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Precision Medicine in Kidney Transplantation: Just Hype or a Realistic Hope?

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Abstract. Desirable outcomes including rejection- and infection-free kidney transplantation are not guaranteed despite current strategies for immunosuppression and using prophylactic antimicrobial medications. Graft survival depends on factors beyond human leukocyte antigen matching such as the level of immunosuppression, infections, and management of other comorbidities. Risk stratification of transplant patients based on predisposing genetic modifiers and applying precision pharmacotherapy may help improving the transplant outcomes. Unlike certain fields such as oncology in which consistent attempts are being carried out to move away from the "error and trial approach," transplant medicine is lagging behind in implementing personalized immunosuppressive therapy. The need for maintaining a precarious balance between underimmunosuppression and overimmunosuppression coupled with adverse effects of medications calls for a gene-based guidance for precision pharmacotherapy in transplantation. Technologic advances in molecular genetics have led to increased accessibility of genetic tests at a reduced cost and have set the stage for widespread use of gene-based therapies in clinical care. Evidence-based guidelines available for precision pharmacotherapy have been proposed, including guidelines from Clinical Pharmacogenetics Implementation Consortium, the Pharmacogenomics Knowledge Base National Institute of General Medical Sciences of the National Institutes of Health, and the US Food and Drug Administration. In this review, we discuss the implications of pharmacogenetics and potential role for genetic variants-based risk stratification in kidney transplantation. A single score that provides overall genetic risk, a polygenic risk score, can be achieved by combining of allograft rejection/loss-associated variants carried by an individual and integrated into practice after clinical validation.

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Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD).[1] Approximately, 100 000 patients are on the kidney transplant waiting list in the United States, but only 21 000 kidney transplantations were performed in 2018.[2] Mortality of ESRD patients, who receive kidney transplantation is lower than patients on maintenance dialysis.[3] However, compared to general population, mortality of kidney transplant recipients is about 14 times higher in the first year posttransplant and 4 times higher thereafter.[4] Furthermore, deceased donor kidney transplant recipients have a 10-year death-censored graft failure of 26% and it is 18% for living donor kidney transplants.[5] Several factors influence long-term transplant outcome, including donor age and comorbidity, allograft ischemic time, degree of HLA mismatch, and recipient factors such as response to immunosuppression and the development of donor-specific antibodies.[6,7] In general, immunosuppressants have a narrow therapeutic index and exhibit a large intraindividual and interindividual variability of their pharmacokinetics, necessitating a personalized immunosuppressive regimen.[8] Other factors also contribute to the suboptimal outcomes in transplant recipients, including cardiovascular disease and infections.[9] Complications related to infection could be attenuated by personalizing immunosuppression and antimicrobial

treatment.[10-13] Furthermore, cardiovascular medications with actionable genetic information are frequently used in kidney transplant recipients.[14] Precision prescribing of these medications could improve efficacy, mitigate risk of drug-drug interactions, and improve outcomes. In this review, we discuss the importance of precision medicine in kidney transplantation and the available tools to implement it. We also highlight genetics-based risk stratification and the role of pharmacogenetics in precision prescribing in transplant medicine.

Precision Medicine

The advances in molecular medicine have prompted the call for a new taxonomy of human disease based on molecular biology, which is expected to provide a strong foundation for the future of precision medicine. The term "precision medicine" was advanced by the National Research Council Working Group, which called for establishing a "new taxonomy of human disease based on molecular biology" to replace the classical descriptive diagnostic terms.[15] Precision medicine seeks to identify safe and effective treatments based on genetics and environment that are unique to an individual.[16,17] Recently, The National Institute of Diabetes and Digestive and Kidney Diseases launched the Kidney Precision Medicine Project with the purpose of understanding and finding new ways to treat chronic kidney disease and acute kidney injury[18] (https://kpmp.org/). In transplantation, the advent of genomic and other molecular profiling techniques provides an unprecedented opportunity to apply precision medicine strategies to improve patient outcome. Although precision medicine is a realistic approach, it is not without pitfalls. Any stratified approach to medicine would potentially restrict the number of patients treated with a therapeutic intervention or discriminate against the people who are otherwise healthy.[19] Therefore, careful assessment of potential implications of precision medicine is warranted.

Genetics and Immune Response

Role of genetics in immune response is well recognized.[20,21] The interplay of innate and adaptive immune response may implicate the outcomes of transplantation including rejection and tolerance.[22] Interindividual variations in immune response could be due to heritable genetics and epigenetic factors.[23,24] Epigenetics refers to a heritable change in the pattern of gene expression that is mediated by a mechanism specifically not due to alterations in the primary nucleotide sequence.[25] Emerging evidence indicates that epigenetic modifications are fundamental to the differentiation and function of immune cells.[26] MicroRNAs are noncoding RNAs that mediate posttranscriptional gene regulation. Specific microRNAs have been shown to be associated with kidney allograft rejection, possibly through modifying the expression of certain genes in regulatory T cells.[27] Therefore, it appears that the crosstalk between the genes and environment through epigenetics leading to alterations in immune response and transplant outcome.

Donor and Recipient Genetics—Beyond HLA

Introduction of HLA in kidney transplantation resulted in improved clinical outcomes.[28] HLA genes are highly polymorphic, and demonstrate the influence of genetic variation in determining long-term transplant outcomes.[1] However, even full house matching of HLA loci does not preclude the need for immunosuppression, suggesting the existence of other genetic variations in that need to be considered. Numerous studies have examined the association between genetic variations in immune response genes and transplant outcome with inconsistent findings.[29] Similarly, a large-scale genome-wide association study (GWAS) was unable to detect convincing association signals outside of the HLA region.[30] Approximately 20% of individuals waitlisted for kidney transplant in the United States are those with failed allograft.[31] Furthermore, the incidence of donor-specific HLA antibodies is relatively low (15%–25%) among transplant recipients.[7,32] Thus, factors beyond HLA may be responsible for graft failure.

Donor Genetics

Survival of kidney allograft from deceased black donors is shorter, when compared with allografts from white donors.[33] Two common variants (G1 and G2) in the last exon of Apolipoprotein L1 (ApoL1) are common in populations of West Sub-Saharan African origin.[34] It is believed that these 2 variants account for much of the disparity in rates of ESRD between black patients and white patients.[35] Kidney transplant recipients from black deceased donors with 2 high-risk ApoL1 variants experience an earlier allograft failure compared with those with 1 or no ApoL1 high-risk variants.[36-38] Although Kidney Donor Profile Index (KDPI) considers all kidneys from deceased black donors as high-risk,[37] only a minority of them possess the 2 high-risk ApoL1 variants.[39,40] Less than 1% of kidney donors develop ESRD, however it is more common among black versus white donors.[41] A faster rate of decline in kidney function after donation has been reported in black living kidney donors with ApoL1 high-risk genotype.[42] Furthermore, kidney function after donation in white donors has been reported to be similar to those black donors with low risk ApoL1 genotype, suggesting that the poor kidney outcomes observed in black donors may be attributable to ApoL1 high-risk genotype.[41] Kidney allograft donated by a healthy individual with 2 ApoL1 high-risk variants is associated with focal segmental glomerulosclerosis (FSGS) and early allograft failure in recipients.[42] Therefore, determining ApoL1 variants may lead to proper risk assessment and improve the current organ allocation system and potentially transplant outcomes. The National Institutes of Health-sponsored APOL1 Long-term Kidney Transplantation Outcomes Network study attempts to improve outcomes after kidney transplantation and to improve the safety of living kidney donation based upon variation in ApoL1 (https://theapollonetwork.org/).[43]

Other genetic variants that may be considered for precision organ allocation include MHC class I-related chain A (MICA), ATP binding cassette subfamily B member 1 (ABCB1), caveolin-1 (CAV1), and Ficolin-2. MICA is a highly polymorphic gene and implicated in innate immunity.[44] Anti-MICA antibodies are associated with acute and chronic rejection in renal transplant recipients.[45,46] Donor MICA A5.1 mutation is associated with anti-MICA sensitization and increased proteinuria in kidney transplant recipients.[47] Furthermore, the donor MICA rs2596538 G allele carrier status is a predictor of development of cytomegalovirus (CMV) infection during the first post–kidney transplantation year.[48] Kidney donor CC genotype at C3435T (rs1045642) of ABCB1 is associated with an increased risk of long-term allograft failure among white recipients.[49] Another study found an association of

the donor ABCB1 c.1199 G>A (exon 11, rs2229109) allele (GA/AA versus GG: HR = 3.22 [1.14–9.09], $P = 0.029$) with an increased risk of allograft loss.[50] CAV1 is an oncogenic membrane protein associated with cell proliferation, inflammation, and transforming growth factor-beta signaling.[51] Common variation in CAV1 was evaluated in 785 white kidney donors and their recipients and replicated in an independent cohort of transplant recipients.[51] Donor AA genotype for the CAV1 rs4730751 was associated with 97% increased risk for allograft failure. Graft failure rate for donor genotype AA was 38.6%, genotype CC was 22.3%, and genotype AC was 22.2%.[51] Ficolin-2 is involved in maintenance of tissue homeostasis through engaging apoptotic and necrotic cells.[52] Ala258Ser variant of Ficolin-2 in donors is associated with lower incidence of severe allograft rejection and graft loss.[52] The strength of evidence to support the role of many of the discussed genetic modifiers varies significantly in reported studies with more consistent evidence available for ApoL1 risk variants. We propose that a combination of these variants in addition to ApoL1 may enhance the prognostic prediction.

Recipient Genetics

Recipient immune response genes could also impact outcomes after transplantation.[53] Copy number variation in C4, an immune response gene, affects long-term allograft survival.[54] A GWAS found an association of acute kidney allograft rejection with protein tyrosine phosphatase receptor type O, a lymphocyte receptor-type tyrosine kinase gene and coiled-coil domain containing 67, a ciliary gene.[55] LIM Zinc Finger Domain Containing 1 gene, which encodes a protein involved in cell adhesion and integrin signaling, predicts transplant outcome.[56] The risk allele is frequent in individuals from European and African ancestry, but not present in those with East Asian ancestry.[56] LIM Zinc Finger Domain Containing 1 locus rs893403 was shown to be associated with kidney allograft rejection in 4 large cohorts involving 2709 transplants.[56] Through a genomic collision scenario, outcomes of renal transplant recipients who were homozygous for a deletion polymorphism at chromosome 2q12.3 and had received allografts from donors with at least 1 normal allele were evaluated.[56] Genomic collision at chromosome 2q12.3 was associated with 60% higher risk for rejection compared with those without the genomic collision.[56] The prevalence of genomic collision at chromosome 2q12.3 is estimated to be 12%–15% in unrelated renal transplantation among individuals with European and African ancestry however not common in individuals with East Asian ancestry.

CMV infection in graft donors is associated with decreased graft survival.[57] A variant of programmed cell death 1 gene, which is involved in viral-induced T-cell exhaustion, is associated with graft survival in patients who had received transplant from CMV-positive donors, whereas no association was found in CMV negative donors.[58] Future studies should be designed to examine the benefit of CMV prevention strategies based on genotype to identify who will benefit from prolonged antiviral prophylaxis.[58] In a cohort of Hispanic kidney transplant recipients the interferon (IFN)-γ +874 AA genotype was associated with a 3.4-fold increased risk for the CMV infection.[59] This may be related to the lower production of IFN-γ in individuals with IFN-γ +874 AA genotype.[59] NOD-like receptor family, pyrin domain containing 3 (NLRP3) is involved in inflammatory response. In a retrospective study of 1271 matched donors and recipients, NLRP3 gain of function SNP (rs35829419) in donors was found to be associated with 91% increased risk of biopsy-proven acute rejection. On contrary, loss of function SNP of NLRP3 (rs6672995) in the recipients was associated with a decreased risk for rejection in the first year after renal transplantation.[60] Interestingly, tubular epithelial cells express NLRP3 and other inflammatory cytokines including IL-1β and IL-18. A gain of function of NLRP3 may lead to increased expression of these cytokines resulting in kidney injury.[60] Polymorphism in genes involved in immune regulation such as regulatory T cells (Treg) function may impact allograft outcomes. In a cohort of 482 black transplant recipients, rs2910164, which can alter the expression of the microRNA (MiR)146A, was associated with acute allograft rejection.[27] MiR146A suppresses inflammation through its effect on target genes such as IL1 receptor-associated kinase gene and tumor necrosis factor (TNF) receptor-associated factor gene.[27] Thus, rs2910164 variant, which reduces the microRNA expression, may lead to enhanced inflammatory response resulting in increased risk for allograft rejection.[27] Other genetic variants involved in immune response such as chemokine receptor (CCR)2 and CCR5,[61,62] Cytotoxic T-Lymphocyte Antigen (CTLA)-4,[63] Toll-Like Receptor (TLR)3,[52] TLR4,[64] IL2 Receptor Beta (IL2RB),[65] IL6 in donors,[66] IL10,[67-69] transforming growth factor-beta,[70] TNF-α,[67-69] CD28,[71] and mannose-binding lectin 2[72] may also influence allograft outcomes. However, these reported association studies are plagued by low sample size studies and confounded by variations in race and ethnicity of the cohorts studied. For instance, polymorphisms of mannose-binding lectin 2 and other complement players including C3 and C4 did not show a consistent association with graft outcomes in different cohorts.[73] Lack of adequately powered and validation studies remains as a major barrier for clinical adoption of these genetic variants.

In addition to genes involved in immune system, prothrombotic genetic variants including Factor II, Factor V Leiden, and C677T variant of methylenetetrahydrofolate reductase gene are also associated with acute rejections and notably vascular rejections.[74] Given the limited number of such studies, the clinical utility of these genetic variants need further investigation before any recommendation for widespread use can be made. It is also possible that these genetic modifiers may or may not have a pathogenic mechanism. A polygenic risk score (PRS) of allograft rejection/loss-associated variants in an individual can be computed to prognosticate transplant outcomes. At present, the PRSs have low discriminative ability in the general population for the conditions tested.[75] A paradigm shift may be needed to change the focus from conventional case-control studies to PRS for a single individual.

A panel of genetic predictors for transplant outcomes is shown in Table 1. Any proposed panel should be dynamically updated based on scientific discoveries.

Precision Pharmacology

Genetic factors can explain 20%–95% of interindividual variability in drug response.[11] Studies comparing the drug response in monozygotic twins with dizygotic twins indicated the role of genetic variants several decades ago. Half-life of many drugs is different in dizygotic twins, whereas monozygotic twins have similar half-life, suggesting genetic underpinning.[76-78] Pharmacogenomics (PGx) is the study of how genes

TABLE 1.

A panel of genetic predictors for transplant outcomes

Reference	Gene	Physiologic function	SNP identifier	Associations with clinical outcomes
Reeves-Daniel et al[36] Freedman et al[37,38]	ApoL1	Trypanosome killing function	rs71785313 rs60910145 rs73885319	Reduced kidney allograft survival
Tonnerre et al[47] Rohn et al[48]	MICA	Stress-induced protein regulated at the cell surface	rs2596538 rs67841474	Anti-MICA sensitization and increased proteinuria in kidney transplant recipients and is a predictor of susceptibility to CMV infection
Eikmans et al[52]	TLR3	Cell-bound receptor involved in innate immune system	rs3775296	Increased acute kidney allograft rejection
Hwang et al[64]	TLR4	Binds to endogenous ligands released from damaged tissues and exogenous ligands such as lipopolysaccharide	rs10759932	Increased rejection-free survival rate
Eikmans et al[52]	FCN2	Soluble recognition molecule that can engage apoptotic and necrotic cells	rs7851696	Reduced incidence of severe kidney allograft rejection and graft loss
Steers et al[56]	LIMS1	A minor histocompatibility antigen	rs893403	Increased kidney allograft rejection
Oetting et al[27]	MIR146A	Modulated Treg and suppression of inflammatory responses	rs2910164	Increased kidney allograft rejection
Moore et al[51]	CAV1	Involved in cholesterol transport and transmembrane signaling	rs4730751	Increased kidney allograft failure
Forconi et al[58]	PD-1	Involved in the dysfunction of HIV-specific T cell response and CMV-specific CD8 T cells	rs11568821	Improved kidney allograft survival in recipients from CMV-positive donors
Vu et al[59]	IFN-γ	Involved in immune response to viral and bacterial infections	rs2430561	Increased risk for the CMV infection
Moore et al[49] Woillard et al[50]	ABCB1	An efflux pump for intestinal transport of medications including tacrolimus	rs1045642 rs2229109	Increased risk of renal allograft loss
Dessing et al[60]	NLRP3	NOD-like receptor family, pyrin domain containing 3 is a member of inflammasome family with a causal role in several inflammatory disorders	rs35829419 rs6672995	Increased acute kidney allograft rejection with rs35829419 and Reduced acute kidney allograft rejection with rs6672995
Abdi et al[61] Cha et al[62]	CCR5	Chemokine receptor specific for the proinflammatory chemokines	rs1799987	Increased acute kidney allograft rejection
Abdi et al[61] Cha et al[62]	CCR2	Involved in immune response including monocyte recruitment and T cell proliferation	rs1799864	Increased acute kidney allograft rejection
Park et al[65]	IL2RB	Stimulating T-cell proliferation through complex of IL2RA-IL2RB-IL2	rs228942 rs228953	Increased acute kidney allograft rejection episodes
Marshall et al[66]	IL6	A pleiotropic cytokine with proinflammatory and anti-inflammatory properties	rs1800795	Increased acute kidney allograft rejection
Sankaran et al[68] Grinyó et al[69]	IL10	An immunomodulatory cytokine with anti-inflammatory effects	rs1800896	Increased acute kidney allograft rejection
Alakulppi et al[67] Sankaran et al[68] Grinyó et al[69] Sánchez-Fructuoso et al[91]	TNF-α	Proinflammatory cytokine	rs1800629	(rs1800629 in Donor and Recipient) Increased acute kidney allograft rejection episodes (rs1800629 in Recipient) Modulates the effect of ATG treatment
Tinckam et al[70] Hueso et al[165]	TGF-β	Anti-inflammatory but profibrotic cytokine	rs1982073 rs1800471	Reduced risk of late acute kidney allograft rejections with rs1800471 and increased kidney allograft subclinical rejection with rs1982073
Pawlik et al[71]	CD 28	A costimulatory molecule involved in T cell-mediated immune response	rs3116496	Increased acute kidney allograft rejection
Golshayan et al[72]	MBL2	Complement-activating MBL, a soluble pattern recognition receptor	rs7096206 rs5030737 rs1800450 rs1800451	Increased acute kidney allograft rejection
Canossi et al[63]	CTLA4	CTLA4 transduces signals that inhibit lymphocyte activation	rs231775 rs3087243	Reduced acute kidney allograft rejection with rs231775 and increased acute kidney allograft rejection with rs3087243
Heidenreich et al[74]	Factor II	Prothrombotic factor	rs1799963	Increased acute kidney allograft rejection, especially vascular rejections, and early allograft failure
Heidenreich et al[74]	Factor V Leiden	Prothrombotic factor	rs6025	Increased acute kidney allograft rejection especially vascular rejections
Heidenreich et al[74]	MTHFR	Prothrombotic factor	rs1801133	Increased acute kidney allograft rejection, especially vascular rejections
Cartron et al[96]	FCGR3A	Encodes the IgG Fc receptor	rs396991	Increased risk of infection following Rituximab in recipients of liver transplant

The panel is not exhaustive of all published literature.

ABCB1, ATP binding cassette subfamily B member 1; ApoL1, Apolipoprotein 1; ATG, antithymocyte globulin; CAV1, caveolin-1; CCR, chemokine receptor; CMV, cytomegalovirus; CTLA, cytotoxic T-lymphocyte antigen; IFN-γ, interferon-gamma; IL2RB, IL2 Receptor Beta; MBL, mannose-binding lectin; MICA, MHC class I-related chain A; MiR, microRNA; MTHFR, methylenetetrahydrofolate reductase; NLRP3, NOD-like receptor family, pyrin domain containing 3; SNP, single nucleotide polymorphism; TGF, transforming growth factor; TLR, Toll-Like Receptor; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cells.

affect a person's response to drugs, that combines pharmacology and genomics to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.[17,79,80] For instance, variations in genes involved in drug metabolism and transport can affect drug pharmacokinetics, whereas variants in genes encoding for drug-target proteins can impact drug pharmacodynamics.[11,17,79,80] During the last decade, the field of pharmacogenetics has evolved into PGx, which involves a shift from a focus on individual candidate gene variants to GWAS.[16] Association studies do not address the underlying mechanism necessitating proteome analysis, indicating a role for pharmacoproteomics approach in precision medicine.[81] Propelled by advances in molecular genetics, the field of pharmacogenetics is rapidly becoming a reality in clinical practice. Over the past 20 years >20 000 new PGx citations are noted in PubMed.[82,83] Furthermore, approximately, 200 Food and Drug Administration approved medications have PGx information available on their labeling.[82,83] Inherited variations in about 20 genes have been found to influence clinical response to at least 80 medications.[79]

Precision Prescribing in Transplant Recipients

Solid organ transplant recipients typically receive induction immunosuppressive therapy at the time of surgery with gradual introduction of maintenance agents. The objective is to mitigate an acute allogeneic response and usually consists of glucocorticoids, T-cell depletion, and B-cell or plasma-cell depletion depending the perceived risk of rejection.[84] Over the last several decades there has been significant evolution in the form of induction agents available, however, no head-to-head randomized controlled trial has been conducted to define the most efficacious and safe regimens. Prescribing patterns among the transplant community have thus been led by practice guidelines such as that from the 2009 Kidney Disease Improving Global Outcomes that are deemed "moderate" in strength of evidence.[85] In terms of maintenance therapy, the calcineurin inhibitor tacrolimus stands as the "backbone" agent, after having shown superiority over other agents in a prospective and randomized fashion.[86] However, side-effect profiles of all maintenance immunosuppressants have effectively preserved a role for each drug in the highly heterogeneous transplant population. There is therefore due need to define and leverage the pharmacodynamics of these agents towards more desirable clinical outcomes. To this end, we herein summarize the pharmacogenetics of various induction and maintenance agents used in the peritransplant and post-transplant settings.

Induction Therapy

Thymoglobulin

Antithymocyte globulin is a polyclonal IgG fraction targeted against human thymocytes derived from rabbits or horses.[87] There is however evidence that ATG may work via additional mechanisms such as through expansion of Treg and enhanced IL10 production causing inhibition of TNF-α production by macrophages.[88,89] Indeed, TNF-α has been demonstrated in the alloimmune process and there is meta-analytic data that TNF-α polymorphism-308, G/A may influence risk of rejection.[90,91] In a retrospective analysis, transplant recipients carrying the risk allele who were not treated with thymoglobulin had a higher risk of rejection compared with those that did.[91] It was thus fathomed that ATG may be beneficial in transplant recipients who generate higher levels of TNF-α via this polymorphism.

Rituximab

Rituximab is a humanized chimeric anti-CD20 monoclonal antibody, which is the Food and Drug Administration approved, for the treatment of certain B-cell malignancies. It is believed to work through CD20+ B-cell depletion to influence complement-mediated and antibody-dependent cell-mediated cytotoxicity.[92] Its potential use in solid organ transplantation was recognized in 2003 in a series of 4 successful ABO-incompatible living donor transplants where it replaced the traditional practice of pretransplant splenectomy.[93] It has subsequently been used in the treatment of posttransplant lymphoproliferative disorder and in rejection.[94] Defining the clinical and biologic predictors of efficacy and safety is paramount given the cost and side effects of B-cell depletion. It has been shown in ABO-incompatible living donor liver transplantation that SNPs of the Fc fragment of IgG receptor (FCGR) gene may influence the risk of infection following Rituximab in this setting.[95] Indeed certain genotypes in this region have also been shown to correlate with clinical and molecular responses to Rituximab in non-Hodgkins lymphoma.[96] The significance of this phenomena on B-cell depletion in renal transplant induction has yet to be established.

Belatacept

Costimulation of the T-cell via the interaction between CD80/CD86 on antigen-presenting cells and CD28 on the T-lymphocyte is a critical activating event in the alloimmune response.[97] Belatacept is a CTLA4-Ig fusion protein that exploits the attenuating effect of CTLA4, which blocks the CD28-CD80/CD86 interaction, hence preventing T-cell activation.[98,99] The Belatacept and Long-Term Outcomes in Kidney Transplantation trial demonstrated superior patient and graft survival of belatacept over cyclosporine.[100] Enthusiasm for this agent, however, was tempered by episodes of histologically severe acute cellular rejection occurring in this trial, which was subsequently found to occur disproportionately in individuals with CD28+ Memory CD8 T cells.[101] The hypothesized mechanism of "belatacept resistance" via CD28 is that executes other signaling pathways to enable costimulation independent rejection. Polymorphism in the *CD28* gene was shown to be associated with acute kidney allograft rejection.[71] Integration of genomics data with pharmacoproteomics analysis may be complimentary in predicting drug response and clinical outcomes.

Maintenance Immunosuppression

Tacrolimus

Tacrolimus is the most common maintenance immunosuppression used in the setting of solid organ transplantation. Currently, we use a standard dose based on body weight, which is titrated to achieve the desired plasma level. Despite close monitoring of the drug plasma level, underimmunosuppression with increased risk of graft rejection and drug toxicity are common.[102] The narrow therapeutic index and wide interindividual variability of tacrolimus pharmacokinetics[103,104] warrant precision pharmacotherapy, which could prevent graft rejection[82] and toxicity.[102]

Tacrolimus is metabolized by Cytochrome P450 (CYP) 3A and transported in the gut by P-glycoprotein, an efflux pump, encoded by *ABCB1* gene. CYP3A4 and CYP3A5 in part explain the interindividual differences of response to calcineurin inhibitors.[105] Several studies showed no significant impact for ABCB1 on pharmacokinetics of tacrolimus.[105-108] Tacrolimus dose-adjusted trough levels were found to be higher in kidney transplant recipients with genotype of CYP3A5*3/*3 compared with recipients with genotype of *1/*3 plus *1/*1.[109] Another study reported that patients with genotype of CYP3A5*1/*1 had dose-adjusted trough concentrations 5.8-fold lower than patients with genotype of CYP3A5*3/*3.[110] The authors concluded that up to 45% of the variability of tacrolimus dose requirement is explained by the CYP3A5*1/*3 polymorphisms.[110] Higher dose of tacrolimus is needed to achieve target plasma level in black population.[111] A recent prospective multicenter study of 2595 kidney transplant recipients showed Native Americans and whites required the lowest median tacrolimus dose, whereas the black recipients required the highest median dose to achieve the therapeutic target.[112] The CYP3A5*3 variant was most common in whites with allele frequency of 0.93. It was 0.84 for Native Americans and 0.72 for Asian Americans and 0.3 for black recipients. The CYP3A5*6 and *7 variants are found only in black recipients. The CYP3A5*3 variant was associated with higher dose-normalized tacrolimus trough levels in all 4 populations compared with other gene variants.[112] Transplant recipients carrying 1 or 2 CYP3A5*1 alleles (CYP3A5 expressers) need a higher tacrolimus dose compared with CYP3A5 nonexpressers.[113] More than 50 studies have shown that individuals with the CYP3A5*1/*1 or CYP3A5*1/*3 genotype have lower dose-adjusted trough level of tacrolimus in comparison with those individuals with the CYP3A5*3/*3 genotype, with *1 carriers requiring 1.5–2 times the standard dose to achieve similar blood levels.[114]

To examine the clinical implication of testing for the *CYP* gene variants, a randomized trial of 280 renal transplant recipients who received tacrolimus according to CYP3A5 genotype versus standard practice was conducted.[115] The proportion of patients at target level C (0) was higher at day 3 after initiation of tacrolimus.[115] However, a randomized controlled trial involving 240 transplant recipients with low immunologic risk showed no change in clinical outcomes when tacrolimus starting dose based on CYP3A5 genotype was adapted.[116] Further inclusive studies, providing more generalizable results are warranted. Before conceiving such studies, we should consider the ethics of randomizing an individual to standard dose despite the knowledge that they will achieve subtherapeutic levels of tacrolimus.

According to Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines, patients with CYP3A5 extensive metabolizer or intermediate metabolizer (CYP3A5 expressers) would need higher tacrolimus starting dose, whereas patients with the CYP3A5 nonexpresser, which are poor metabolizers, would need standard tacrolimus starting dose (https://cpicpgx.org). A starting dose 1.5–2 times standard dose, not exceeding 0.3 mg/kg/d in CYP3A5 extensive metabolizer or intermediate metabolizer is recommended to achieve therapeutic target levels. Drug monitoring to guide dose adjustments should be performed.[114] Additionally, in whites incorporating CYP3A4*22 genotype into the CPIC recommendation may improve the performance of CYP3A5 genotype adjusted tacrolimus dosing. Tacrolimus dose may be decreased for CYP3A4*22 carriers-CYP3A5 defectives to 0.14 mg/kg/d, whereas it can be allowed to be increasing up to 0.4 mg/kg/d in those with CYP3A4*22 noncarriers-CYP3A5 expresser starting at 0.35 mg/kg/d.[117] CYP3A4 and CYP3A5 variants may also predict tacrolimus-related nephrotoxicity. In a study of 95 genotyped recipients, CYP3A4*1/CYP3A5*1 and CYP3A4*1B/CYP3A5*1 variants were found to be more frequently associated with the development of biopsy-proven tacrolimus-related nephrotoxicity than the CYP3A4*1/CYP3A5*3 genotype.[118] Additionally, other genetic variants may influence CYP3A4 and CYP3A5 activities. The POR*28 allele (rs1057868) has been shown to be associated with increased in vivo CYP3A5 activity for tacrolimus in those who are CYP3A5 expressers, which indicates an increased CYP3A5 activity for POR*28 carriers. POR*28 homozygosity was found to be associated with a significant higher CYP3A4 activity in those who are CYP3A5 nonexpressers for tacrolimus and cyclosporine.[119]

Cyclosporine

The effect of variable CYP3A5 expression on cyclosporine dosing, blood pressure, and long-term graft survival in renal transplant patients was evaluated in 399 white patients with stable graft function for >10 weeks posttransplantation.[120] The recipient CYP3A5*1 allele was found to have no effect on cyclosporine dose and blood concentrations at trough with and without dose adjustment. Also blood pressure, number of antihypertensive compounds used for treatment, and graft survival were not influenced by CYP3A5*1 allele.[120] The impact of variations in the ABCB1, ATP binding cassette subfamily C member 2, solute carrier organic anion transporter family member 1B1, CYP3A4, CYP3A5, or Nuclear Receptor Subfamily 1 Group I Member 2 (NR1I2) genes on the pharmacokinetics of cyclosporine was assessed in 104 pediatric renal transplant candidates. Among children older than 8 years, carriers of the ABCB1 c.1236C>T or c.2677G>T variant allele were found to have approximately 1.3–1.6 times higher oral bioavailability and lower prehepatic extraction ratio of cyclosporine than noncarriers.[121] About 30%–37% of the variability in oral bioavailability and prehepatic extraction was explained by the genetic variants. In addition, a corresponding tendency in the dose requirement was found. Overall, the variability in the pharmacokinetics of cyclosporine remained largely unexplained by those investigated genetic variants.[121]

Mycophenolic Acid (Myfortic)

Myfortic is an inosine monophosphate dehydrogenase inhibitor that should be avoided in individuals with deficiency of hypoxanthine-guanine phosphoribosyl-transferase. Individuals including those with partial deficiency of the enzyme can develop elevated uric acid level resulting in gout, kidney failure, and kidney stones.[122] There are limited data about pharmacogenetic testing for myfortic in kidney transplant recipients. However, CPIC recommends pharmacogenetic testing of hypoxanthine phosphoribosyl-transferase 1 gene as it may provide actionable information[122,123] such as consideration of using alternative agent in those with hypoxanthine-guanine phosphoribosyl-transferase deficiency.

Azathioprine

Azathioprine is an antimetabolite that has been used for posttransplant immunosuppression.[85] As a prodrug, azathioprine should be converted to mercaptopurine. Polymorphic thiopurine methyltransferase (TPMT) inactivates mercaptopurine through methylation. Activity of TPMT can be influenced by genetic variants.[124] At least 1 slow metabolizer variant can be found in approximately 10% of whites, which leads to accumulation of toxic metabolites resulting in severe myelosuppression.[125] One in 300 whites is homozygous for the allele causes complete deficiency of TPMT activity.[125] Genotyping of TPMT may be informative as there are 3 TPMT SNPs accounting for >90% of inactivating alleles.[126,127] CPIC guideline recommends that patients with TPMT heterozygous with 1 of alleles *2, *3A, *3B, *3C, and *4 should receive lower initial dose of thiopurine medications. Risk of life-threatening severe myelosuppression exists for patients with the homozygous variant genotype with 2 of the alleles (*2, *3A, *3B, *3C, and *4) during therapy with thiopurine medication. Therefore, significant dose reduction or use of an alternative agent is recommended.[125] Nucleoside diphosphate linked moiety X (Nudix)-type motif 15 (NUDT15) is involved in catalyzing the conversion of cytotoxic thioguanine triphosphate metabolites to a less toxic substance, thioguanine monophosphate. R139C variant of NUDT15 is also linked with thiopurine toxicity with consequent severe myelosuppression.[128] In individuals who are NUDT15 intermediate metabolizer, a reduction in starting dose should be considered to decrease toxicity. For those who are NUDT15 poor metabolizer, a significant dose reduction or using an alternative agent should be considered.[128]

Everolimus

Everolimus is a macrolide immunosuppressive agent used in solid organ transplant recipients. It is structurally related to tacrolimus and binds to FK-binding protein and blocks the transduction signal from the IL2 receptor, thus inhibiting T- and B-cell proliferation. In a study of 53 renal transplant patients who had been switched from a regimen consisting of cyclosporin, mycophenolate, mofetil and prednisolone to a calcineurin inhibitor-free regimen consisting of everolimus and prednisolone, polymorphisms in genes coding for ABCB1, CYP3A5, CYP2C8, and Pregnane X Receptor found to have no clinically relevant effect on everolimus pharmacokinetics.[129]

Precision Prescribing of Nonimmunosuppressive Drugs

Among the drugs that are commonly used in transplant population, there are evidence-based guidelines available for voriconazole, clopidogrel, warfarin, narcotics, simvastatin, and allopurinol. Trough voriconazole concentrations are lower in patients with CYP2C19 ultra-rapid metabolizers compared with poor metabolizers resulting in delay in achieving therapeutic level, which may be critical in a life-threatening infections such as invasive aspergillosis in transplant recipients.[130] CPIC guideline recommends that patients with CYP2C19 ultra-rapid or rapid metabolizer status (*17/*17 or *1/*17, respectively) to receive an alternative agent other than voriconazole as therapeutic level may not be achievable. Patients with CYP2C19 poor metabolizer status (2 alleles of either *2 or *3) should use an alternative agent because of high-risk for developing adverse effects.[131] Clopidogrel is a prodrug that needs to be activated by CYP2C19.[132] According to American College of Cardiology Foundation/American Heart Association Acute Coronary Syndrome guidelines, genetic testing for CYP2C19 loss-of-function alleles may be considered on a case-by-case basis, especially in those with recurrent Acute Coronary Syndrome despite treatment with clopidogrel.[133] "Error and trial approach" in case of a life-threatening condition such as acute coronary event especially in transplant recipients may not be advisable. PGx-guided antiplatelet therapy in the highly vulnerable and heavily invested population such as transplant recipients should be considered. The CPIC guideline recommends using an alternative agent in patients with at least 1 decreased function allele because of risk for decreased response. Patients with genotype of increased metabolism should be monitored for increased bleeding risk.[134] Warfarin, a vitamin K antagonist, is a commonly used anticoagulation medication with significant interindividual variability and narrow therapeutic index leading to frequent complications due to overdosing and underdosing. Genetic variants in CYP2C9, CYP4F2, and vitamin K epoxide reductase complex subunit 1 can predict the dose needed to meet the therapeutic level.[135] Codeine may not be effective in patients who are CYP2D6 poor metabolizers, whereas there is a higher risk for toxicity in those patients who are CYP2D6 ultra-rapid metabolizers.[136] Life-threatening side effects have been reported in CYP2D6 ultra-rapid metabolizers including those patients who had received even standard doses of codeine. CYP2D6 is also involved in metabolism in other opioids such as tramadol, hydrocodone and oxycodone, hydromorphone, and oxymorphone.[136] Concomitant use of statins such as simvastatin with certain drugs such as cyclosporine may lead to increased blood concentration of simvastatin resulting in myotoxicity.[137] An alternative agent or a reduced dose of simvastatin should be prescribed to patients with at least 1 reduced function allele in solute carrier organic anion transporter family member 1B1 (*5, *15, or *17).[138] Variants of the *HLA-B* gene are associated with allopurinol related cutaneous conditions. Patients with at least 1 HLA-B* 58:01 allele are at higher risk for developing allopurinol related cutaneous conditions.[139] The CPIC guideline recommends avoiding use of allopurinol in patients with at least 1 HLA-B*58:01 allele.[140] A list of commonly used medications with actionable genetic information in transplant population is shown in Table 2.

Pharmacogenetics in Transplantation

Cost of kidney care in the United States is $114 billion per year.[141] Cost of allograft failure and return to dialysis is estimated $70 000–$106 000 per year compared with $16 000 per year for those ESRD patients with functioning graft.[142] Additionally, >2 million adverse drug reactions with approximately 100 000 associated death occur annually in the United States.[143] The cost for adverse drug reactions has been estimated up to $136 billion per year.[144] Drugs interactions are very common among kidney transplant recipients in part due to narrow therapeutic index of commonly used medications in transplant population.[145,146] In certain fields in medicine such as oncology, due to high side-effect profile and astronomic costs of new biologic and chemotherapy medications, precision medicine is rapidly being implemented in clinical practice.[147-149] Despite the enormous cost of caring for transplant patients and vulnerability of these patients, transplant medicine is lagging behind in

TABLE 2.

Gene-drug pairs with sufficient evidence for at least 1 prescribing action to be recommended

Author	Gene	Medication	Pharmacogenetics implications
Birdwell et al[114] CPIC[166]	CYP3A5	Tacrolimus	Higher starting dose at 1.5–2 times standard dose, not exceeding 0.3 mg/kg/d in CYP3A5 extensive metabolizer or intermediate metabolizer.
Birdwell et al[114] CPIC[166]	CYP3A4	Tacrolimus	Higher starting dose as above
Elens and Haufroid[117]	POR	Tacrolimus	POR*28 homozygosity is associated with a significant higher CYP3A4 activity in those who are CYP3A5 nonexpressers
Relling et al[128] CPIC[166]	TPMT	Azathioprine	Reduce initial dose in TPMT heterozygous with 1 of alleles *2, *3A, *3B, *3C, and *4
Relling et al[128] CPIC[166]	NUDT15	Azathioprine	Reduce initial dose for NUDT15 intermediate metabolizer. Consider an alternative agent for NUDT15 poor metabolizer
CPIC[166]	HPRT1	Mycophenolic acid	Consider using alternative agent in HGPRT deficiency
Crews et al[136] CPIC[166]	CYP2D6	Codeine Oxycodone	Use alternative analgesics in CYP2D6 poor metabolizers or ultra-rapid metabolizers
Moriyama et al[131] Scott et al[134] CPIC[166]	CYP2C19	Voriconazole Clopidogrel	Use an alternative agent other than voriconazole in CYP2C19 ultra-rapid or rapid or poor metabolizers Use an alternative agent other than Clopidogrel in patients with at least 1 decreased function allele
Johnson et al[135] CPIC[166]	VKORC1	Warfarin	Consider an alternative oral anticoagulant/calculate warfarin dosing according to CPIC guideline pharmacogenetic algorithm[a]
Johnson et al[135] CPIC[166]	CYP2C19	Warfarin	Consider an alternative oral anticoagulant/calculate warfarin dosing according to CPIC guideline pharmacogenetic algorithm
Johnson et al[135] CPIC[166]	CYP4F2	Warfarin	Consider an alternative oral anticoagulant/calculate warfarin dosing according to CPIC guideline pharmacogenetic algorithm
SEARCH Collaborative Group[138] CPIC[166]	SLCO1B1	Simvastatin	Use an alternative agent or a reduced dose of simvastatin in patients with at least 1 reduced function allele
Hershfield et al[140] CPIC[166]	HLA-B*58:01	Allopurinol	Avoid allopurinol in patients with at least 1 HLA-B*58:01 allele

[a]CPIC guideline pharmacogenetic algorithm https://cpicpgx.org/content/guideline/publication/warfarin/2017/28198005.pdf.
CPIC, Clinical Pharmacogenetics Implementation Consortium; CYP, Cytochrome P450; HGPRT, hypoxanthine-guanine phosphoribosyl-transferase; NUDT15, nucleoside diphosphate linked moiety X-type motif 15; SLCO1B1, solute carrier organic anion transporter family member 1B1; TPMT, thiopurine methyltransferase; VKORC1, vitamin K epoxide reductase complex subunit 1.

implementing precision prescribing. Therefore, in addition to potential optimization of transplant outcomes, precision medicine in kidney transplantation may be cost-effective from payer's standpoint.

GWAS AND GENETIC PANEL TESTING

GWAS is a powerful tool to identify causal genetic variants, by simultaneously analyzing millions of single nucleotide polymorphisms (SNPs) distributed across the genome.[30,55] A GWAS conducted by the United Kingdom and Ireland Renal Transplant Consortium and the Wellcome Trust Case Control Consortium-3 failed to identify strong donor or recipient genetic effects outside the HLA region contributing to long- or short-term allograft survival.[30] Several reasons could explain the lack of discovery including small sample size and heterogeneous cause for graft loss. Results from the International Genetics and Translational Research in Transplantation Network, a multisite consortium (n = 28 015) with adequate power to capture both rare and common genetic contributions to ESRD and posttransplant outcomes is expected soon.[150]

It is evident that further studies are required before recommending the utility of genetic variants in clinical setting. Pending new discoveries, a panel of genetic variants could be tested in the research setting for kidney transplant recipients and potential donors consist of genetic variants with pharmacogenetic implications and genetic variants with prognostic value for clinical outcomes. A risk estimate could be derived integrating the genetic, demographic, and clinical data, which if combined to pharmacogenetic of immunosuppressive medications could be a useful tool in clinical setting (Figure 1). This can be achieved by combining a panel of allograft loss-associated variants carried by an individual into a single score that provides overall genetic risk, a PRS.[151] The combination of PRSs with clinical risk factors could improve the risk stratification further.[152] Efforts are underway to integrate findings from GWAS with expression quantitative trait loci from scRNAseq as well as known regulatory region maps could identify novel genes associated with graft loss.[153] In addition to rare renal genetic diseases, there are currently available resources such as Natera (https://www.natera.com/organ-health/renasight-genetic-testing) and Invitae (https://www.invitae.com/en/chronic-kidney-disease/) offering genetic panel testing for patients with chronic kidney disease.[154] A transplant genetic panel implicating the rejection risk could be complementary in care to transplant population and potentially improving outcomes. Clinical validation through prospective trials supporting the clinical decision outlined in Figure 1 is required.

Noninvasive Transplant Immune Monitoring

Solid-organ transplantation is effectively genomic transplantation—a concept depicted by Lo and colleagues who demonstrated that donor-derived cell-free DNA (dd-cfDNA) is present in the plasma of kidney and liver transplant recipients.[155] They envisioned that dd-cfDNA might be used as a diagnostic tool for

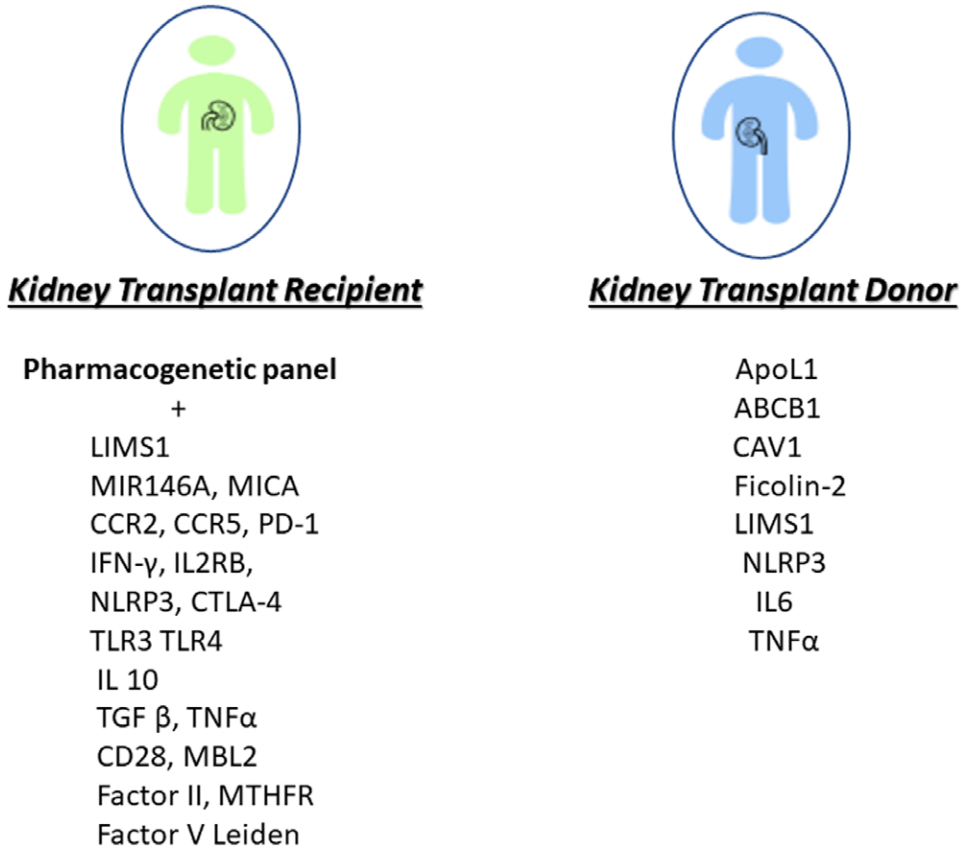

FIGURE 1. A panel of genetic variants for transplant recipients and donors. This panel functions as an additional tool at disposition of transplant physicians to provide individualized care. Clinical validation through prospective trials supporting the clinical decision outlined is required. ABCB1, ATP binding cassette subfamily B member 1; ApoL1, Apolipoprotein L1; CAV1, caveolin-1; CCR, chemokine receptor; CTLA, Cytotoxic T-Lymphocyte Antigen; IFN-γ, interferon-gamma; IL2RB, IL2, Receptor Beta; MBL, mannose-binding lectin; MICA, MHC class I-related chain A; MiR, microRNA; MTHFR, methylenetetrahydrofolate reductase; NLRP3, NOD-like receptor family, pyrin domain containing 3; TGF-β, transforming growth factor; TLR, Toll-Like Receptor; TNF-α, tumor necrosis factor-alpha.

detecting transplant rejection. Indeed, distinctive graft and recipient genotype SNPs have been exploited to barcode donor DNA circulating in recipient serum for this purpose. This approach was first demonstrated as proof of concept in a retrospective analysis of heart transplant recipients in 2011[156]. Genome transplant dynamic methodology was subsequently clinically validated in solid organ transplantation.[157] A multicenter study of renal allograft recipients evaluated the role of circulating dd-cfDNA in blood for diagnosis of acute rejection.[158] The assay uses targeted amplification and sequencing of SNPs to quantify donor and recipient DNA contributions. The study showed that plasma levels of dd-cfDNA can discriminate active rejection status of the renal allograft. Extending this concept further to incorporate epigenetic analyses may unravel distinct "signatures" of allograft states such as rejection, infection, or fibrosis. Furthermore, the sheer granularity of epigenetic methods may decipher new and more accurate categories of allograft diseases than the nebulous clinical definitions currently in use.

Pharmacomicrobiomics

Human gut harbors a complex community of >100 trillion microbial cells, which constitute the gut microbiota.[159] The gut microbiome encodes about 3.3 million genes, which is 150 times more genes than our own genome.[160] The symbiotic gut microbiota provides complementary biologic and metabolic functions that cannot be performed by humans.[161,162] There is a growing evidence that gut bacteria can affect the response to drugs by modulating either efficacy or toxicity.[163] Pharmacomicrobiomics is an emerging field that investigates the interplay of microbiome variation and drugs response.[164] Future investigations should consider gut microbiome in delivering precision therapies in kidney transplantation.

FUTURE DIRECTION AND CONCLUSION

Precision pharmacotherapy in conjuncture with genotype-based risk stratification of transplant recipients and donors may help with donor selection, identification of high-risk recipients, and individualization of pharmacotherapy. Efficient drug monitoring may not function as an alternative for gene-based guidance in pharmacotherapy of transplant recipients. Incorporation of genetic predictors into routine clinical practice may be challenging for physicians in part due to perceived difficulty with interpretation of genetic information. Integration of clinical decision support tools with electronic health records (EHRs) can facilitate the use of available actionable genetic information. Nephrologists have been traditionally advocating precision prescribing based on the level of kidney function. Adjustment of dose of a drug according to glomerular filtration rate through an alert system in EHR is an example of precision prescribing. Similarly, relevant genetic information can be incorporated to EHR and provide guidance to clinicians for precision prescribing (Figure 2). The concept of personalized medicine based on individual patient

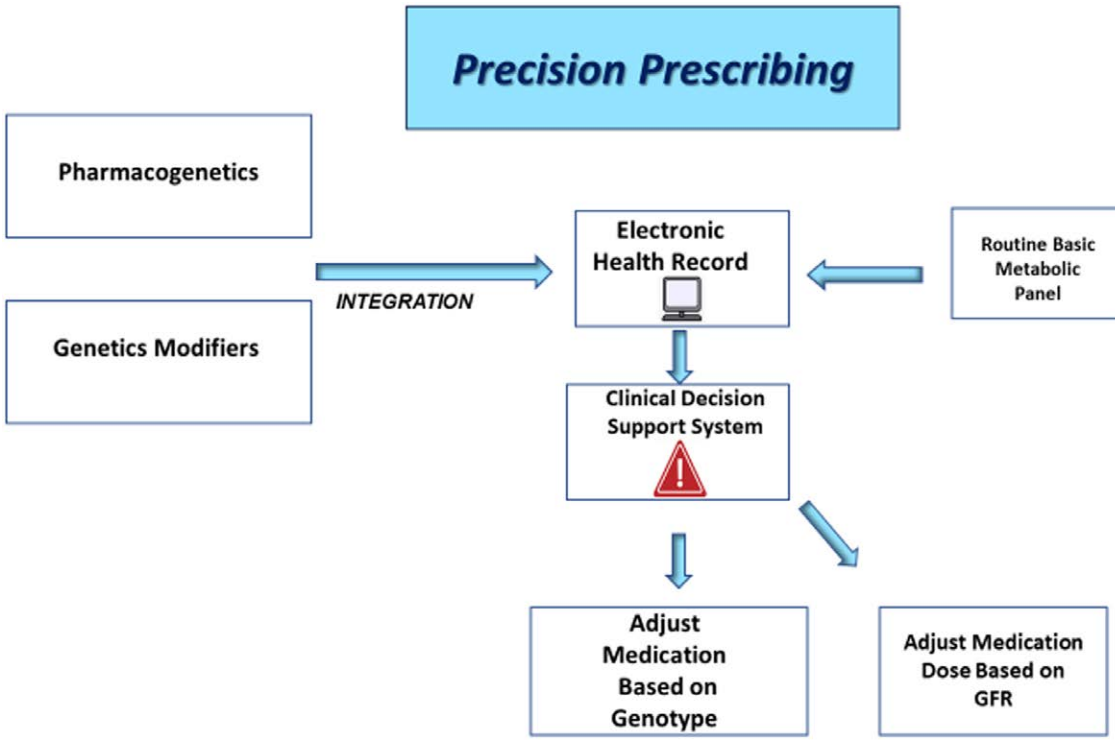

FIGURE 2. Integration of clinical decision support (CDS) tools with electronic health records (EHRs) can facilitate the use of available actionable genetic information. Adjustment of dose of a drug according to glomerular filtration rate (GFR) through an alert system in EHR is an example of precision prescribing. Similarly, relevant genetic information can be incorporated to EHR and provide guidance to clinicians for precision prescribing. Further studies are required to validate the proposed model.

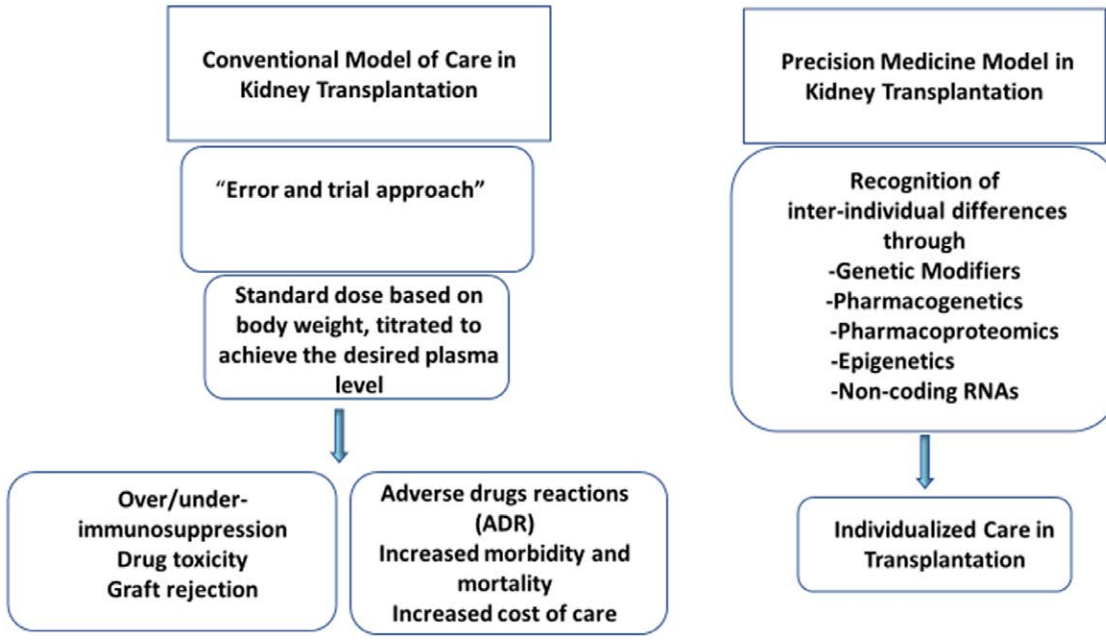

FIGURE 3. Recognition of interindividual differences is becoming possible through integration of pharmacogenetics, pharmacoproteomics, epigenetics, and noncoding RNAs data into clinical practice. Further studies are required to validate the proposed model. ADR, adverse drug reaction.

characteristics, including genetics, molecular markers, and environmental factors, rather than on population averages is attractive (Figures 3 and 4). Precision medicine through incorporation of available genetic information into clinical practice to individualize care for kidney transplant recipients is a realistic hope and on the horizon in the light of ever-decreasing cost of genetic testing and advances in molecular diagnostics. Lack of high-quality data derived from traditional case-control studies remains a barrier for routine use of PRSs in the clinical practice. However, it is noteworthy that precision medicine may a blind spot for conventional randomized trials considering the current low discriminative ability of PRSs

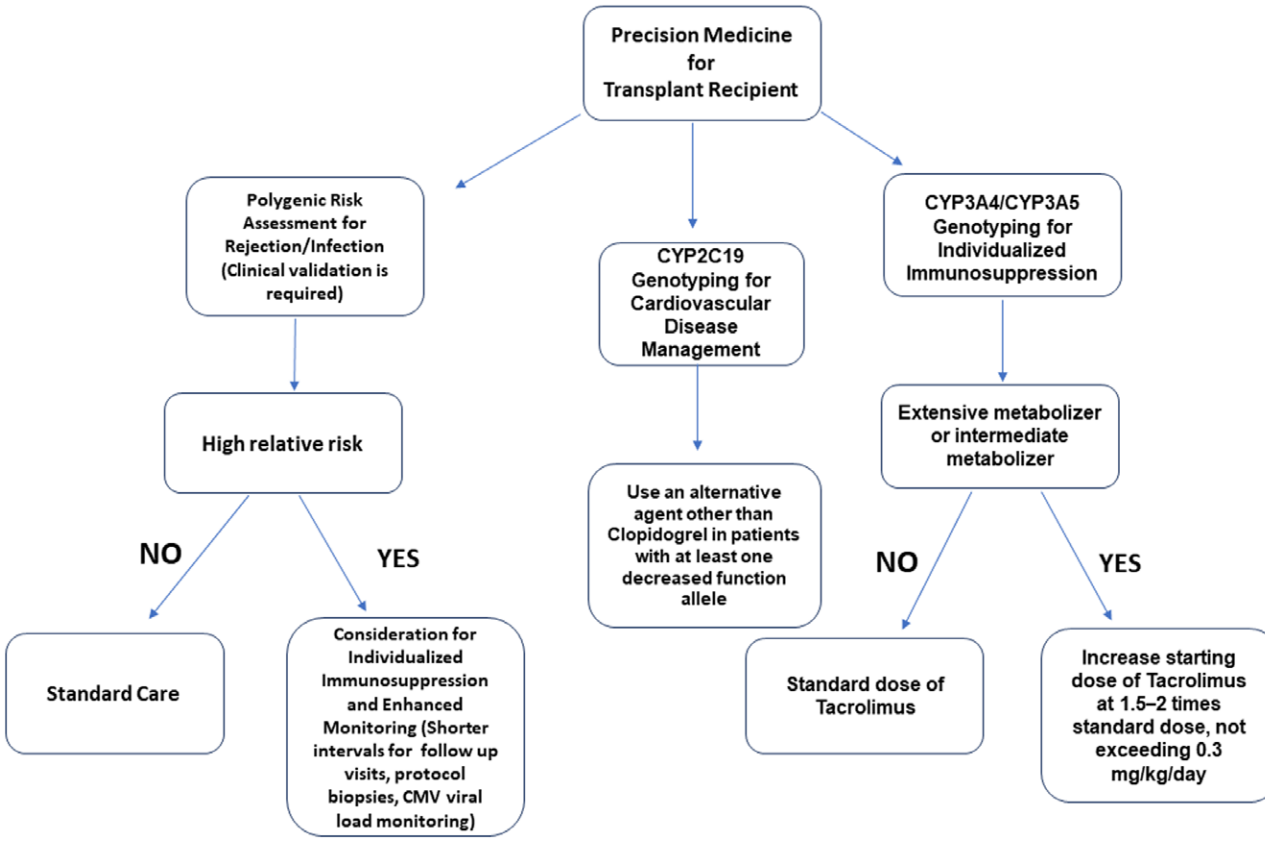

FIGURE 4. A single score that provides overall genetic risk, a polygenic risk score (PRS) can be achieved by combining of allograft rejection/loss associated-variants carried by an individual and in conjuncture with pharmacogenetics may be integrated into practice after clinical validation through prospective clinical trial supporting the clinical decision outlined. CMV, cytomegalovirus; CYP, Cytochrome P450.

in the general population. Increasing access to large datasets has fostered data-driven sciences that are poised to transform personalized medicine.

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