PRECISION MEDICINE & GENETICS:
IMPLICATIONS FOR THE ADVANCED PRACTICE PROVIDER

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Objectives

- Understand what precision medicine is and how it can be applied to the transplant patient.
- Identify historic and current challenges to managing immunosuppression.
- Evaluate certain groups of patients that pose challenges in being immunosuppressed.
- Discuss specific testing used in precision medicine and how to utilize the test in the transplant patient.
- Understand pharmacogenomic testing and how this can be applied to immunosuppression.
- Identify ways in which the Advanced Care Provider can use precision medicine in the care of the transplant recipient.

What is Precision Medicine?

- Human Genome Project (1990-2003) by the U.S. Department of Energy and National Institute of Health- human blueprint. Accounted for over 90% of the human genome (what makes up a human).
- Genome-complete set of DNA. Humans have one genome which contains 23 pairs of chromosomes and 3 billion base pairs of DNA.
- The Human Genome Project is the foundation for modern precision medicine.
- Movement to: Predictive, Preventive, Personalized, Participatory Care.
- Pioneered in Oncology.

Advancements in Transplant

"Where we have been..?"

- Between 1980's-2000's we have made progress in immunosuppression
  - Cyclosporine → Tacrolimus
  - Azathioprine → Mycophenolate
  - Steroids → Steroid Sparing
- Change in how we treat infections:
  - Ganciclovir/Foscarnet → Valganciclovir/Letermovir
- Sirolimus (1999), Everolimus (2010)
- Atgam (equine-1974) → Thymoglobulin (rabbit-1998)
- Polyclonal Antibodies (Atgam/Thymoglobulin) → Monoclonal Antibodies (Rituximab/Basiliximab)
- Reduced acute rejection rates and improved survival within the first year.

Advancements in Transplant

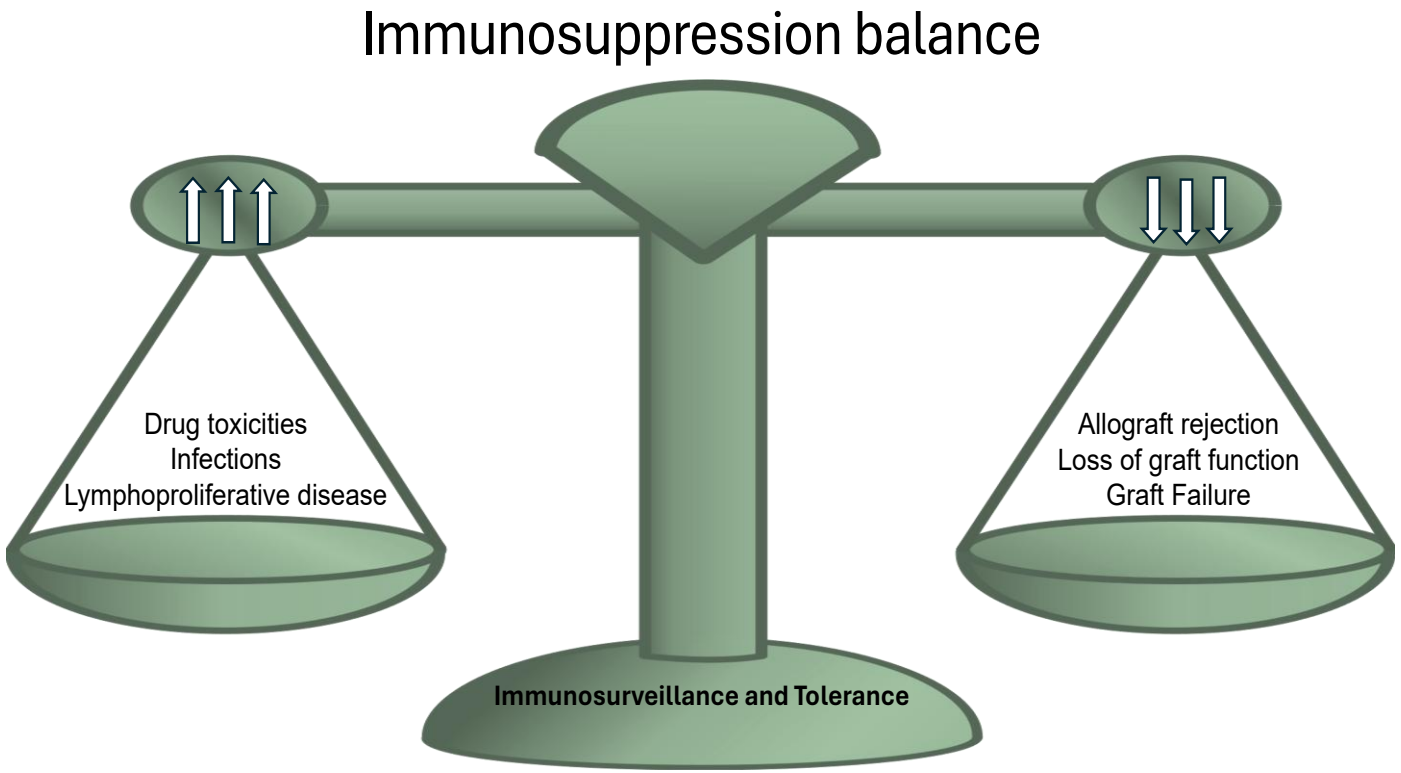
"…and where we are today?"

- Standardization of histological classification of rejection in biopsies (Banff Foundation for Allograft Pathology and ISHLT).
- Move from qualitative viral testing to quantitative (BK/CMV)- viral DNA-PCR.
- Dosing protocols/guidelines vary between transplant centers and the type of organ transplanted.
- More medications available as generic.
- More sizes/strengths/dosage forms of medications/extended-release formulations.

Precision Medicine

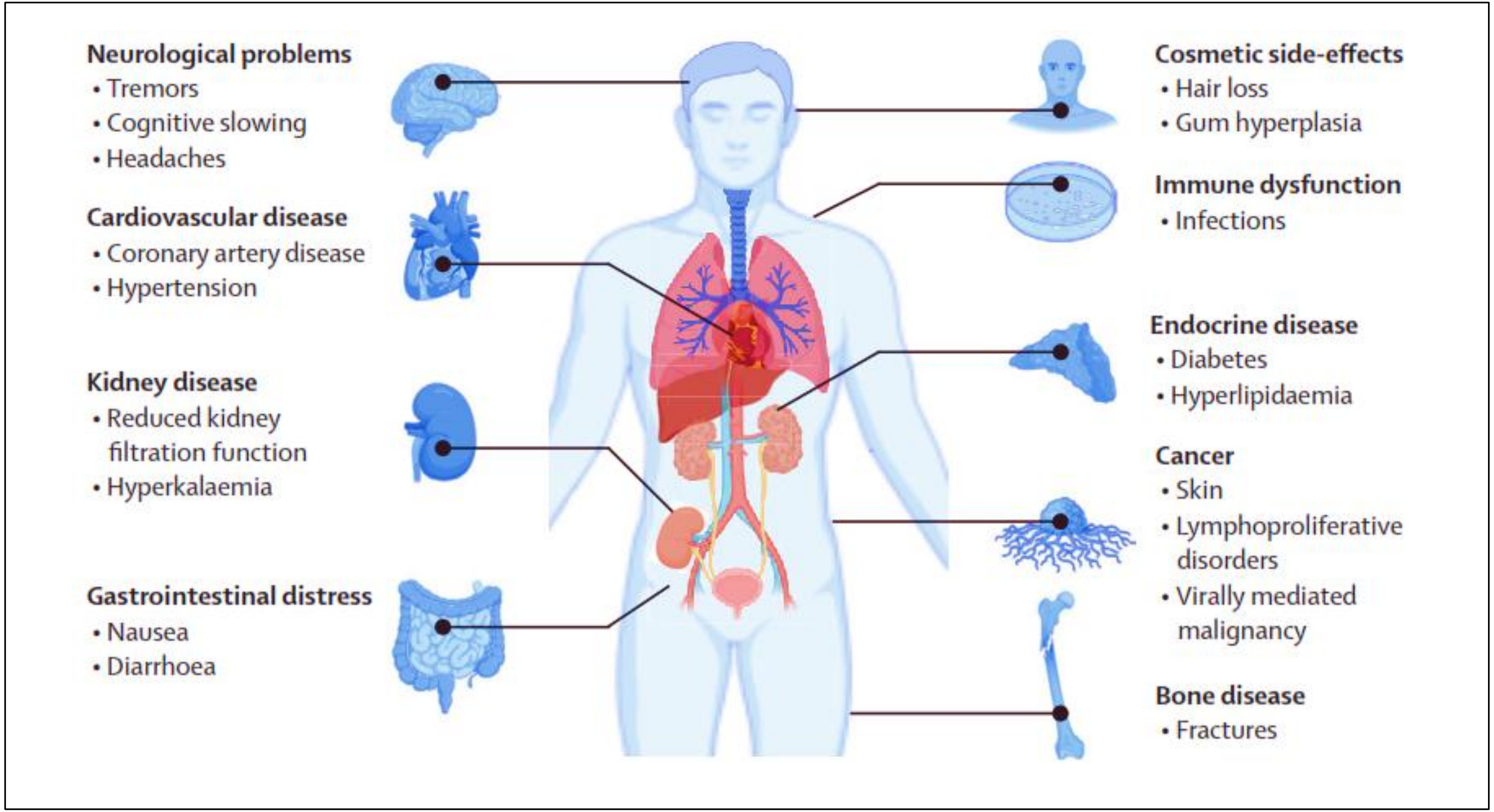
Where we have been?

- "One size fits all" for immunosuppression: tacrolimus, mycophenolate and prednisone.
- Balance between overimmunosuppression and underimmunosuppression.
- We run immunosuppression the same regardless of underlying disease, age, race, or sex.
- Standard dosing based on weight and titrated to desired level.
- Immunosuppression is adjusted based on a goal to reduce and avoid toxicities while preventing rejection.
  - Organ specific tests (Creatine, Alk Phos, AST/ALT, WBC, PLT).



Approaching Precision Immunosuppression Management

- Therapeutic Drug Monitoring
- Prospective Immunophenotyping to guide agent selection & dosing
- Risk stratification for adverse effects



Loupy,A., et al., The Lancet. 2025 Jul 25;406 (1050):389-402.

Precision Medicine

…and where are we headed?

- Immunosuppression is adjusted based on a goal to reduce and avoid toxicities while preventing rejection.
  - Organ specific tests (Creatine, Alk Phos, AST/ALT, WBC, PLT).
- Current advancements look at tailored immunosuppressive strategies.
- Understanding how genetic factors contribute to disease and using genetic markers to guide pharmacotherapy.
- Detecting disease at an early stage - From "reactive to proactive!".
- Minimizing invasive testing - "biopsy!"

Challenges with Immunosuppression

- Tacrolimus has wide pharmacokinetic variability and inter-patient / intra-patient variability.
- Dose requirements dependent upon:
  - Age, Race, Sex, Body Weight, hepatic metabolism, and other co-administered drugs.
- Mycophenolic Acid: polymorphisms in UGT1A9 impact MPA clearance.
  - Unpredictable! Obtaining levels is difficult because of pharmacokinetic variability. No evidenced based recommendation for therapeutic range.
  - Dose adjustments are reactionary and based on clinical outcomes (GI side effects, neutropenia.)
  - Imuran: risk of myelosuppression based on genetics.
- Variability in drug pharmacokinetics can affect rejection risk.

Challenges with Immunosuppression

- Age – variation in pediatric and elderly populations
- Race – genetic variation across different ethnic groups
- Short Telomere Syndrome (ILD)
- Patients with diseases that affect absorption/metabolism
  - Cystic Fibrosis
- Pre-transplant infections/colonization
- Patients with malignancies
- Patients with kidney disease
- Financial burden to patients
- Managing side effects and promoting compliance

Aging population and Transplant

- Rising aging population hence more elderly transplant recipients (>65 years).
- Improved short term graft survival and decreased acute rejection events.
- Higher risk of chronic allograft loss due to age related immune and nonimmune factors.
- Increased risk of infection, cardiovascular disease, malignancy, diabetes, fractures, myopathy (higher risk of death with functioning graft).
- Decreased renal/hepatic clearance of drugs.
- Decrease cytochrome P450 enzyme concentration.
- Reduce immunogenicity.

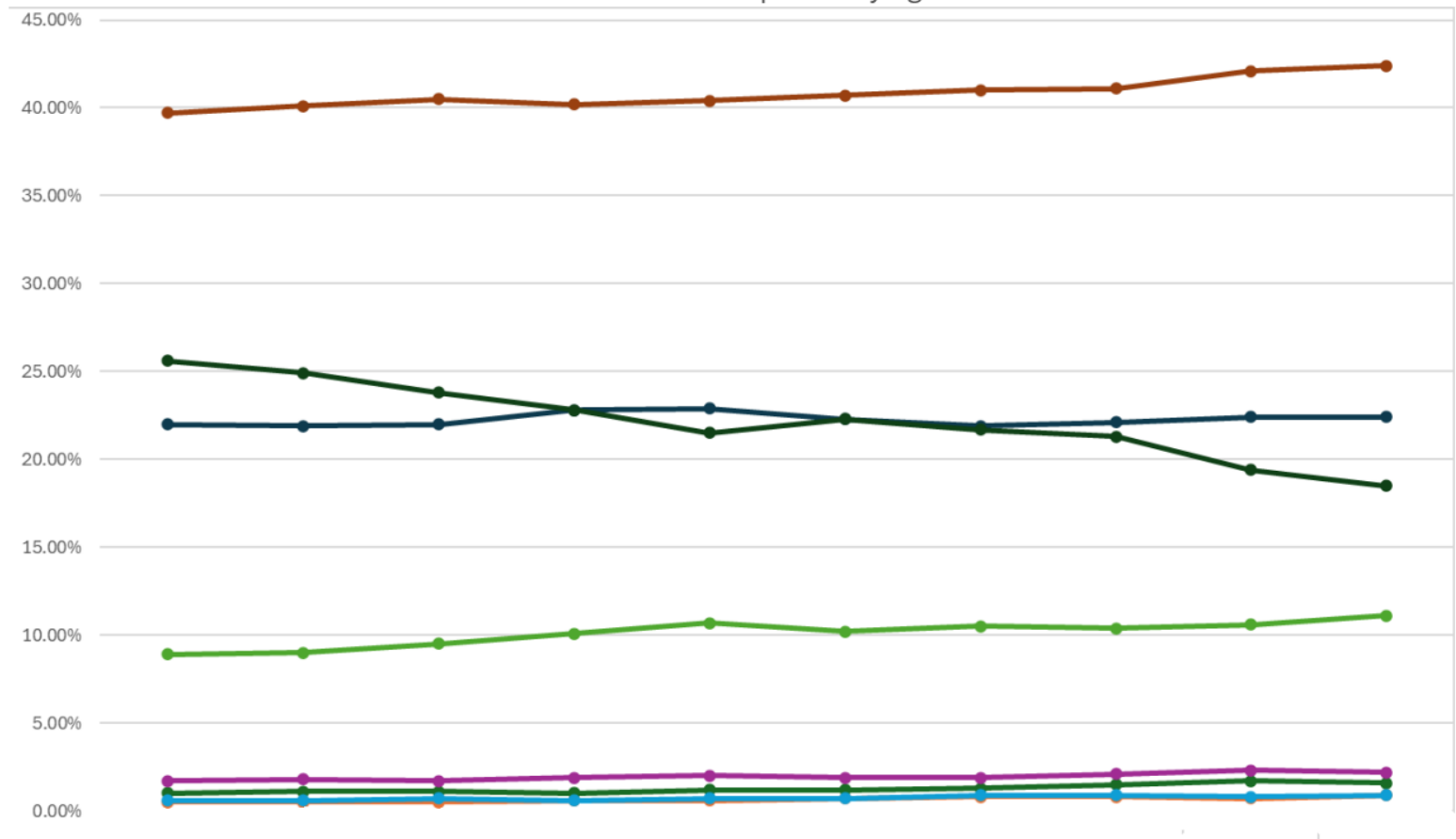
Lentine,K.,et al., *Transplantation*,2021, 105:1840-1849.

Aging population and Transplant

- Retrospective Study looking at immunosuppression in elderly Kidney recipients: using US Transplant Registry data from 2005-2016 (14,887 patients ≥65)
  - Lower risk of acute rejection 6 months-3 years post-transplant compared to younger patients with all immunosuppression regimens except IL2rAb + triple therapy.
  - Older adults are less likely to tolerate 3 drug immunosuppression.
    - Lower- intensity immunosuppression regimens including steroid sparing had statistically equivalent graft outcomes compared to T cell depleting + triple drug immunosuppression regimens.
  - CSA based, mTOR based, and Tacrolimus + anti-metabolite avoidance regimens were associated with poorer graft outcomes.
  - A reduced immunosuppressive regimen is recommended particularly steroid sparing (Tacrolimus/MMF/Steroid minimization or withdrawal).

Lentine,K.,et al., *Transplantation.*2021, 105:1840-1849.
Cheungpasitporn,W.,et al., *Current Transplantation Reports*, 2021

National Transplants by Age



	2025	2024	2023	2022	2021	2020	2019	2018	2017	2016
< 1 Year %	0.50%	0.50%	0.50%	0.60%	0.60%	0.70%	0.80%	0.80%	0.70%	0.90%
1-5 Years %	1.00%	1.10%	1.10%	1.00%	1.20%	1.20%	1.30%	1.50%	1.70%	1.60%
6-10 Years %	0.60%	0.60%	0.70%	0.60%	0.70%	0.70%	0.90%	0.90%	0.80%	0.90%
11-17 Years %	1.70%	1.80%	1.70%	1.90%	2.00%	1.90%	1.90%	2.10%	2.30%	2.20%
18-34 Years %	8.90%	9.00%	9.50%	10.10%	10.70%	10.20%	10.50%	10.40%	10.60%	11.10%
35-49 Years %	22.00%	21.90%	22.00%	22.80%	22.90%	22.30%	21.90%	22.10%	22.40%	22.40%
50-64 Years %	39.70%	40.10%	40.50%	40.20%	40.40%	40.70%	41.00%	41.10%	42.10%	42.40%
65 + %	25.60%	24.90%	23.80%	22.80%	21.50%	22.30%	21.70%	21.30%	19.40%	18.50%

< 1 Year % 1-5 Years % 6-10 Years % 11-17 Years % 18-34 Years % 35-49 Years % 50-64 Years % 65 + %

OPTN

The Aging Immune System

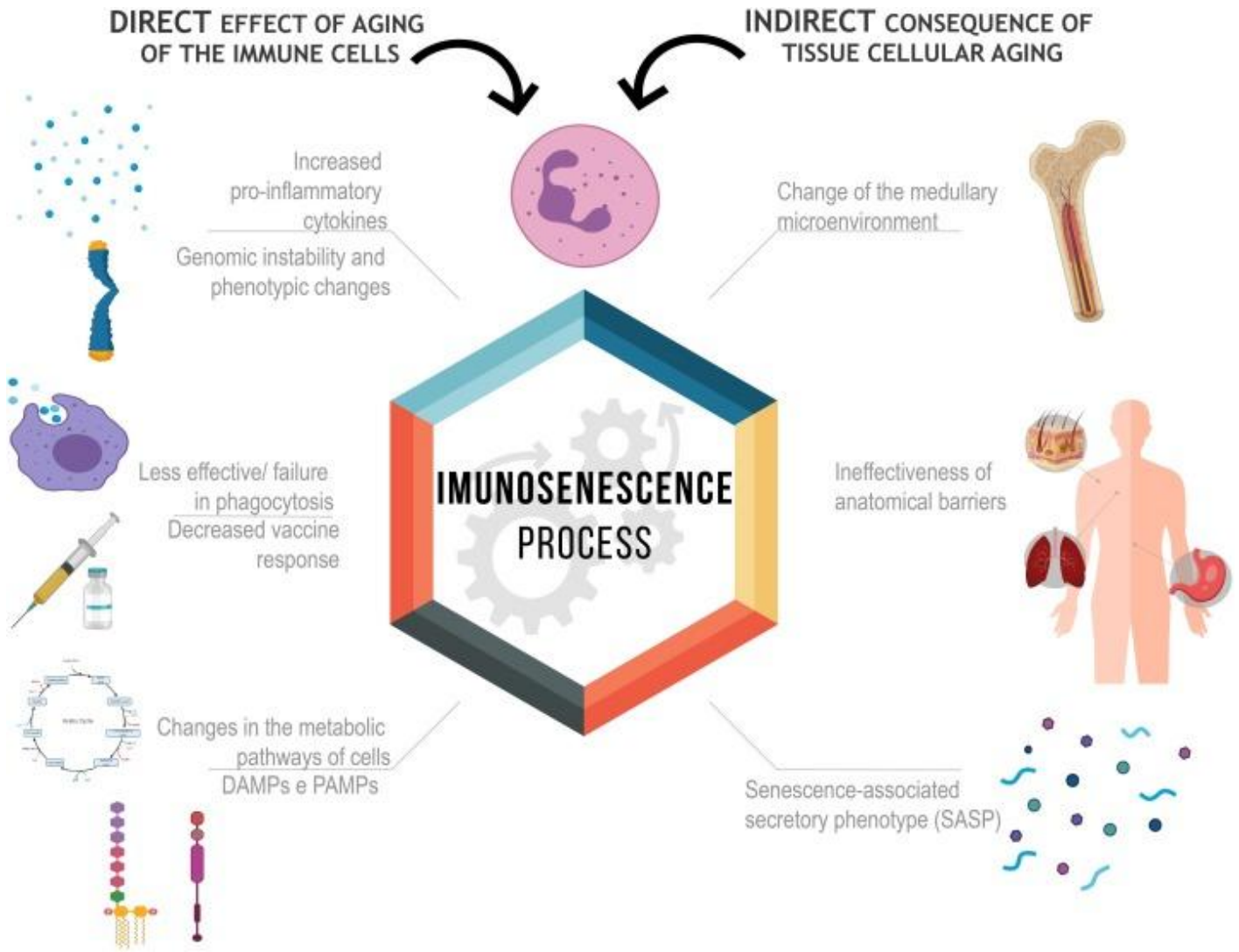
"Immunosenescence"

- Decline in immune response
- Thymic involution, reduced naïve T and B cells, impaired antigen uptake/presentation,
- Impaired Wound Repair and decrease ability to fight infections/cancers, reduced vaccine responsiveness, coronary artery disease.

"Cellular senescence" (Cell Cycle Arrest) and "Inflammaging"

- Mitochondrial dysfunction, decline in phagocytosis and shortened telomeres
- Senescent cells are not cleared as efficiently by the innate immune system.
  - Persistent low- grade inflammation (inflammaging)-increase in IL-6, TNF-alpha,CRP, IL-1β
- Defective autophagy, activation of inflammasome and DNA damage response
  - Increase in senescent cells-stimulation of inflammasome-release of IL-1β/IL-18 (Senescent-Associated Secretory Phenotype)
- Loss of physical function, osteoarthritis, frailty, and loss of insulin sensitivity

Haynes L . *Frontiers In Aging.*,2020 Oct 14;1.602108.
Karpuzoglu,E.,et al. *Frontiers In Immunology*. 2025 Dec 5;16:1704203.



Cellular Senescence

- Aging → Defective Autophagy → Inflammasome Activation → DNA Damage → Persistent DDR → Senescence → SASP → Inflammation & Tissue Damage → More DNA Damage & Senescence →"Age Related Diseases"

Precision Medicine and Transplant

- **What is it:** using biomarkers along with traditional clinical data to tailor and individualize medical care.
- Movement from reactive to proactive approach to care.
- Evaluating individual disease risk, evaluating for disease at an earlier stage, guiding drug dosing, guiding drug dosing, evaluating disease activity to estimate prognosis, and predict therapy responses.
- Precision health care incorporates genomics, patient and family history, comprehensive physical and clinical assessment, patient behaviors, and the patient's environment.
- Emergence of Targeted treatments.

Types of Precision Testing

- Pharmacogenetic testing
- Donor derived Cell Free DNA
- HLA DSA
- Urinary mRNA (CXCL9, TIM-3) Reflecting renal T-cell/immune activation and predicts risk of rejection
- High-resolution HLA-DQ/DP typing
- BK/CMV viral load qPCR
- CMV T cell immunity panels (CMV inSIGHT™ T Cell Immunity Panel)
- KIR-ligand mismatch-May increase NK cell-mediated immune response to graft/ rejection
- Cytokines (TNF-α,IL-2, IFN-γ)- Differences in the intensity of inflammatory responses regulated by cytokine polymorphisms
- APOL1- high-risk genotype associated with graft functional decline
- TLR4 rs49867-CMV/Bacterial Infection Susceptibility
- AI Tools (diagnosing/prognosing/guiding therapy)

Zhang Y.,et al.,Frontiers In Immunology.2026, 16:1713293

Pharmacogenetics in Transplant

- Pharmacogenomics describes how one's genetic makeup affects drug metabolism
  - Correlates gene expression or single-nucleotide polymorphisms with drug efficacy and/or toxicity
- Clinical Pharmacogenetics Implementation Consortium (CPIC) provides evidence-based guidelines to interpret pharmcogenetic testing

Pharmacogenetic Testing in Transplant

Gene Tested	Medication
CYP3A5	tacrolimus
TPMT / NUDT15	azathioprine
CYP2C19	voriconazole
G6PD	dapsone

CYP3A5: tacrolimus

- Enzymes in the cytochrome P450 (CYP) 3A family are responsible for the oxidative metabolism of tacrolimus.
  - CYP3A4 and CYP3A5 are thought to be relevant in adults
- First pass metabolism and systemic clearance of drugs metabolized by CYP3A5 are susceptible to genetically determined differences in enzyme expression
- While CYP3A4 poor metabolizers are rare, absence of functional CYP3A5 is the norm in many populations.
  - most notable for white people
  - 80–85% of the population being homozygous for the variant CYP3A5*3 allele
- Retention of CYP3A5 expression has been under some evolutionary selection pressure in populations originating close to the equator

Birdwell et al. *Clin Pharmacol Ther*. 2015 Jul;98

CYP3A5: tacrolimus

CPIC GUIDELINES

Table 1 Assignment of likely metabolism phenotypes based on *CYP3A5* diplotypes

Likely phenotype	Genotypes	Examples of diplotypes[a]
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	**1/*1*
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one nonfunctional allele	**1/*3*, **1/*6*, **1/*7*
Poor metabolizer (CYP3A5 nonexpresser)	An individual carrying two nonfunctional alleles	**3/*3*, **6/*6*, **7/*7*, **3/*6*, **3/*7*, **6/*7*

[a]Additional rare variants, such as *CYP3A5*2*, **8*, and **9* may be found, which are of unknown functional significance. However, if a copy of **1* is present, expected phenotype would be intermediate metabolizer.

Birdwell et al. *Clin Pharmacol Ther.* 2015 Jul;98

CYP3A5: tacrolimus

- "Poor metabolizer" generally indicates lower dose required
- ffor tacrolimus this indicates standard dose requirements

Table 2 Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

Birdwell et al. *Clin Pharmacol Ther*. 2015 Jul;98

CYP3A5 and liver transplant

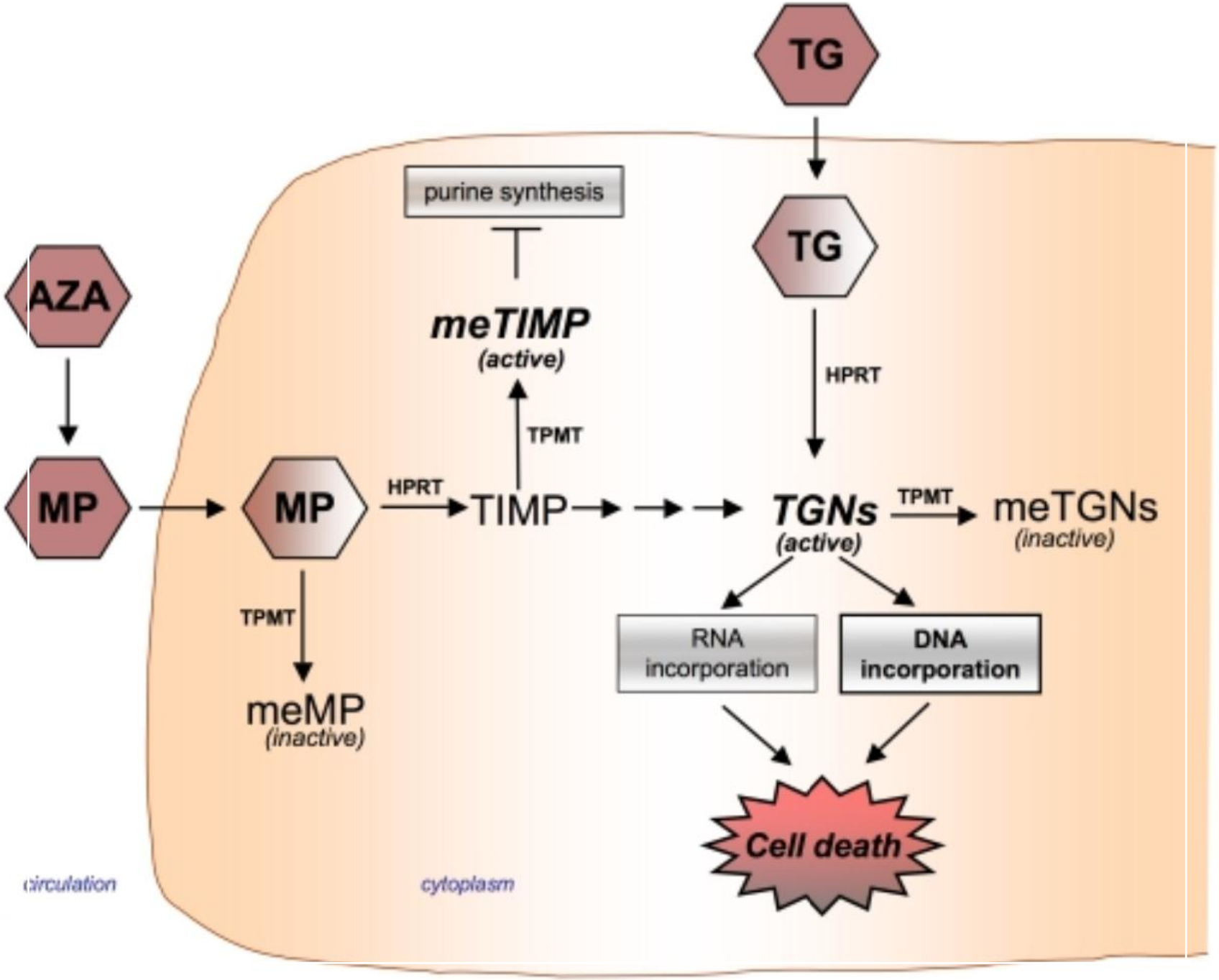
- In liver transplant recipients, the CYP3A5 genotype of the donor liver may not be the same as the CYP3A5 genotype of the recipient intestine.
- Often difficult to obtain donor pharmacogenomic testing
- Studies to date have been inconclusive as to the relative influence of the donor and recipient genotypes, and whether donor liver and recipient intestinal genotypes come into play at different points posttransplant.
  - some studies show that the donor genotype affects dose-adjusted trough concentrations from the first week posttransplant,
  - others show that it does not begin to play a role until the second week or even the sixth month posttransplant.

Birdwell et al. *Clin Pharmacol Ther*. 2015 Jul;98

TPMT / NUDT15: azathioprine

- Azathioprine is a thiopurine that is converted to mercaptopurine intracellularly
- TPMT is expressed in red blood cells, liver, and hematopoietic stem cells.
- TPMT catabolizes mercaptopurine to an inactive methylmercaptopurine base, leaving less parent drug available for potential anabolism to pharmacologically active forms
- Thioinosine monophosphate (intermediate metabolite of mercaptopurine)is also a substrate for TPMT
  - Downstream metabolites have pharmacologic activity: they inhibit de novo purine synthesis and may contribute to some of the adverse effects of mercaptopurine, particularly hepatotoxicity

Birdwell et al. *Clin Pharmacol Ther*. 2015 Jul;98



TPMT / NUDT15: AZATHIOPRINE

Table 1 Assignment of predicted TPMT and NUDT15 phenotypes based on genotypes

Predicted phenotype	Genotypes	Examples of diplotypes[a]
Assignment of predicted TPMT phenotypes based on genotypes		
Normal metabolizer	An individual carrying two normal function alleles OR one normal function allele PLUS one decreased function allele	*1/*1 *1/*8
Intermediate metabolizer	An individual carrying one normal function allele PLUS one no-function allele OR two decreased function alleles	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4 *8/*8
Possible intermediate metabolizer	An individual carrying one uncertain/unknown function allele PLUS one no-function allele OR one no-function allele PLUS one decreased function allele	*2/*9, *3A/*12 *3A/*8
Poor metabolizer	An individual carrying two no-function alleles	*3A/*3A, *2/*3A, *3A/*3C, *3C/*4, *2/*3C, *3A/*4
Indeterminate	An individual carrying one normal function allele PLUS one uncertain/unknown function allele OR one decreased function allele PLUS one uncertain/unknown function allele OR two uncertain/unknown function alleles	*1/*19 *8/*30 *19/*40
Assignment of predicted NUDT15 phenotypes based on genotypes		
Normal metabolizer	An individual carrying two normal function alleles OR one normal function allele PLUS one decreased function allele	*1/*1 *1/*5
Intermediate metabolizer	An individual carrying one normal function allele PLUS one no-function allele OR an individual carrying two decreased function alleles	*1/*2, *1/*3 *5/*5
Possible intermediate metabolizer	An individual carrying one uncertain/unknown function allele PLUS one no-function allele	*2/*15, *3/*21
Poor metabolizer	An individual carrying two no-function alleles OR one no-function allele PLUS one decreased function allele	*2/*2, *2/*3, *2/*4 *3/*5
Indeterminate	An individual carrying one normal function allele PLUS one uncertain/unknown function allele OR one decreased function allele PLUS one uncertain/unknown function allele OR two uncertain/unknown function alleles	*1/*12 *5/*20 *11/*14

TPMT / NUDT15: azathioprine

Birdwell et al. *Clin Pharmacol Ther.* 2015 Jul;98

TPMT / NUDT15: azathioprine

- A high dose of azathioprine (2mg/kg) exposes TPMT and/or NUDT15 poor metabolizers to extremely high concentrations of TGNs and potentially fatal myelosuppression.

Table 4 Azathioprine dosing recommendations based on TPMT and/or NUDT15 phenotypes for nonmalignant conditions

TPMT/NUDT15 phenotype	Implications for toxicity	Implications for phenotypic measures[a]	Therapeutic recommendations[b]	Classification of recommendation[c]
TPMT and NUDT15 normal metabolizer	Normal risk of thiopurine-related leukopenia, neutropenia and myelosuppression	TPMT NMs have lower erythrocyte concentrations of TGN metabolites and higher concentrations of MeMPNs compared to TPMT IMs and TPMT PMs. This is the 'normal' pattern.	Initiate therapy with standard starting dose (e.g., 2 mg/kg/day for autoimmune diseases). During therapy, adjust doses of azathioprine based on disease-specific guidelines. It usually takes at least 2 weeks to reach steady state after each dose adjustment.	Strong
TPMT normal metabolizer and NUDT15 (possible) intermediate metabolizer OR TPMT (possible) intermediate metabolizer and NUDT15 normal metabolizer	Increased risk of thiopurine-related leukopenia, neutropenia and myelosuppression	TPMT IMs have moderate to high erythrocyte concentrations of TGN metabolites and low concentrations of MeMPNs compared to TPMT NMs.	Initiate therapy with reduced starting doses (30–80% of standard starting dose) if standard starting dose is ≥2 mg/kg/day If starting dose is already below standard starting dose, dose reduction might not be necessary. During therapy, adjust the doses of azathioprine based on the degree of myelosuppression and disease-specific guidelines. It usually takes at least 2–4 weeks of stable dosing to reach steady state after each dose adjustment.	Strong
Any combination with TPMT poor metabolizer and/or NUDT15 poor metabolizer[d]	Greatly increased risk of thiopurine-related leukopenia, neutropenia and myelosuppression. *Fatal toxicity possible without dose decrease*	TPMT PMs have extremely high erythrocyte concentrations of TGN metabolites and no MeMPN compared to TPMT NMs.	Consider alternative nonthiopurine immunosuppressant therapy	Strong
TPMT intermediate metabolizer and NUDT15 intermediate metabolizer (i.e., TPMT/NUDT15 compound intermediate metabolizer)	Increased risk of thiopurine-related leukopenia, neutropenia and myelosuppression Higher risk of toxicity compared to single IM	TPMT IMs have moderate to high erythrocyte concentrations of TGN metabolites and low concentrations of MeMPNs compared to TPMT NMs.	Initiate therapy with reduced starting doses (20–50% of standard starting dose) if standard starting dose[a] is ≥2 mg/kg/day If starting dose is already below standard starting dose, dose reduction might not be necessary. During therapy, adjust the doses of azathioprine based on the degree of myelosuppression and disease-specific guidelines. It usually takes at least 2–4 weeks of stable dosing to reach steady state after each dose adjustment.	Moderate

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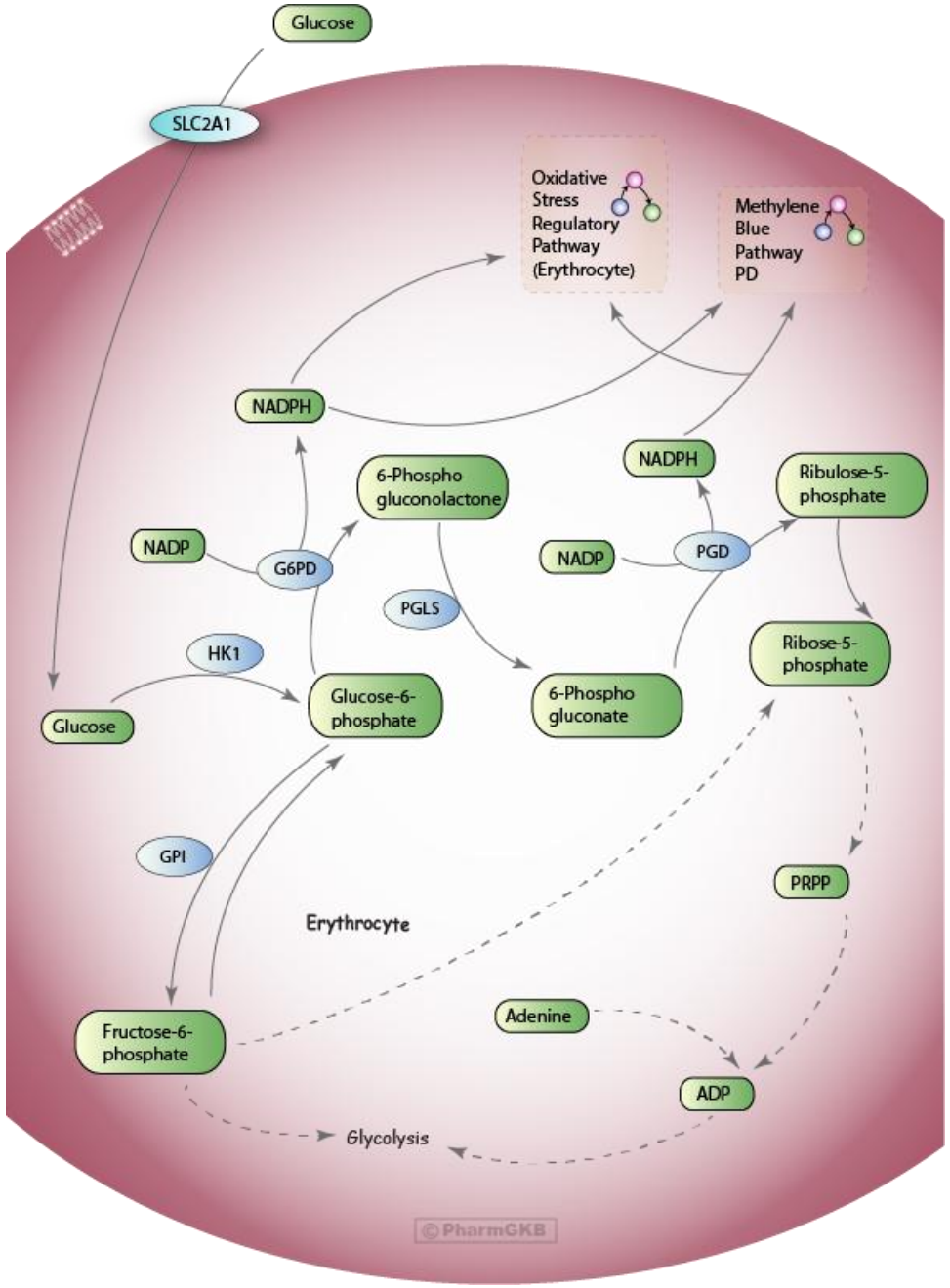
G6PD: dapsone

- The G6PD gene encodes the G6PD enzyme, which converts glucose-6-phosphate into 6-phosphogluconolactone, the first step of the pentose phosphate pathway



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G6PD: dapsone

Table 1 Assignment of predicted G6PD phenotype based on genotype

Predicted phenotype	Genotype[a]	Examples of *G6PD* genotypes[b]
Normal	A person with one X chromosome carrying a nondeficient (class IV) allele A person carrying two nondeficient (class IV) alleles	B, Sao Borja, IV B/B, B/Sao Borja, B/A, IV/IV
Deficient	A person with one X chromosome carrying a deficient (class II–III) allele A person carrying two deficient (class II–III) alleles OR one class I allele and one class II or III allele	A-, Orissa, Kalyan-Kerala, Mediterranean, Canton, Chatham, II, III A-/A-, A-/Orissa, Orissa/Kalyan-Kerala, Mediterranean/Mediterranean, Chatham/Mediterranean, Canton/Viangchan, II/II, II/III, III/III, I/II, I/III
Deficient with CNSHA	A person with one X chromosome carrying a deficient (class I) allele A person carrying two deficient (class I) alleles[c]	Bangkok, Villeurbanne, I Bangkok/Bangkok, Bangkok/Villeurbanne, I/I
Variable[d]	A person carrying one nondeficient (class IV) allele and one deficient (class I–III) allele	B/Bangkok, B/Mediterranean, B/A-, IV/I, IV/II, IV/III
Indeterminate	A person carrying at least one uncertain function allele	Laibin, Yunan B/Yunan, II/Yunan, III/Laibin, IV/Yunan

Birdwell et al Clin Pharmacol Ther. 2015 Jul;98

Predicted G6PD phenotype based on genotype	Implications for phenotypic measures	Therapeutic recommendations for high-risk drugs
Normal	Low risk of acute hemolytic anemia	No reason to avoid high-risk drugs based on G6PD status
Deficient	High risk of acute hemolytic anemia	Avoid use of high-risk drugs
Deficient with CNSHA	High risk of acute exacerbation of chronic hemolysis	Avoid use of high-risk drugs
Variable	Variable risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype
Indeterminate	Unknown risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype

G6PD: dapsone

Birdwell et al. *Clin Pharmacol Ther*. 2015 Jul;98

CYP2C19: voriconazole

- Voriconazole demonstrates wide interpatient variability in serum concentrations, due in part to variant CYP2C19 alleles
- CYP2C19 is highly polymorphic with 35 defined variant star (*) alleles

Table 1 Assignment of likely CYP2C19 phenotypes based on genotypes

Likely phenotype	Genotypes[a]	Examples of *CYP2C19* diplotypes
CYP2C19 ultrarapid metabolizer (~2–5% of patients)[b]	An individual carrying two increased function alleles	**17/*17*
CYP2C19 rapid metabolizer (~2–30% of patients)[b]	An individual carrying one normal function allele and one increased function allele	**1/*17*
CYP2C19 normal metabolizer[c] (~35–50% of patients)[b]	An individual carrying two normal function alleles	**1/*1*
CYP2C19 intermediate metabolizer (~18–45% of patients)[b]	An individual carrying one normal function allele and one no function allele or one no function allele and one increased function allele	**1/*2*, **1/*3*, **2/*17*[d]
CYP2C19 poor metabolizer (~2–15% of patients)[b]	An individual carrying two no function alleles	**2/*2*, **2/*3*, **3/*3*

Birdwell et al *Clin Pharmacol Ther.* 2015 Jul;98

CYP2C19: voriconazole

- Alternative agents recommended for ultrarapid, rapid, and poor metabolizers

Table 2 Dosing recommendations for voriconazole treatment based on CYP2C19 phenotype for adult patients

CYP2C19 phenotype	Implications for voriconazole pharmacologic measures	Therapeutic recommendations	Classification of recommendations[a]
CYP2C19 ultrarapid metabolizer (*17/*17)	In patients for whom an ultrarapid metabolizer genotype (*17/*17) is identified, the probability of attainment of therapeutic voriconazole concentrations is small with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b]	Moderate[c]
CYP2C19 rapid metabolizer (*1/*17)	In patients for whom a rapid metabolizer genotype (*1/*17) is identified, the probability of attainment of therapeutic concentrations is modest with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b]	Moderate
CYP2C19 normal metabolizer	Normal voriconazole metabolism	Initiate therapy with recommended standard of care dosing[b]	Strong
CYP2C19 intermediate metabolizer	Higher dose-adjusted trough concentrations of voriconazole compared with normal metabolizers	Initiate therapy with recommended standard of care dosing[b]	Moderate
CYP2C19 poor metabolizer	Higher dose-adjusted trough concentrations of voriconazole and may increase probability of adverse events	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b] In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice, for a patient with poor metabolizer genotype, voriconazole should be administered at a preferably lower than standard dosage with careful therapeutic drug monitoring.	Moderate

Birdwell et al. *Clin Pharmacol Ther*. 2015 Jul;98

Pharmacogenomic Results

CYP2C19 *1/*17 (Drug response)
Genotypes: CYP2C19 *1/*17

CYP2C9 *1/*1 (Drug response)
Genotypes: CYP2C9 *1/*1

CYP2D6 (*4/*4)2N (Drug response)
Genotypes: CYP2D6 (*4/*4)2N

CYP3A5 *3/*3 (Drug response)
Genotypes: CYP3A5 *3/*3

CYP4F2 *1/*3 (Drug response)
Genotypes: CYP4F2 *1/*3

DPYD Reference/Reference (Drug response)
Genotypes: DPYD Reference/Reference

NUDT15 *1/*1 (Drug response)
Genotypes: NUDT15 *1/*1

SLCO1B1 *1/*1 (Drug response)
Genotypes: SLCO1B1 *1/*1

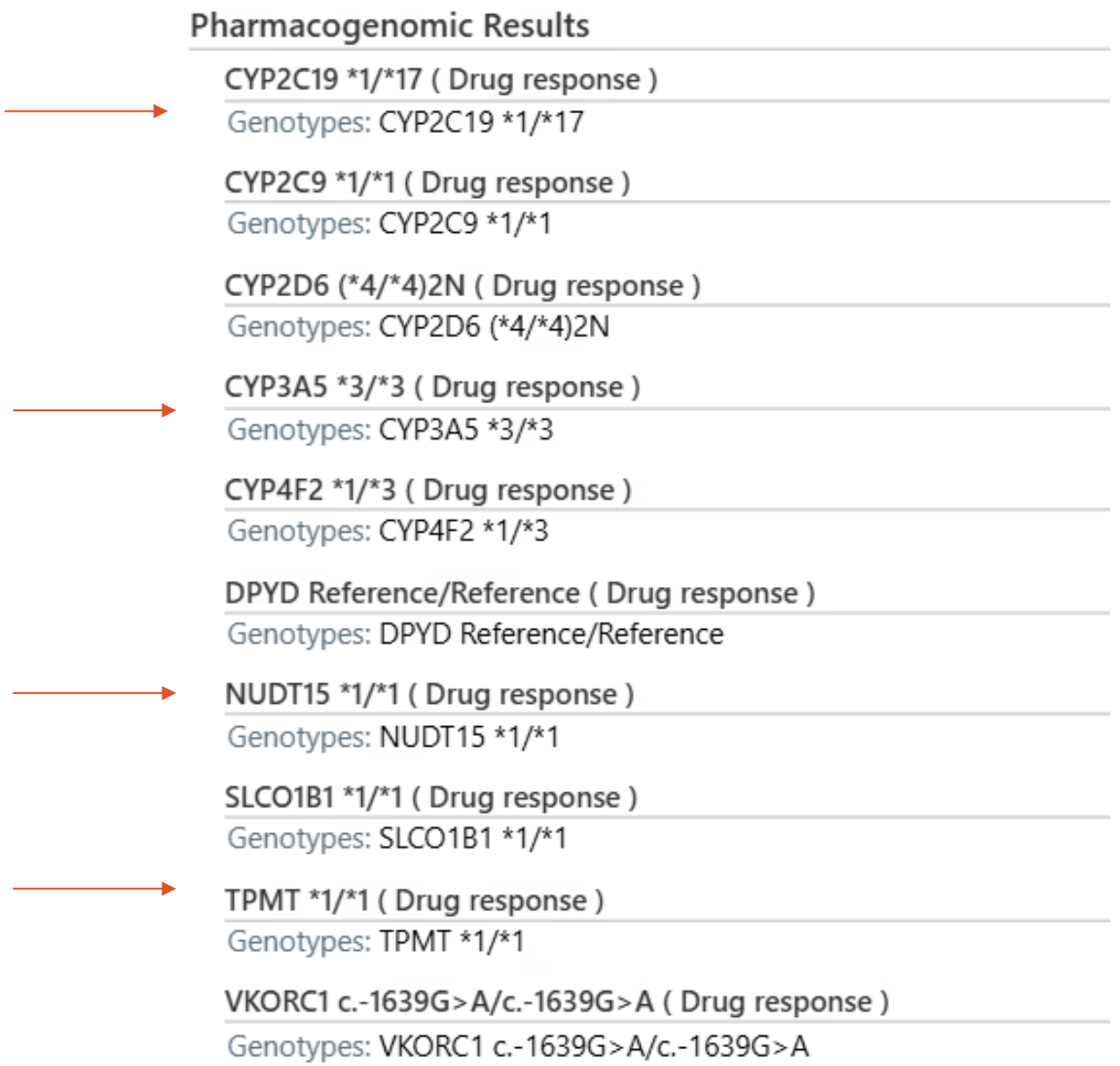
TPMT *1/*1 (Drug response)
Genotypes: TPMT *1/*1

VKORC1 c.-1639G>A/c.-1639G>A (Drug response)
Genotypes: VKORC1 c.-1639G>A/c.-1639G>A

Practical Application

Practical Application

- CYP2C19 *1/*17
  - Voriconazole rapid metabolizer
- CYP3A5 *3*3
  - Tacrolimus poor metabolizer
- NUDT15 / TPMT *1*1
  - Azathioprine normal metabolizer



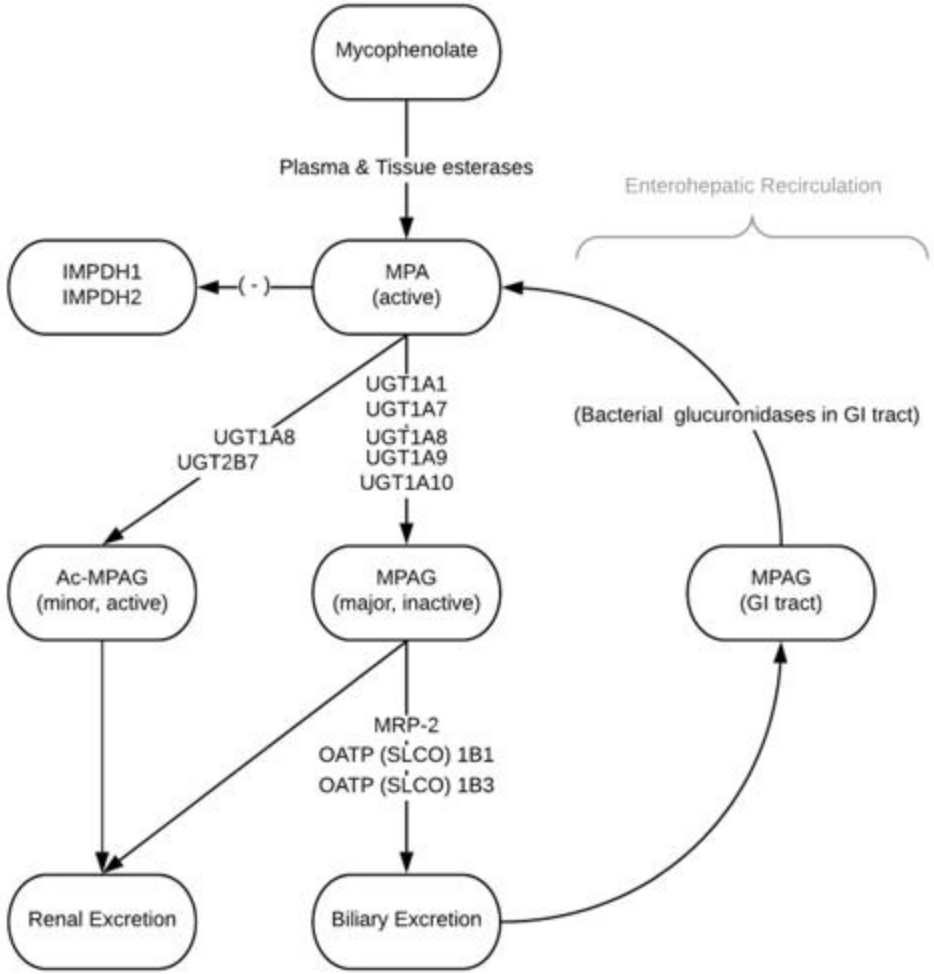
UGT1A9: mycophenolate mofetil

- Mycophenolic acid (MPA), the active metabolite of the prodrug mycophenolate mofetil (MMF), is a standard immunosuppressive drug used after hematopoietic stem cell and solid organ transplantation.
- The pharmacokinetic profile of the drug and its phenolic (MPAG) and acyl (AcMPAG) glucuronides is characterized by unexplained interindividual variation.
- CPIC does not have a published clinical guideline for UGT1A9 and its impact on MMF.

Levesque et al. *Blood*. 2006 108(11), 3191

Mycophenolate therapeutic drug monitoring

- Single time point drug levels not accurate due to complicated pharmacokinetics
  - Non-linear absorption kinetics
  - Enterohepatic circulation
- Estimated MPA area under the curve (AUC) is more successful
  - Impractical because it requires multiple lab draws across several hours



Beran et al. *Ther Drug Monitoring*. 2021 April 43(2)

ROLE OF THE APP IN PRECISION MEDICINE

Precision Medicine and the APP- Implementation

- Obtain Thorough History:
  - Family
  - Patient
- Clinical Assessment
- Assess Patient Behavior
- Economic Issues/Financial Burden
- Evaluate environmental factors
- Biomedical Results (labs, biopsies, PFT's, Echo)
- Review of Imaging/Ordering New Imaging
- Goal is to determine disease susceptibility, exposures, and potential response/lack of response to treatment
- Initiate precision testing pre-transplant/post-transplant

Precision Medicine at all Phases of Transplant

- Pre-Transplant:
  - High Resolution HLA Typing
  - PRA (panel reactive antibody)
  - CYP3A5 Genotype/Polymorphisms
  - UGT1A9-Mycophenolic acid exposure/toxicity
  - TPMT and NUDT15 –azathioprine metabolism/risk of myelosuppression
- Peri-Operatively: Pharmacogenetic Guide Dosing
  - Refer to results of pharmacogenetic testing
- Post-Transplant: Non-invasive rejection Monitoring
  - dd-cfDNA
  - HLA DSA (donor specific anti-HLA antibodies)
  - CMV/BK Virus Monitoring

Donor Derived Cell Free DNA (dd-cfDNA)

- DNA fragments released in bloodstream and detected at molecular level
  - Allosure-CareDx and Pospera-Natera
  - DNA fragments released during cellular apoptosis and necrosis
- Non-invasive biomarker of allograft injury(not necessarily specific to rejection but can be a marker of rejection). Can also be a marker of subclinical graft injury in the absence of clinical symptoms.
- Absolute dd-cfDNA values are not directly comparable across laboratories due to differences in extraction methods, sample preservation, and quantification techniques

Kang,H., et al., *Clinical Transplantation and Research*. 2025 Sep 30;39(3):200-213.

Donor Derived Cell Free DNA (dd-cfDNA)

- May be used in place of or in conjunction with a biopsy.
- May be used to direct/tailor immunosuppression.
- Combining dd-cfDNA with other biomarkers:
  - DSA testing
  - Labs
  - Imaging in addition to clinical picture can help guide clinical decisions
- Recommended to measure serial measurements and monitor trends (false-positives and false-negatives).
- Can be elevated in setting of infection, ischemia, or inflammation.
- Interpretation based on:
- Type of transplant
  - Time post-transplant
  - Clinical picture (malignancy, infection, leukopenia, ischemia).

Kang,H., et al., *Clinical Transplantation and Research*. 2025 Sep 30;39(3):200-213.

Donor Derived Cell Free DNA (dd-cfDNA) and Role of the APP

- Establish protocol for obtaining dd-cfDNA in the post-transplant recipient.
- Identify high risk patients that could benefit from dd-cfDNA vs biopsy.
- Educate patient as to usefulness of dd-cfDNA.
- Make sure samples are obtained in correct tube as provided by the company running the test (cannot use conventional EDTA tubes).
- Providers typically supply collection kits, prepaid shipping, and electronic reporting.
- Obtain dd-cfDNA along with DSA, biopsy, lab, imaging, and/or clinical evaluation to drive treatment or observation. Biopsy is still "Gold Standard".
- Using dd-cfDNA may minimize the need for invasive procedure, guide treatment, and detect injury earlier.

Kang,H., et al., *Clinical Transplantation and Research.* 2025 Sep 30;39(3):200-213.

Cell Free DNA (dd-cfDNA)
What is currently available?

- **Allosure (Caredx)**
- **Prospera (Natera)**
- TRAC (Viracor Eurofins)
- AlloNext (Eurofins Genome)
- One Lambda Devyser Accept cfDNA (Devyser)
- GraftAssureCore (previously VitaGraft)
- iMDx (previously Oncocyte)
- HoloGRAFT ONE (Omixon)

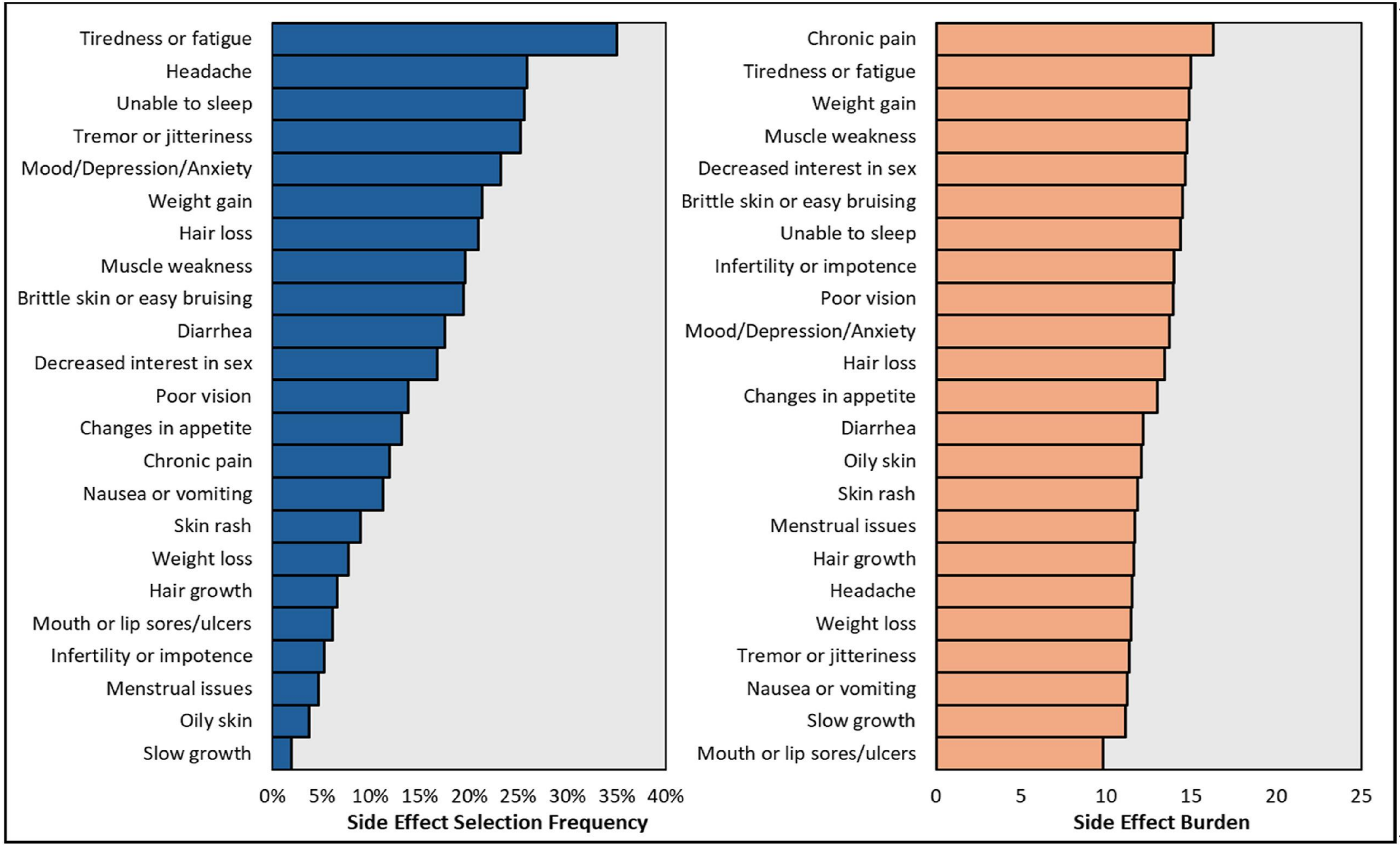
WHAT DOES ALL THIS MEAN FOR PATIENTS?

"The Patient Experience"

Immunosuppression and Side Effects

- American Society of Transplantation: Web-based study of 10,091 responses included (9543 adults, 548 pediatric respondents) to assess burden of immunosuppression and quality of life.
- **92%** reported at least one side effect and **63%** reported side effect as occurring "often" or "always"
- **54%** of side effects were rated as having a "moderate" or "great deal" of impact on daily life.
- Those ≥60 years had **23%** higher side effect burden compared to <60 year
- Immunosuppression causes side effects and heavy burden to patients.
- More concern among respondents about infection and cancer versus graft loss and rejection although still rated as high concern.
- Most concerning issues related to self-care: interference related to travel for work or vacation, feeling dependent, interference in hobbies or daily activities.
- Issues with lowest concern: tracking medical appointments, keeping appointments, monitoring health conditions.
- Despite burden adherence is HIGH. (**25%** skipped doses due to side effects and **40%** missed refill due to cost)

Taber,K., et al., *American Journal of Transplantation.Volume* 25, Issue 12, December 2025, Pages 2565-2577



Taber,D., et al., *American Journal of Transplantation*, Volume 25, Issue 12, December 2025, Pages 2565-2577.

Precision Medicine & the APP

Moore,D,et al., *J Adv Pract Oncol.* 2023 Apr 1;14(Suppl 1):39-48.

Precision Medicine and the Advanced Provider

- Personalize and tailor care to improve care while maintaining a holistic approach to care.
- Implement biomarker testing.
- Develop a treatment plan.
- Order specific tests and/or biopsies.
- Administer therapy and monitor/manage adverse effects.
- Collaborate with pharmacist and physician to coordinate care (multidisciplinary).
- Educate patients and colleagues about precision testing.
- Aim to improve graft survival, reduce cost due to lower immunosuppression, and avoid side effects.

Moore,D.,et al.,*J Adv Pract Oncol.* 2023 Apr 1;14(Suppl 1):39–48

Summary

- Immunosuppression continues to evolve and we are trying to move from a "one size fits all" approach to a more patient specific and tailored strategy.
- Certain patient populations present challenges to immunosuppression, and this must be taken into consideration.
- In the last 10-20 years there has been an increase in transplant recipients 65 years and older and precision medicine could lend insight into how this patient population's more fragile immune system is impacted by immunosuppression.
- Despite side effects of immunosuppression there is high compliance however, precision medicine offers a better balance between over and underimmunosuppression while minimizing side effects.
- Precision medicine should be implemented at specific times in the transplant phase to help guide treatment and improve outcomes.
- Recommended precision testing if feasible: pharmacogenetic testing, HLA DSA, dd-cfDNA, Viral PCR testing to name a few can be implemented.
- The APP is an integral part of the interdisciplinary team who can determine how and when to implement precision testing in the transplant recipient.
- It is crucial for the APP to be aware of what precision testing is available and educate the patient and colleagues about these tests.
- Leverage patient outcomes, treatment burden, and graft survival.