; GSTM1, glutathione S-transferase Mu 1; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin; KPD, kidney paired donation; KTR, kidney transplant recipient; NMSC, nonmelanoma skin cancers; RNA, ribonucleic acid; PRA, panel reactive antibody; PREMs, patient-reported experience measures; PROMs, patient-reported outcome measures; PTLD, posttransplantation lymphoproliferative disorder; pg, peritubular capillaritis/glomerulitis; SNP, single-nucleotide polymorphism; TCMR, T-cell-mediated rejection.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

All authors read and approved the final version of the manuscript.

Availability of Data and Materials

Not applicable.

Acknowledgment

We would like to thank Bénédicte Nauche and Ibtisam Mahmoud, McGill University Health Centre Library, for their assistance with the electronic database search.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: M.M. is funded by the Canada Graduate Scholarships-Master's (CGS-M) Program of the CIHR; R.S.-P. is funded by the KRESCENT-CIHR New Investigator Award and Kidney Foundation of Canada Infrastructure Award. The work is also supported by a grant from the Kidney Foundation of Canada (to T.T.).

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