What the Diabetes Team Needs to Know About Kidney Transplant

Indian Health Service Division of Diabetes Treatment and Prevention CME/CE Webinar

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University of Utah Campus

Resources

- https://esrdncc.org/en/patients/ (Transplant Section)
- https://kdigo.org/guidelines/ (Transplant Recipient Tile)
  - https://kdigo.org/wp-content/uploads/2017/02/Managing-Your-Adult-Patients-Who-Have-a-Kidney-Transplant-kdigo.pdf
  - https://kdigo.org/wp-content/uploads/2017/02/KDIGO_TX_NephsTool-Managing-Kidney-Transplant-Recipients.pdf
- https://www.myast.org/guidelines-post-kidney-transplant-management-community-setting

AMERICAN SOCIETY OF TRANSPLANTATION

Learner Objectives and Outcomes

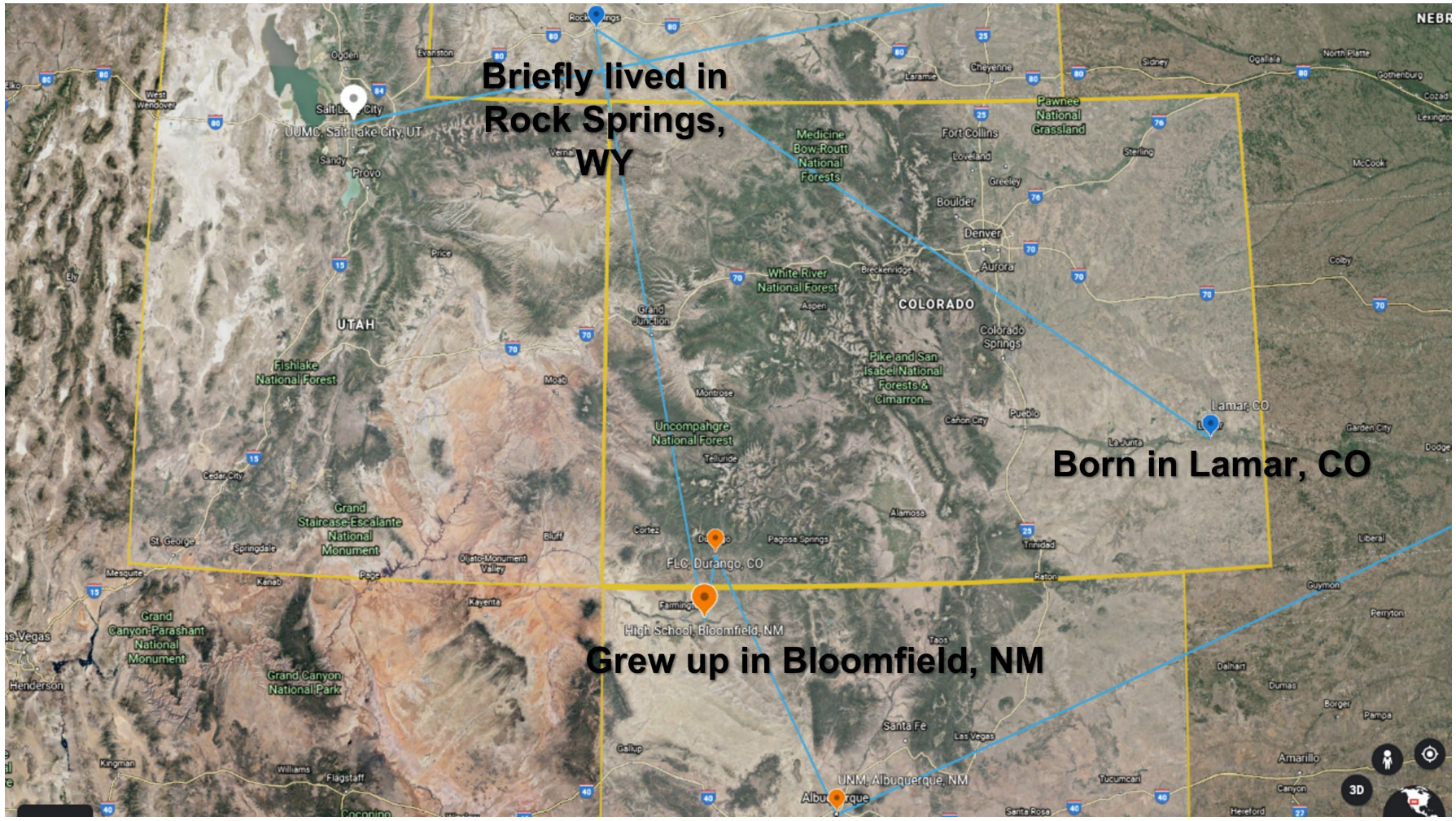
At the end of the presentation, participants will be able to:

1. Utilize lab tests for monitoring kidney graft function.
2. Describe important long-term complications of kidney transplantation.
3. Discuss prevention and management strategies for common complications in patients with kidney transplants.
4. Identify at least one change you will incorporate into your clinical or community health practice as a result of the training.

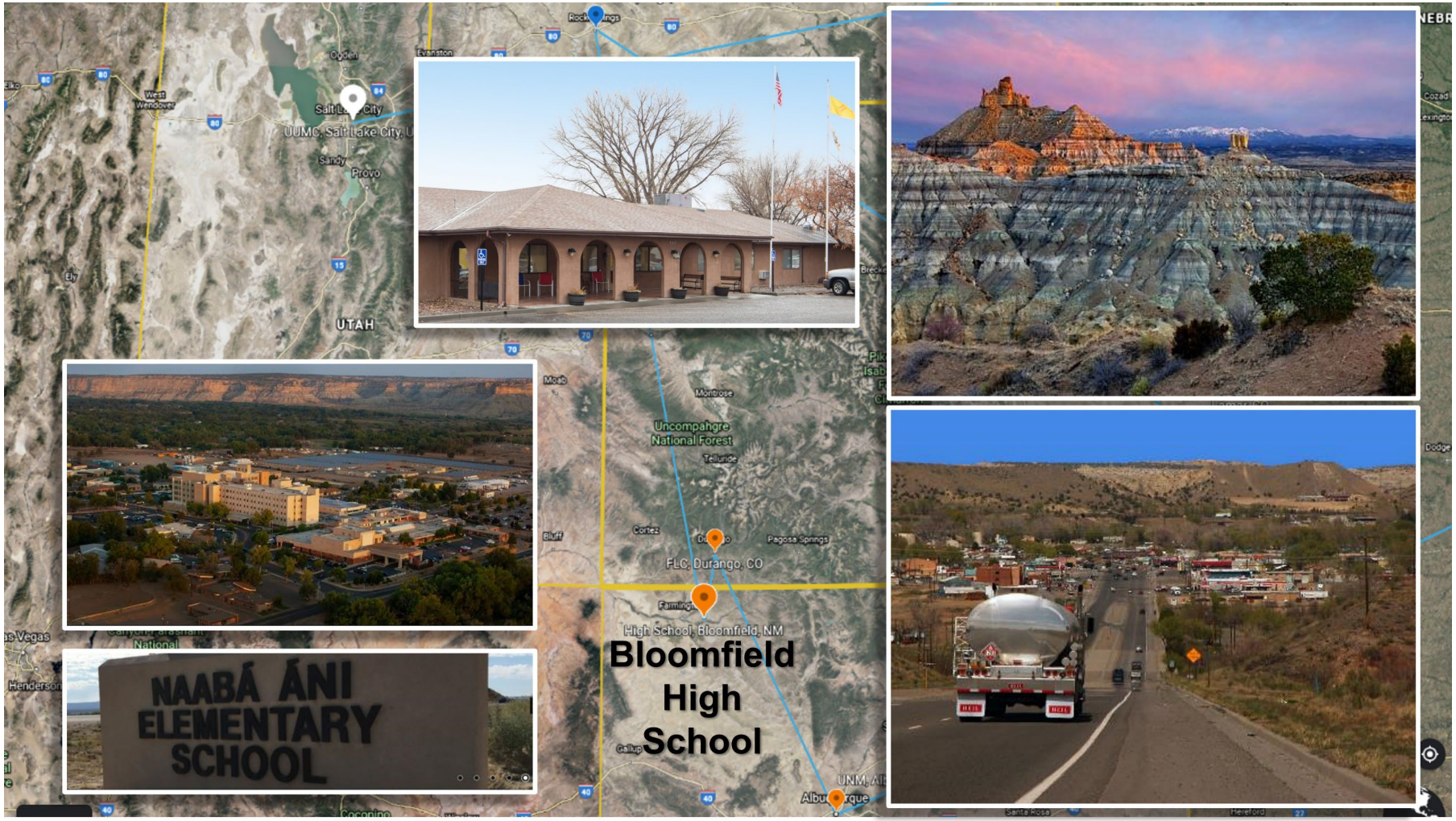
Outline

1. Brief introduction of myself
2. Kidney transplant as one of the options for renal replacement therapy
3. Immunosuppressive transplant medications
4. Long-term care of kidney transplant recipients
    i. Kidney allograft dysfunction
    ii. Cardiovascular disease risk reduction
    iii. Diabetes after transplant
    iv. Infection
    v. Cancer
    vi. Other issues/complications

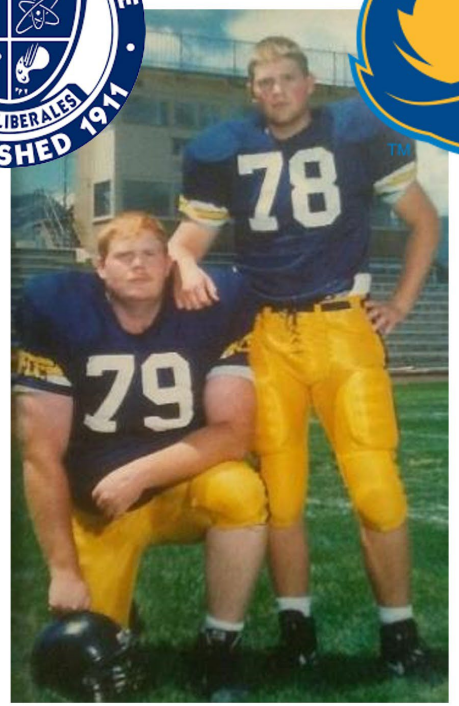
Backstory

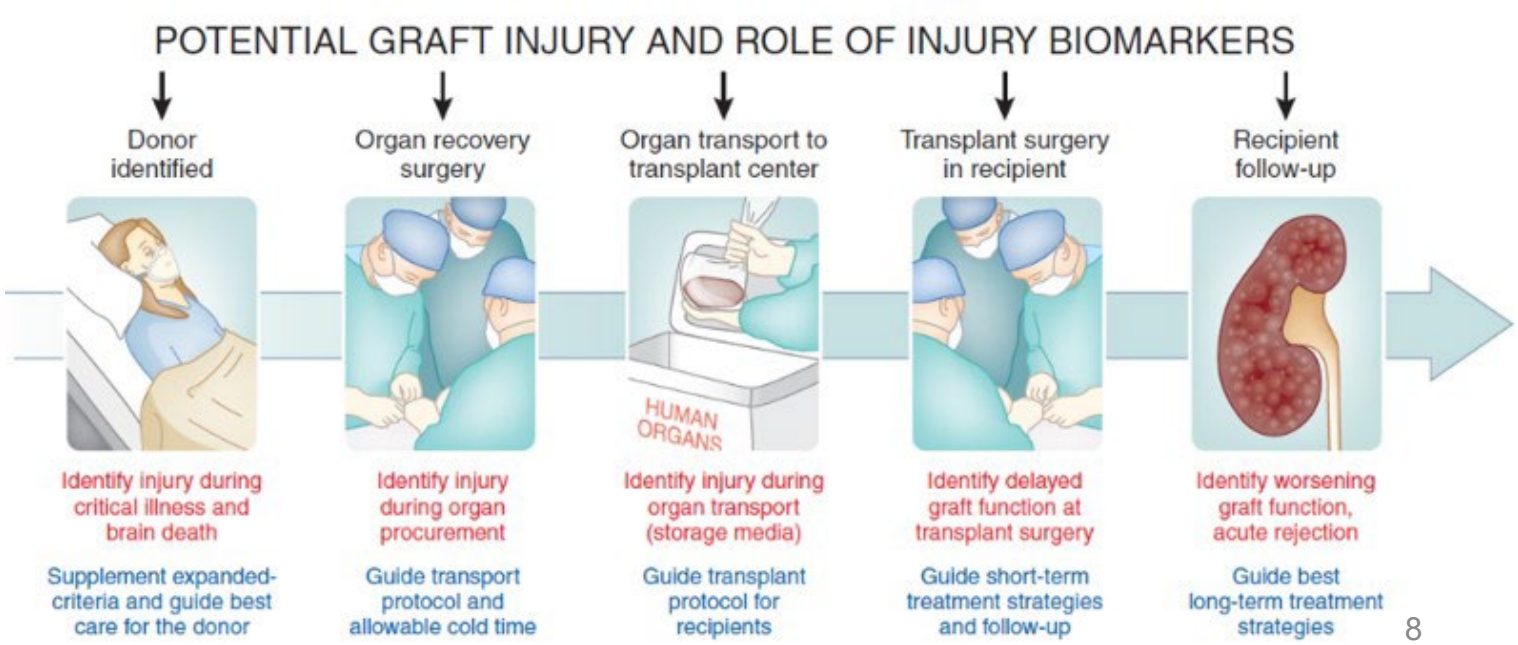

Briefly lived in Rock Springs, WY
Born in Lamar, CO
Grew up in Bloomfield, NM
UUMC, Salt Lake City, UT
FLC, Durango, CO
High School, Bloomfield, NM
UNM, Albuquerque, NM
UTAH
COLORADO
Lamar, CO
Rock Springs
Salt Lake City
Durango
Bloomfield
Albuquerque

Bloomfield

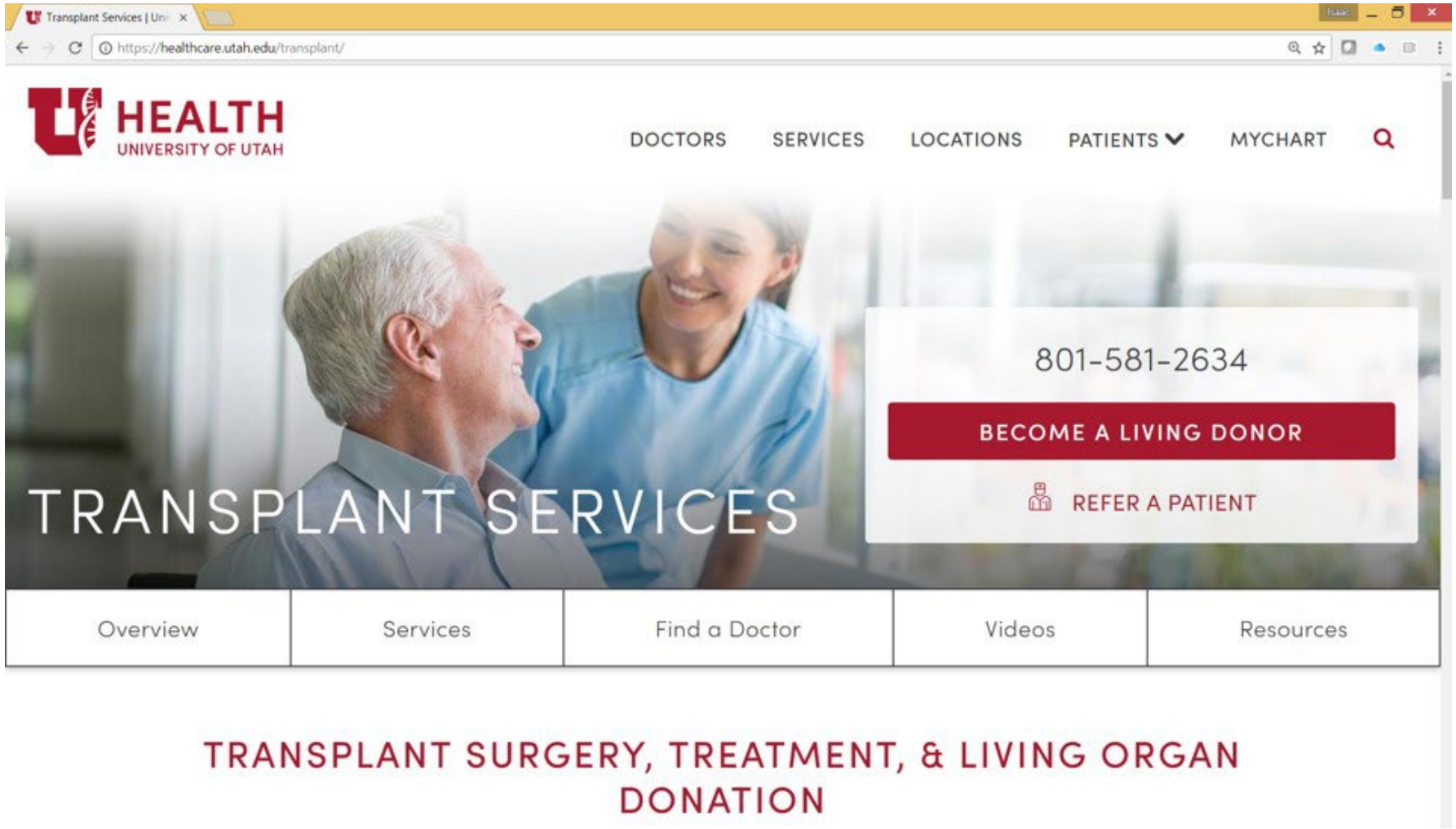

UTAH
Uncompahgre National Forest
FLC, Durango, CO
High School, Bloomfield, NM
Bloomfield High School
NAABÁ ÁNI ELEMENTARY SCHOOL

College, Medical School, Residency/Fellowship/Research





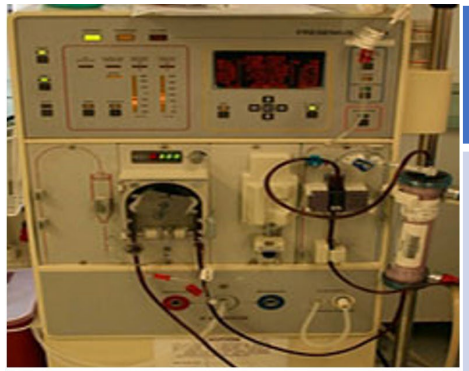
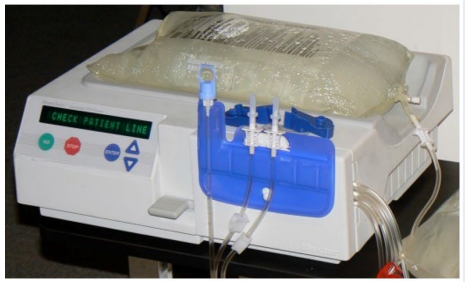
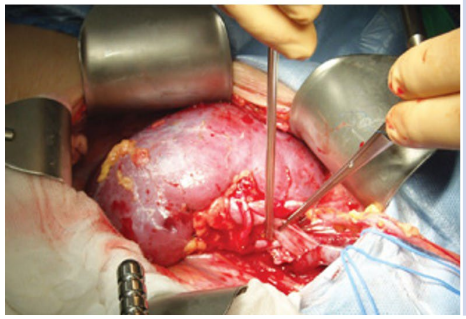
Email: isaac.hall@hsc.utah.edu



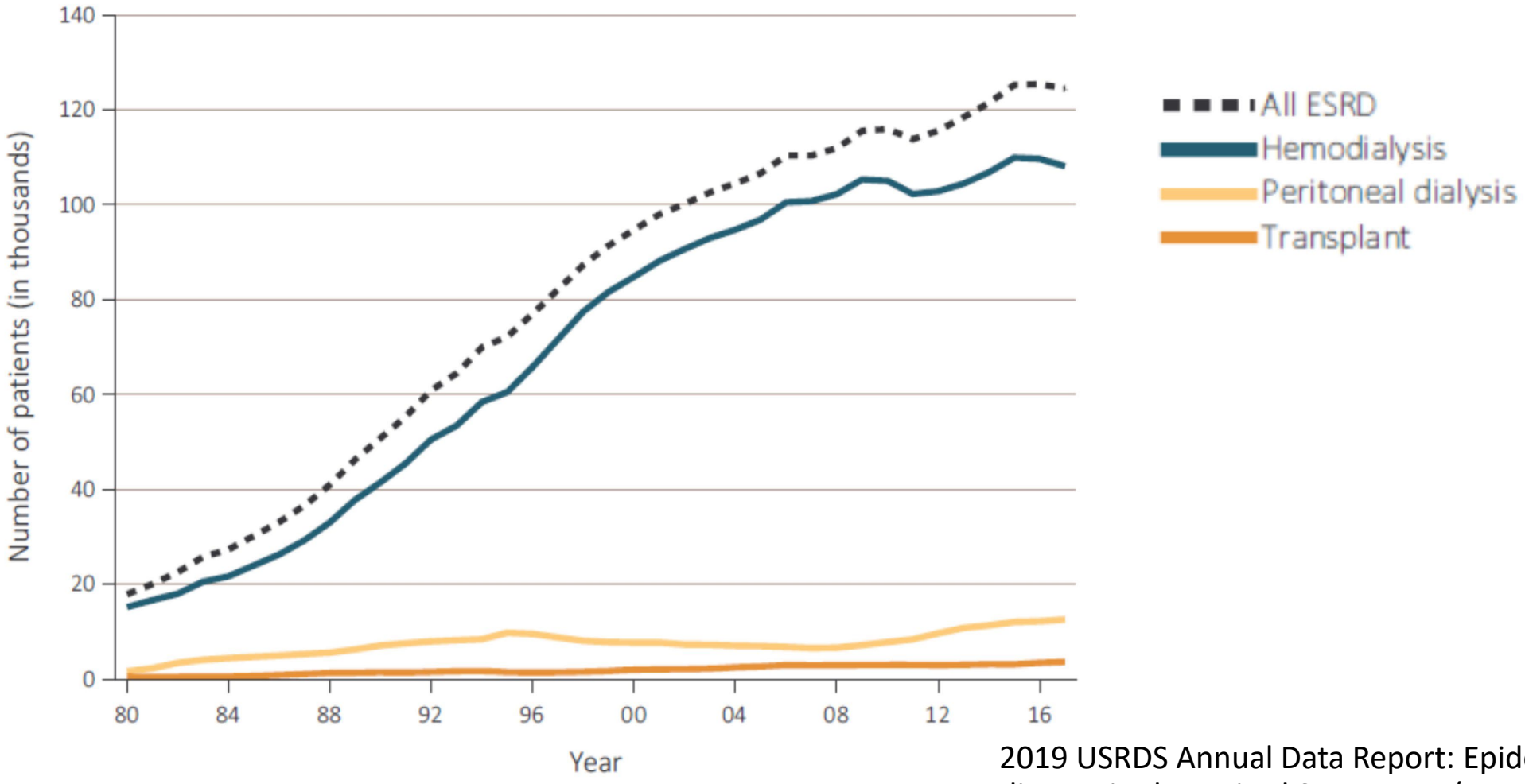
Outline – Step 2

Step 2: Kidney transplant as one of the options for renal replacement therapy.

Renal Replacement Therapies

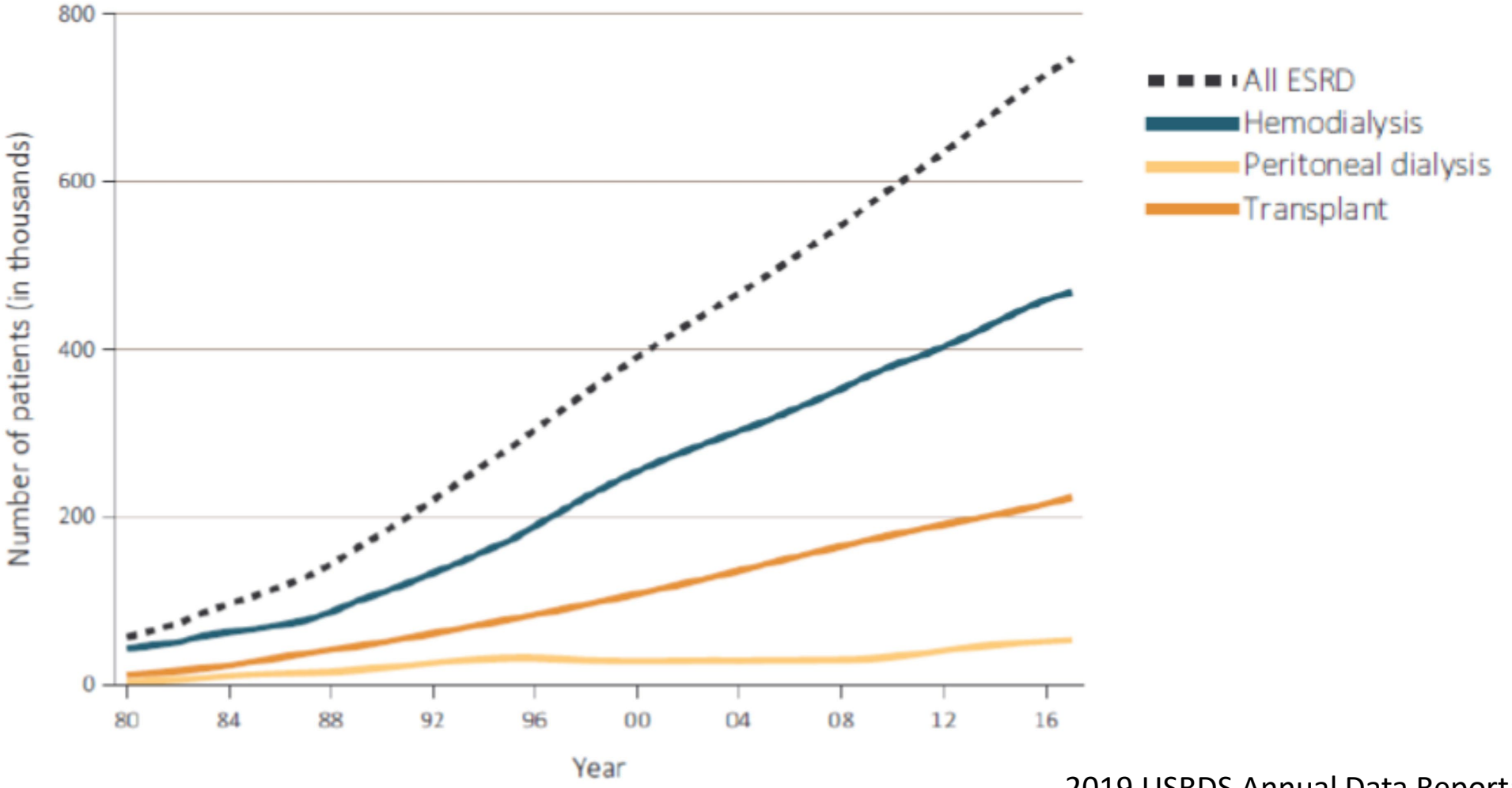
	Therapy	Pros	Cons
	**Hemo-dialysis (HD)**	Short treatments Good small salute removal Socialization at dialysis	Vascular access Strict diet, fluid intake Variable fluid status & BP Fatigue post dialysis
	**Peritoneal Dialysis (PD)**	Self-care treatments Good large salute removal Better Hgb & steady labs More liberal diet	Peritoneal access Frequent/daily treatments High glucose/obesity Protein loss/malnutrition Hernias/back pain
	**Kidney Transplant (KT)**	No dialysis treatments Normal solute removal Most liberal diet Improved sex-repro function Best quality/quantity of life	Chronic immunosuppression Strict med adherence, pill burden & interactions Clinic visits & complications Diabetes, obesity, lipids

Though Recently Slowed, End-stage Renal Disease (ESRD) Incidence Continues to Rise in the U.S.



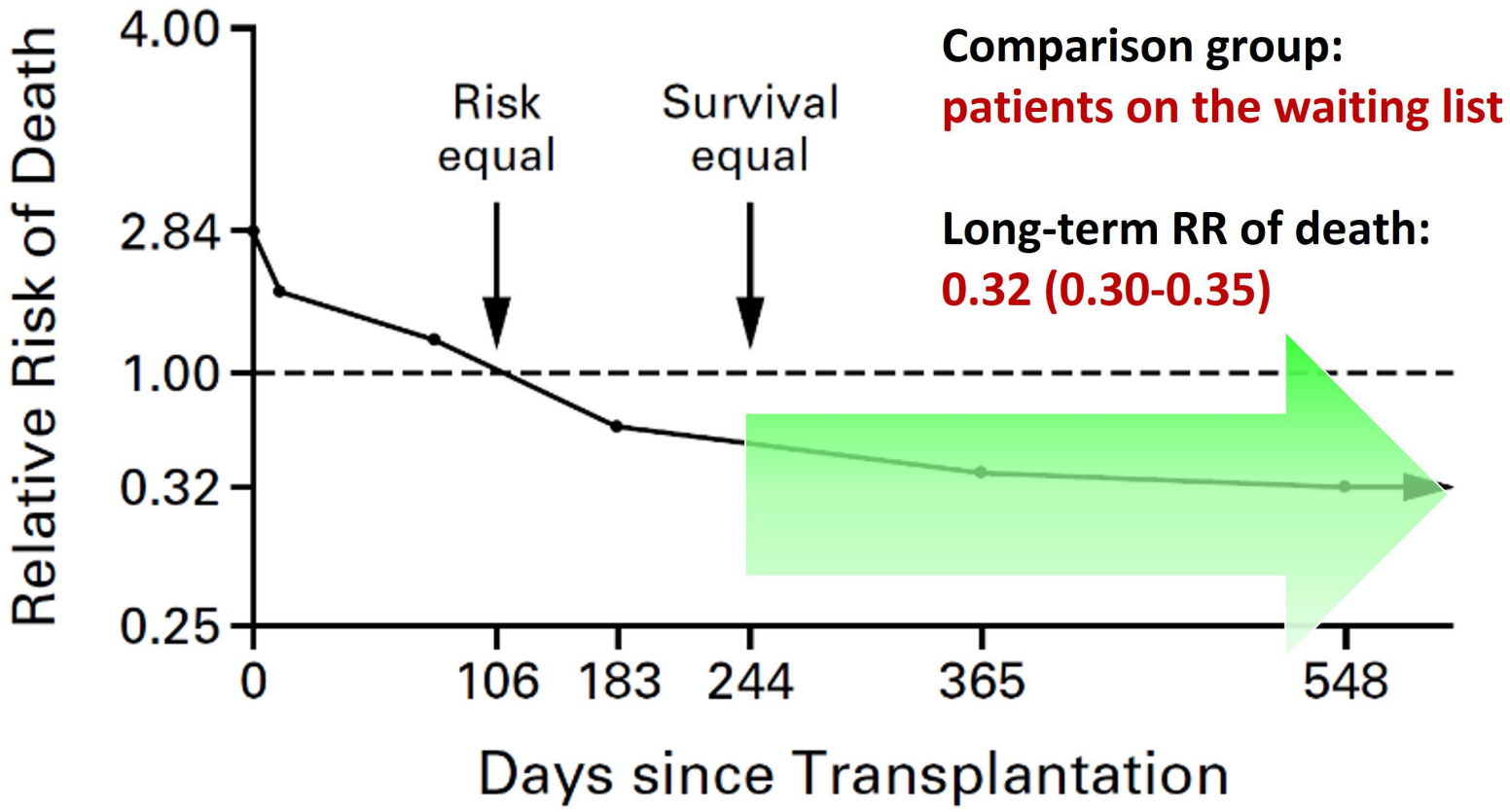
2019 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. NIH/NIDDK, Bethesda, MD.

Patients are Living Longer With Renal Replacement Leading to Increasing ESRD Prevalence



2019 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. NIH/NIDDK, Bethesda, MD.

Transplant Improves Survival



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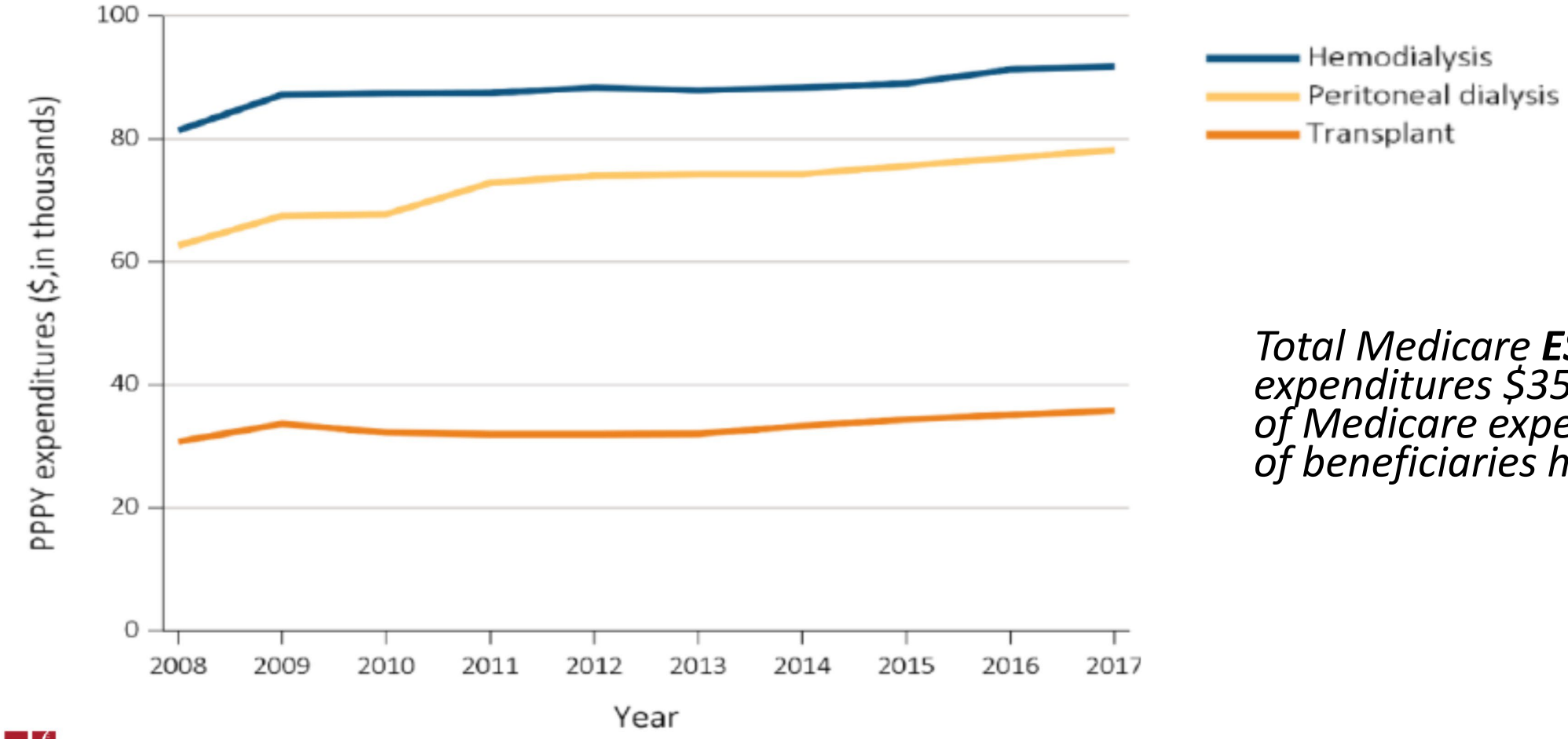
Wolfe RA, et al. *NEJM* 1999; 341;1725-30

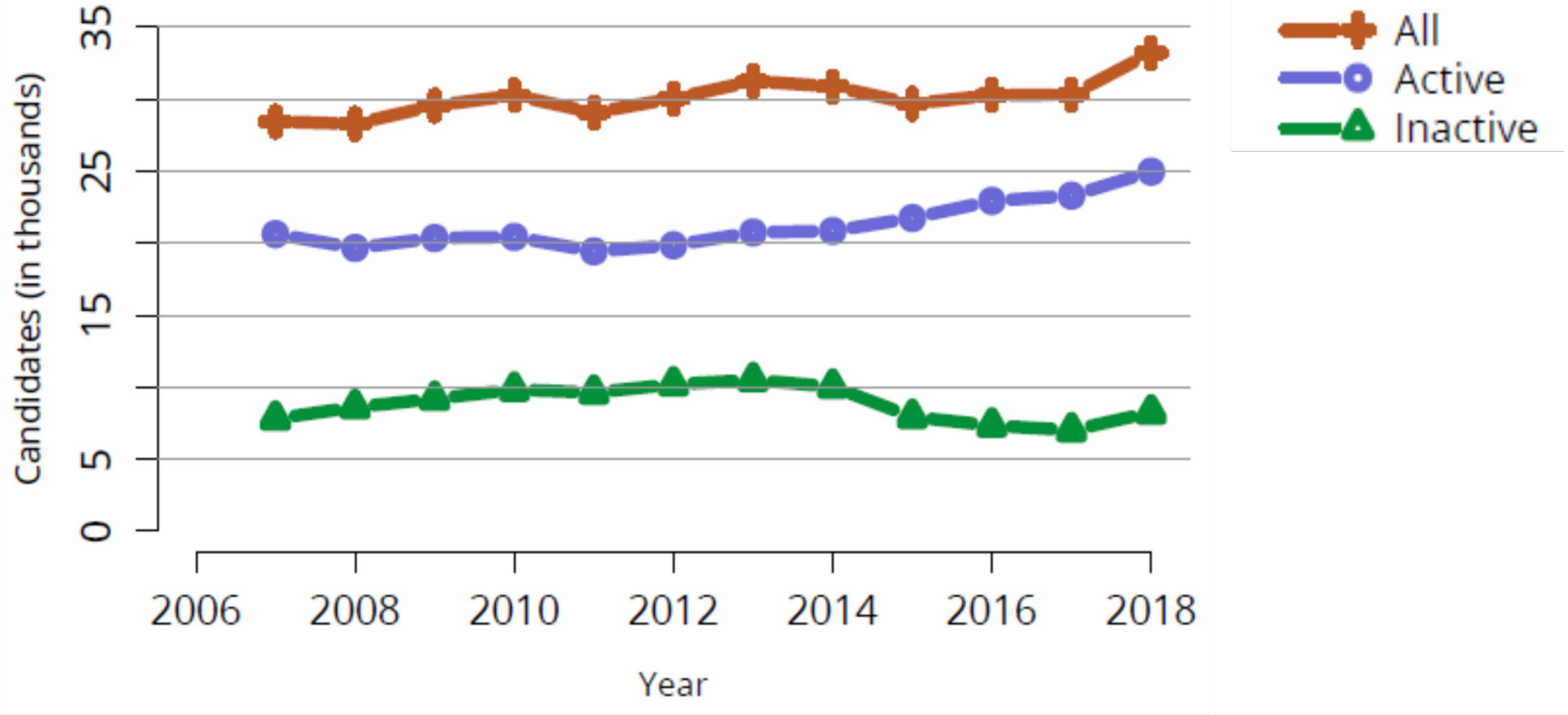
Kidney Transplantation is Less Than Half the Cost of Hemodialysis Per Patient Per Year



*Total Medicare **ESRD** expenditures $35B annually (7% of Medicare expenditures, <1% of beneficiaries have ESRD)*

2019 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. NIH/NIDDK, Bethesda, MD.

Over 30,000 Patients are Added to the Kidney Waiting List Every Year



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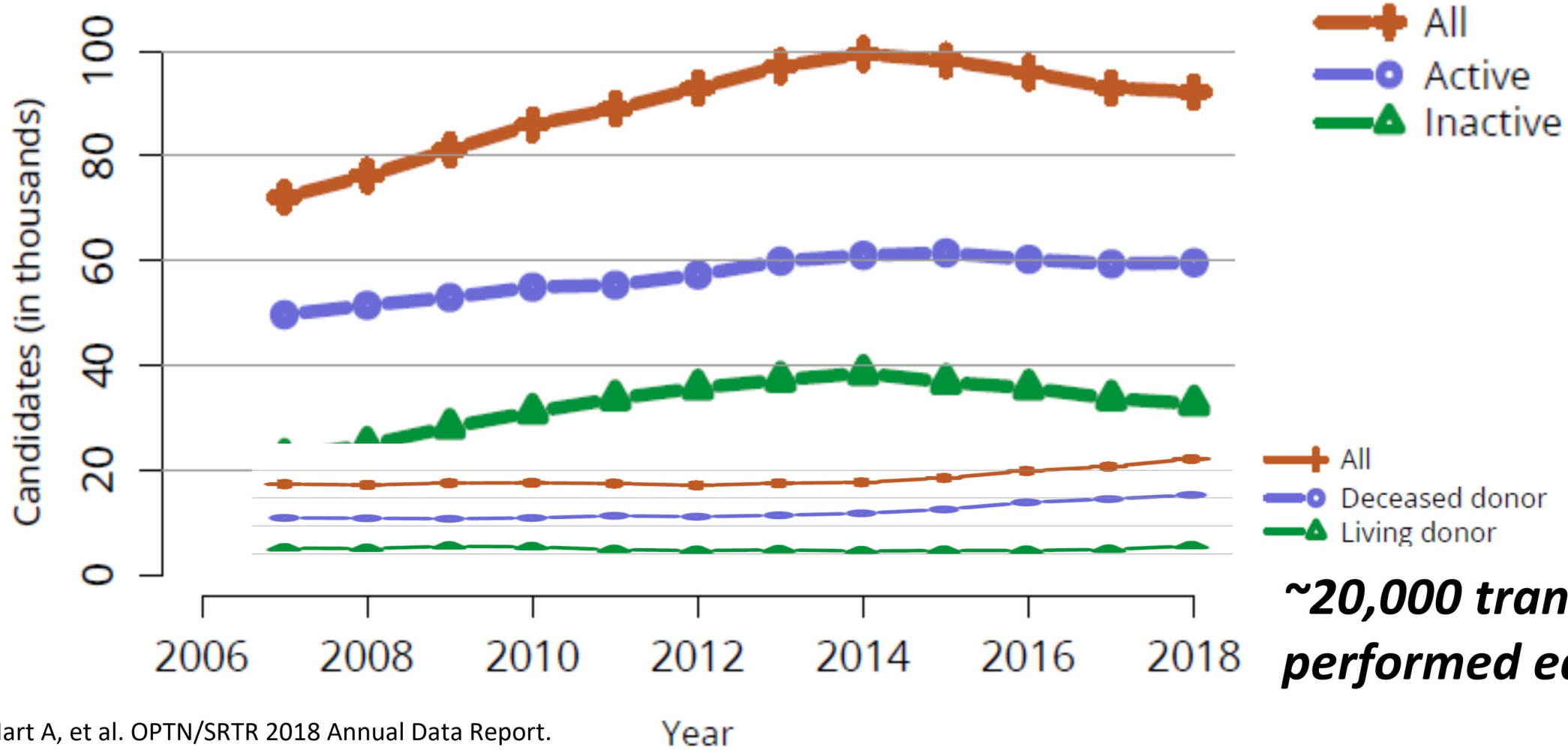
Hart A, et al. OPTN/SRTR 2018 Annual Data Report. *Am J Transplant* 2020;20:20-130.

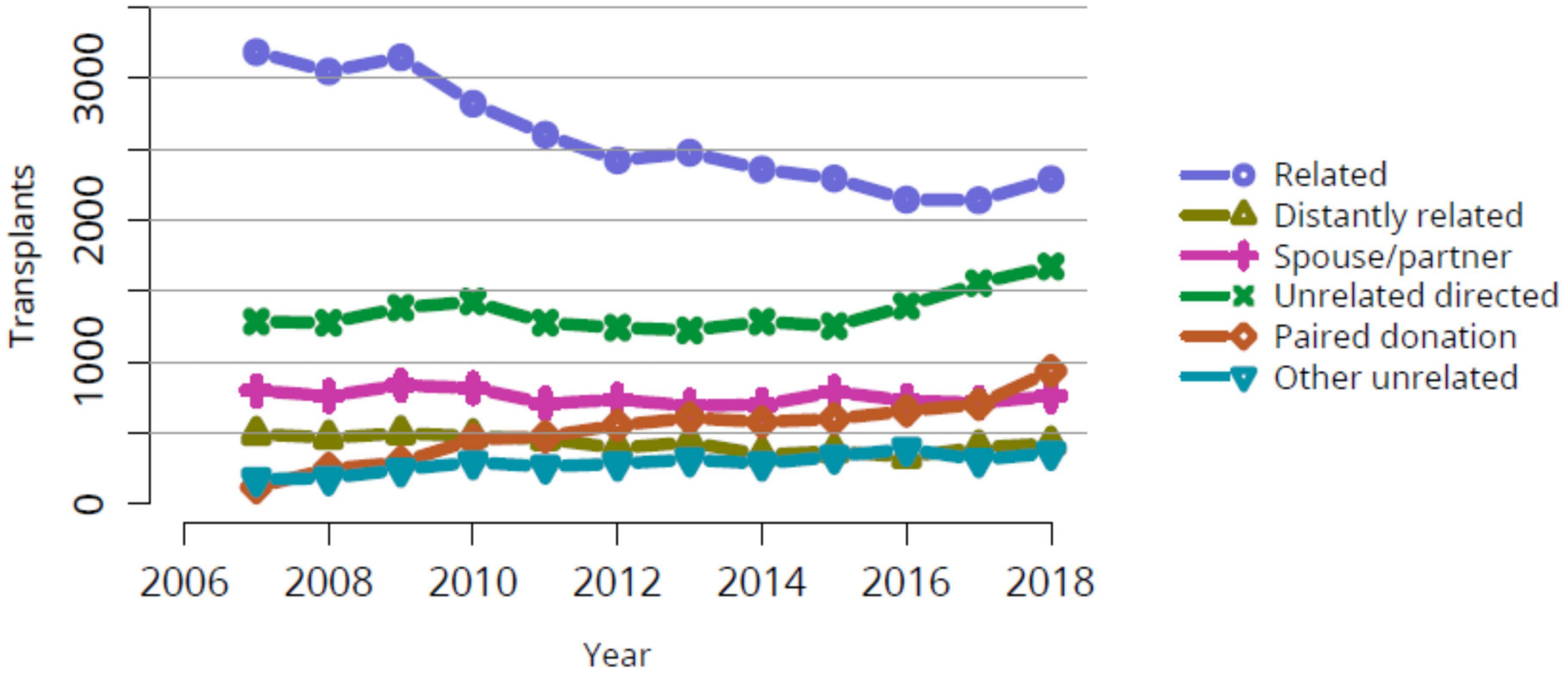
Nearly 90,000 Candidates are Currently Waiting for a Kidney Transplant



~20,000 transplants performed each year

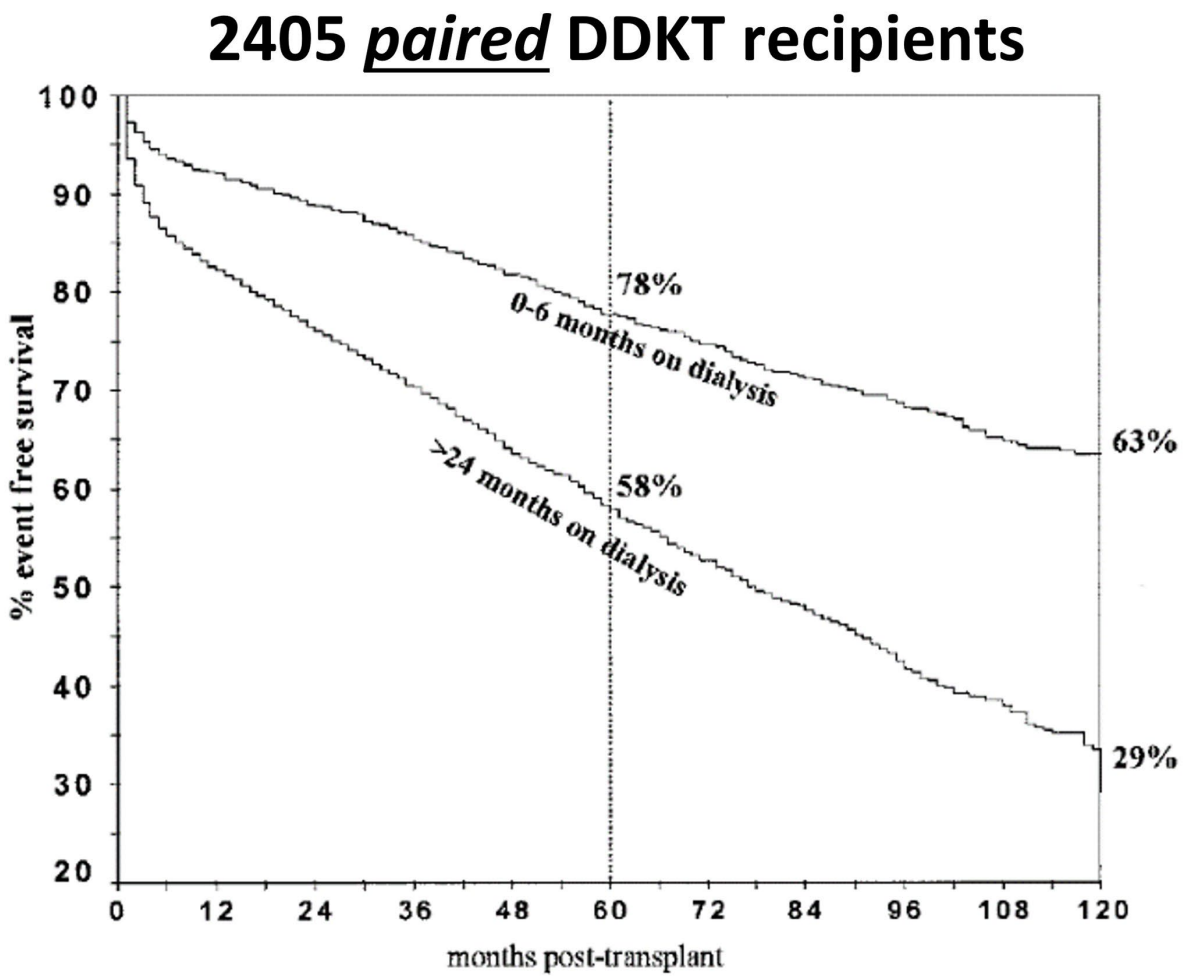
Hart A, et al. OPTN/SRTR 2018 Annual Data Report. *Am J Transplant* 2020;20:20-130.

After years of steady declines in living-donor kidney transplants, slight increase recently in unrelated directed and paired donation



Hart A, et al. OPTN/SRTR 2018 Annual Data Report. *Am J Transplant* 2020;20:20-130.

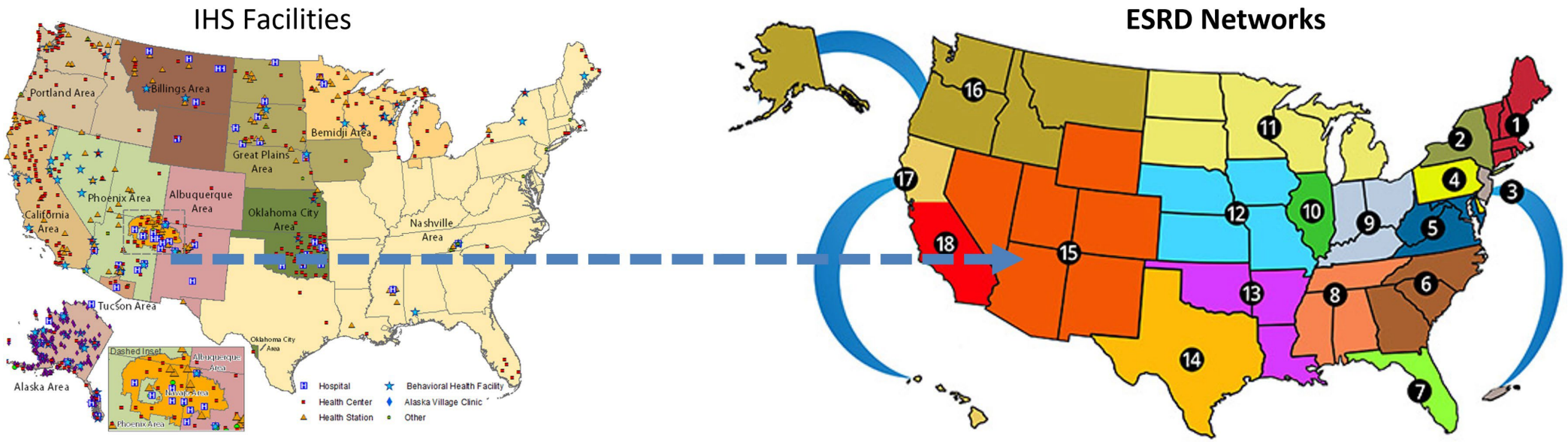
Less Time on Dialysis Before transplant → Better Survival

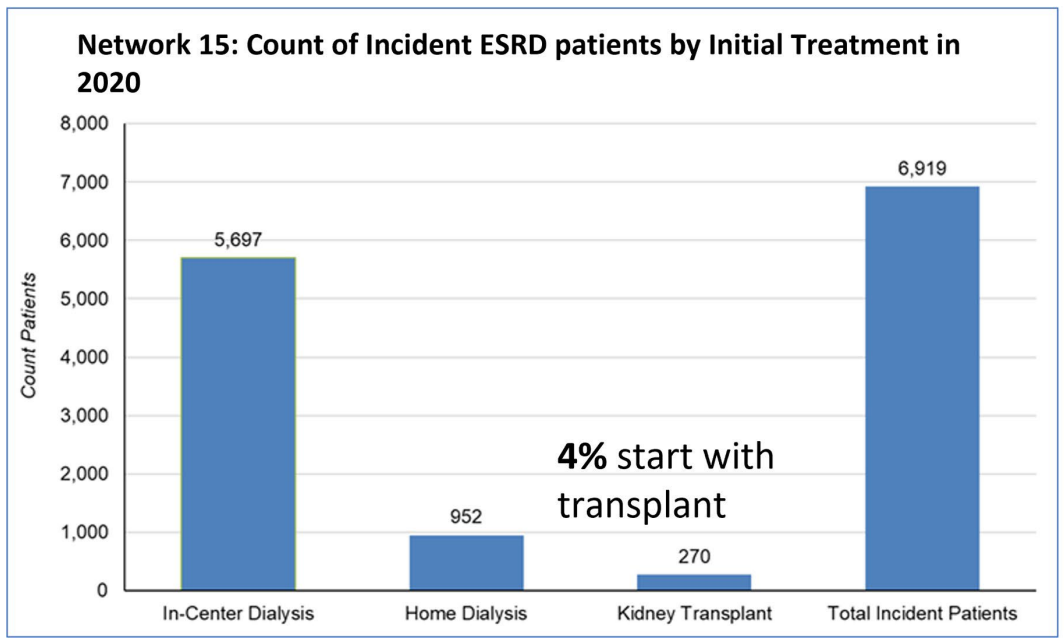


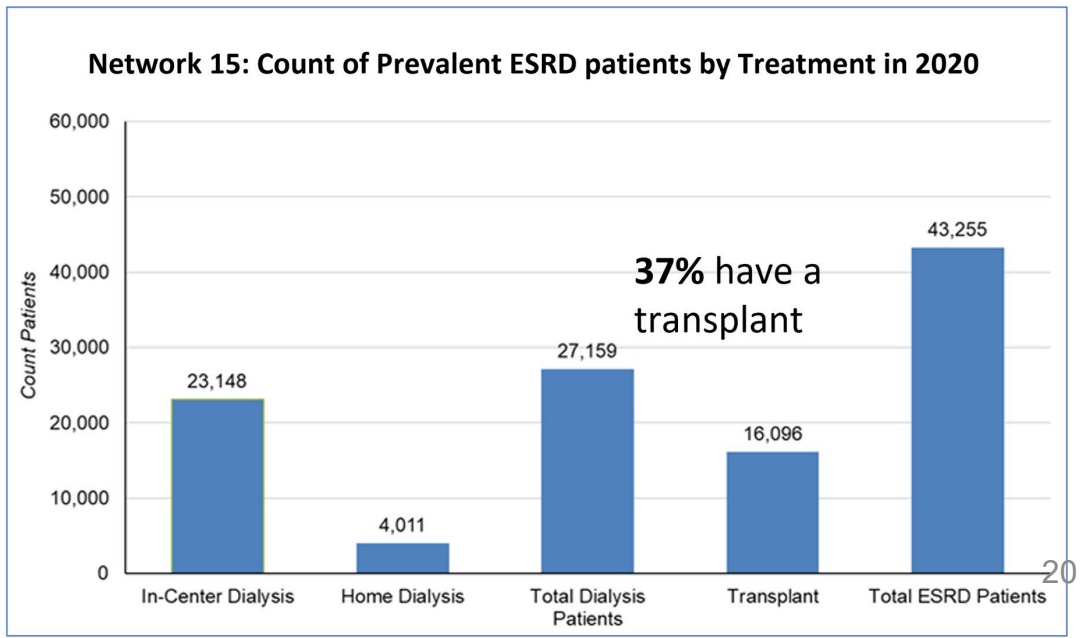
Having a living donor usually means <u>minimal</u> waiting for transplant

Meier-Kriesche. *Transplantation* 2002; 74:1377-81

ESRD Networks







Disparities Remain Between Races/Ethnicities for Kidney Transplantation

Ethnicities	Current kidney waiting list	Current kidney waiting list	Total kidney transplants in 2021	Total kidney transplants in 2021
All Ethnicities	89,965	-	24,670	-
White, Non-Hispanic	32,369	35.98%	10,381	42.08%
Black, Non-Hispanic	27,960	31.08%	7,074	28.67%
Hispanic/Latino	19,460	21.63%	4,948	20.06%
Asian, Non-Hispanic	8,442	9.38%	1,766	7.16%
American Indian/Alaska Native, Non-Hispanic	775	0.86%	181	0.73%
Pacific Islander, Non-Hispanic	570	0.63%	123	0.50%
Multiracial, Non-Hispanic	780	0.87%	197	0.80%

Source: HRSA. U.S. Organ Procurement and Transplantation Network (OPTN). Based on OPTN data as of May 25, 2022. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/

Disparities Remain Between Races/Ethnicities for Kidney Transplantation and Donation

The percent of transplants that were from **living donors** was 35.7% for Whites vs. 19.3% for AI/AN people

Ethnicity	Current kidney waiting list	Total kidney transplants in 2021	Deceased kidney donors in 2021	Living kidney donors in 2021
All Ethnicities	**89,965**	**24,670**	**13,214**	**5,972**
White, Non-Hispanic	32,369 (35.98%)	10,381 (42.08%)	8,864 (67.08%)	4,188 (70.13%)
Black, Non-Hispanic	27,960 (31.08%)	7,074 (28.67%)	1,896 (14.35%)	465 (7.79%)
Hispanic/Latino	19,460 (21.63%)	4,948 (20.06%)	1,951 (14.76%)	938 (15.71%)
Asian, Non-Hispanic	8,442 (9.38%)	1,766 (7.16%)	314 (2.38%)	251 (4.20%)
American Indian/Alaska Native, Non-Hispanic	775 (0.86%)	181 (0.73%)	92 (0.70%)	21 (0.35%)
Pacific Islander, Non-Hispanic	570 (0.63%)	123 (0.50%)	45 (0.34%)	13 (0.22%)
Multiracial, Non-Hispanic	780 (0.87%)	197 (0.80%)	52 (0.39%)	96 (1.61%)

Source: HRSA. U.S. Organ Procurement and Transplantation Network (OPTN). Based on OPTN data as of May 25, 2022. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/

Evaluation of Kidney Transplant Candidates

- Contraindications:
  - Reversible kidney failure
  - Current infection
  - Active malignancy
  - Active substance abuse
  - Uncontrolled psychiatric disease
  - Chronic illness with substantially shortened life expectancy
  - Documented active and ongoing treatment non-adherence
- Many relative contraindications (careful case-by-case evaluation), examples:
  - Malnutrition
  - Primary oxalosis (requires evaluation for combined liver-kidney transplant)
  - Active systemic diseases that may have caused kidney failure (e.g., ANCA vasculitides, systemic amyloidosis)
- Initial evaluation:
  - Thorough medical, surgical, and psychosocial history
  - Physical, laboratory, and other studies as needed (e.g., age-appropriate cancer screening, stress testing/cardiac clearance depending on risk factors)

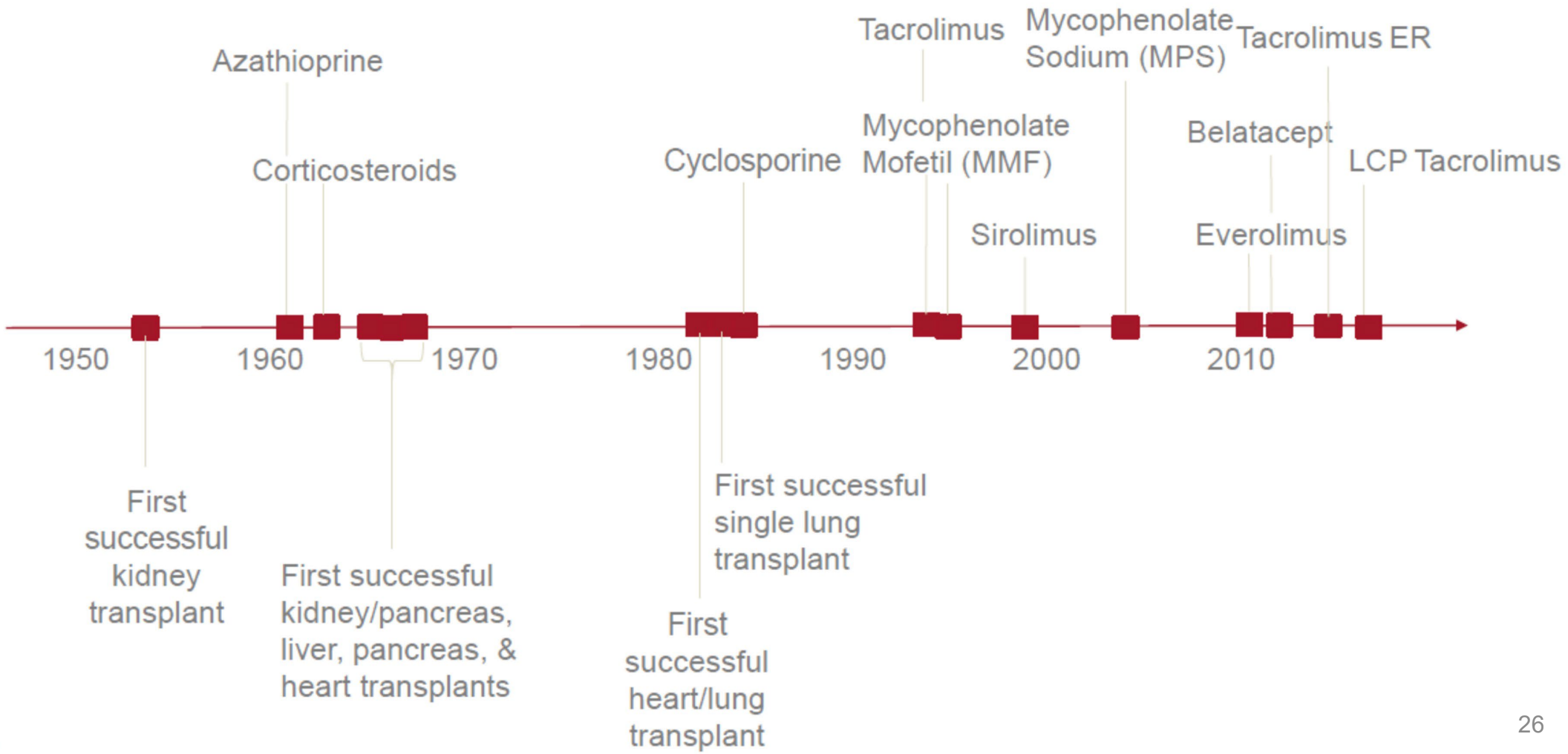
Take Away Messages About Renal Replacement Therapy

- Early initial referral to nephrology for patients with chronic kidney disease (then partner with those providers to prevent progression)
- Early (when eGFR <30 mL/min/1.73 m2) and frequent discussions about renal replacement therapy types – HD / PD / Transplant
- Encourage transplantation as the best replacement therapy
- Normalize kidney donation (both living and deceased)

Outline – Step 3

Step 3: Immunosuppressive transplant medications.

Evolution of Immunosuppression Medications



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Typical Immunosuppression Maintenance

Calcineurin Inhibitor	±	Antimetabolite	±	Steroid
Cyclosporine (Gengraf, Neoral)		Mycophenolate mofetil (Cellcept)		Prednisone
or		or		
Tacrolimus (Prograf)		Mycophenolate sodium (Myfortic)		
		or		
		Azathioprine (Imuran)		

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Toxicity Profiles of Immunosuppressive Medications

Adverse effect	Steroids	CsA	Tac	mTORi	MMF	AZA
New-onset diabetes mellitus	↑	↑	↑↑	↑		
Dyslipidemias	↑	↑		↑↑		
Hypertension	↑↑	↑↑	↑			
Osteopenia	↑↑	↑	(↑)			
Anemia and leucopenia				↑	↑	↑
Delayed wound healing				↑		
Diarrhea, nausea/vomiting			↑		↑↑	
Proteinuria				↑↑		
Decreased GFR		↑	↑			

AZA, azathioprine; CsA, cyclosporine A; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s); Tac, tacrolimus.
↑ indicates a mild-moderate adverse effect on the complication.
↑↑ indicates a moderate-severe adverse effect on the complication.
(↑) indicates a possible, but less certain adverse effect on the complication.

KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

Examples of Common Drug Interactions: Cyclosporine, Tacrolimus, Sirolimus, and Everolimus (https://www.uptodate.com/contents/image?imageKey=NEPH%2F110436)

Common types of drug interactions	Examples of interacting drugs	Approach to management in the absence of appropriate noninteracting alternatives
Coadministration of drugs that inhibit CYP3A metabolism and/or P-gp efflux can **increase immunosuppressant serum concentrations**, leading to significant toxicities.	• Amiodarone • ART-boosting agents (e.g., ritonavir, cobicistat) • Azole antifungals (e.g., fluconazole, posaconazole, voriconazole) • HIV protease inhibitors (e.g., atazanavir, nelfinavir, saquinavir) • Macrolide antibiotics • Non-dihydropyridine calcium channel blockers • Ombitasvir-paritaprevir-ritonavir with or without dasabuvir (an HCV, direct-acting antiviral regimen) • Grapefruit juice	• Closely monitor immunosuppressant concentrations and signs of toxicity (e.g., tremors and headaches). • Substantial, including preemptive, dose reduction of immunosuppressant drug may be needed (eg, on average, only 25% of the standard dose of cyclosporine is required if administered concomitantly with HIV protease inhibitors).
Coadministration of drugs that induce CYP3A metabolism and/or P-gp efflux pumping can **decrease immunosuppressant serum concentrations**, increasing the risk of organ rejection.	• Antiseizure medications, enzyme inducing (e.g., carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) • Enzalutamide • Nafcillin • Rifamycins (e.g., rifabutin, rifampin, rifapentine) • St. John's wort	• Closely monitor immunosuppressant serum concentrations and signs of organ rejection. • Significant immunosuppressant dose increases may be needed. • Enzyme induction can require up to 2 weeks to achieve maximum effect and persists for up to 2 weeks after discontinuation of the interacting medication. Clinically significant effects can occur within hours to days of starting a CYP inducer.
Coadministration of nephrotoxic drugs with cyclosporine or tacrolimus can cause **additive or synergistic kidney injury**.	• Aminoglycosides • Amphotericin B • Colchicine • Nonsteroidal anti-inflammatory drugs (NSAIDs)	• Concomitant administration of cyclosporine and tacrolimus with other potentially nephrotoxic drugs should be avoided.
Coadministration of drugs that increase serum potassium with cyclosporine or tacrolimus may cause **severe hyperkalemia**.	• ACE inhibitors/ARBs • Amiloride • Spironolactone • Triamterene • Trimethoprim, trimethoprim-sulfamethoxazole (cotrimoxazole)	• Closely monitor serum potassium levels.
Coadministration of cyclosporine with sirolimus can **increase sirolimus concentrations**.	• Cyclosporine	• Separate administration of sirolimus from cyclosporine by 4 hours; give sirolimus at a consistent time with respect to cyclosporine. • Closely monitor immunosuppressant serum concentrations.
Coadministration of statin drugs with cyclosporine can **increase statin levels and risk of myotoxicity**.	• Atorvastatin • Lovastatin • Pitavastatin • Rosuvastatin • Simvastatin	• Pravastatin and fluvastatin are preferred due to decreased interactions. • Tacrolimus may be preferred over cyclosporine in patients receiving statin therapy. • Cyclosporine and simvastatin should not be used together.

Take Away Messages About Immunosuppressive Transplant Medications

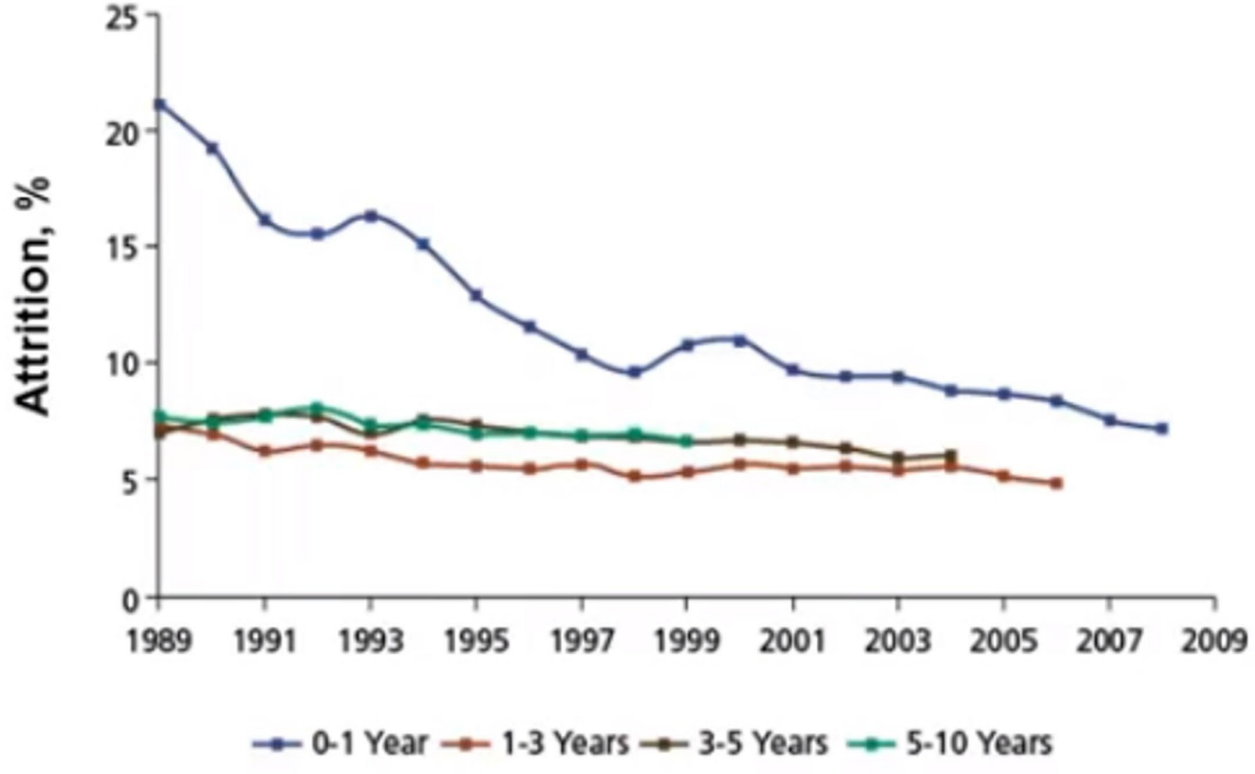
- Many different side effects
  - For new/worsening symptoms/complaints, consider possible side effects of their medications. If any question/concern, discuss with the Transplant Center.
- Many potential drug-drug, drug-food/supplement interactions
  - OTC medications can cause major problems (also marijuana/CBD/THC).
  - When adding new medications or changing doses, consider and look-up possible interactions. If any question/concern, discuss with the Transplant Center.

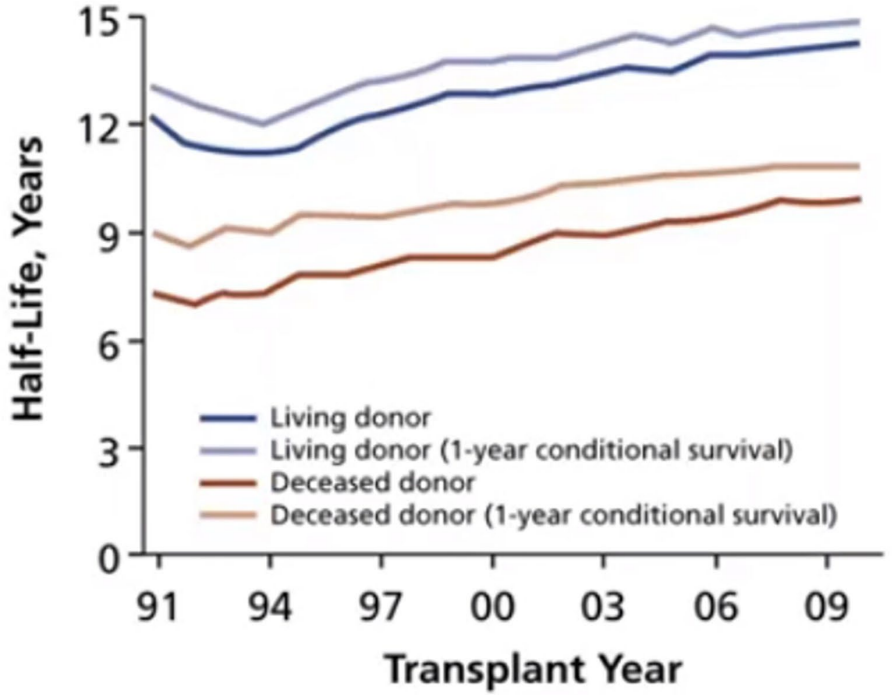
Outline – Step 4

Step 4: Long-term care of kidney transplant recipients

i. Kidney allograft dysfunction
ii. Cardiovascular disease risk reduction
iii. Diabetes after transplant
iv. Infection
v. Cancer
vi. Other issues/complications

Much of the progress in graft outcomes since the 1980s is due to better 1-year outcomes (less early rejection, but only incremental progress with longer-term survival)





2012 OPTN/SRTR Annual Data Report

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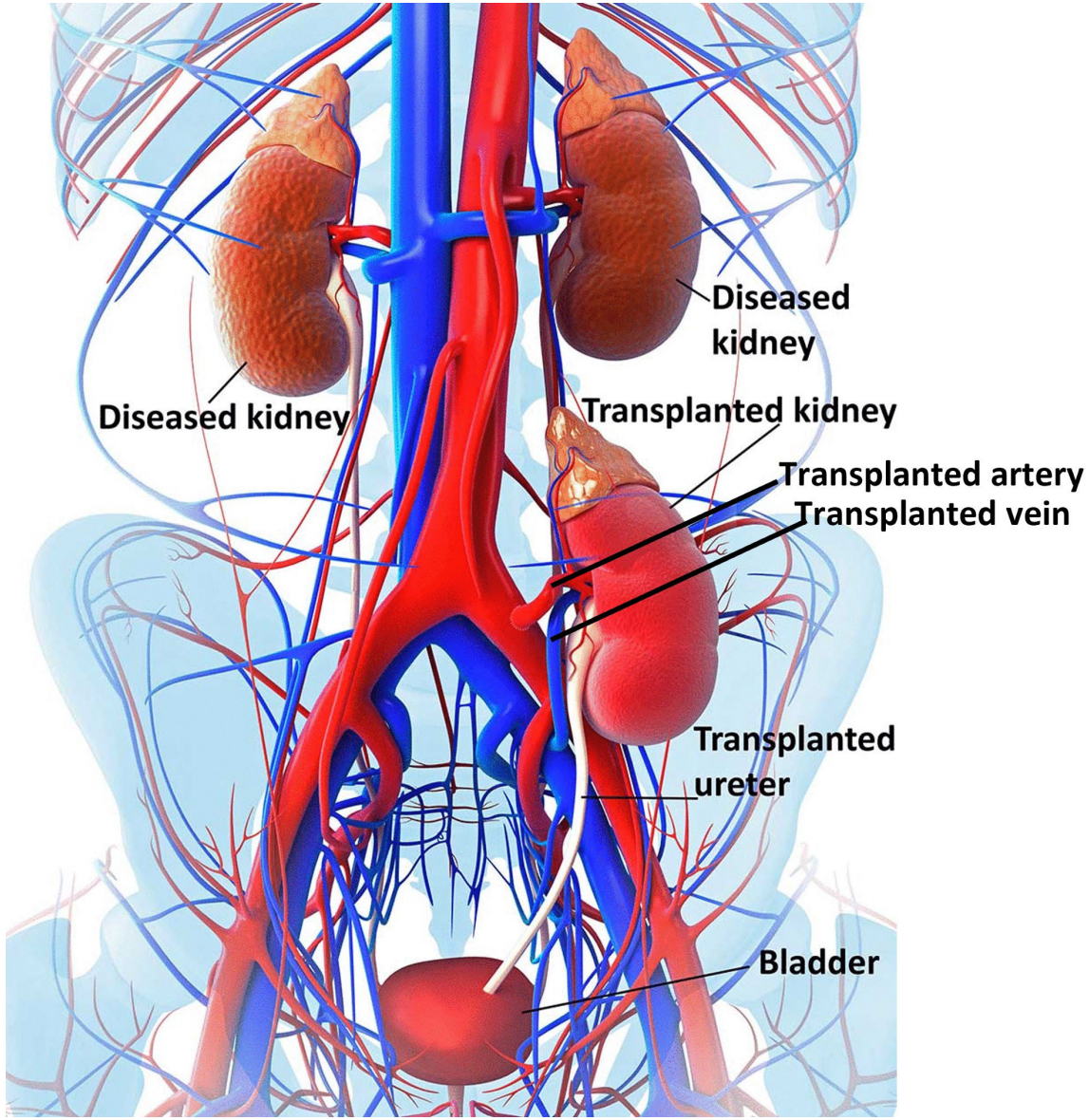
Kidney Allograft Dysfunction

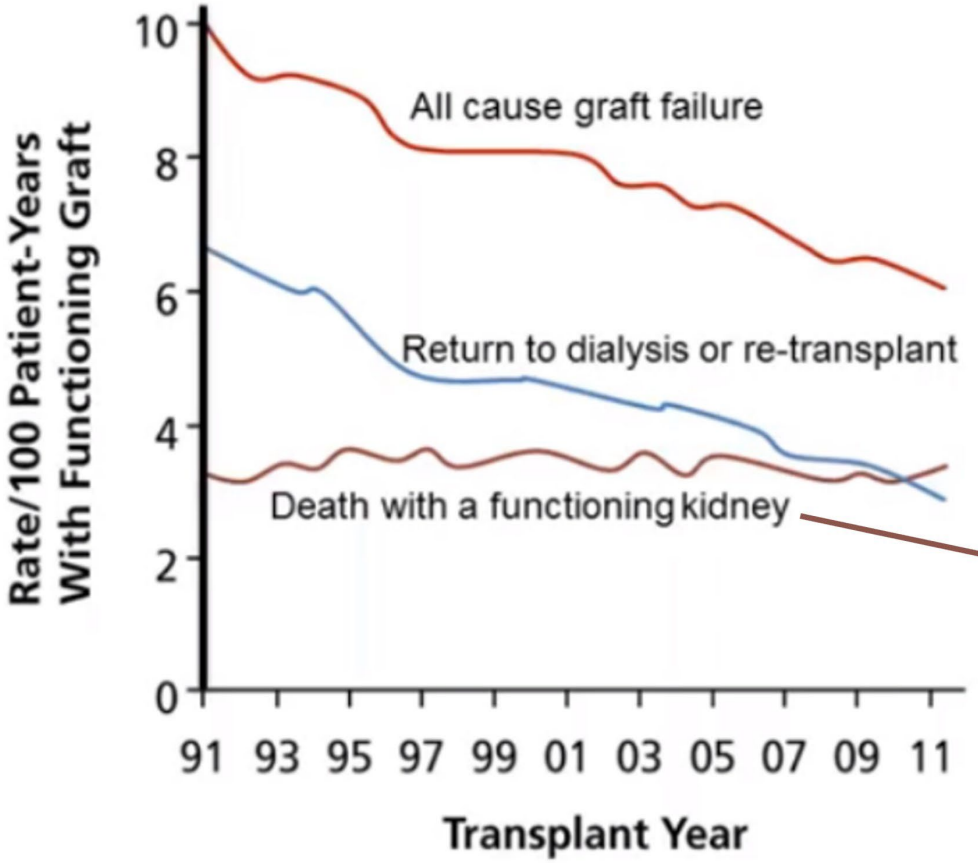


- Early detection via routine labs provides best chance for timely diagnosis and effective treatment:
  - Serum creatinine (SCr)
  - Urine protein/creatinine ratio (UPCR)
- SCr above baseline not explained by dehydration ("pre-renal") or urinary obstruction ("post-renal") is most likely an "intra-renal" allograft process:
  - Acute rejection (any medication non-adherence?)
  - Drug toxicity (e.g., high tacrolimus level)
  - Recurrent or new kidney disease (e.g., diabetic nephropathy, glomerulonephritis)
  - BK virus nephropathy
  - Chronic allograft injury (often chronic rejection)

1. Careful history, including medication/supplement review
2. Careful exam, especially volume status
3. Kidney transplant ultrasound
4. Very low threshold for kidney transplant biopsy

https://www.healthdirect.gov.au/kidney-transplants

Graft Loss After Transplant (Failed Graft or Death)



Death with graft function:

1) Cardiovascular disease
2) Infection
3) Malignancy

- **No major improvements in rate of death with a functioning graft**

2014 USRDS Annual Data Report

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Cardiovascular Disease Risk Reduction

Address modifiable risk factors…

- Kidney disease
- ***Obesity***
- ***Diabetes***
- ***Hypertension***
- ***Dyslipidemia***
- ***Tobacco use***
- ***Physical inactivity***
- Family history
- Age

Metabolic syndrome (30-60% of patients with kidney disease)

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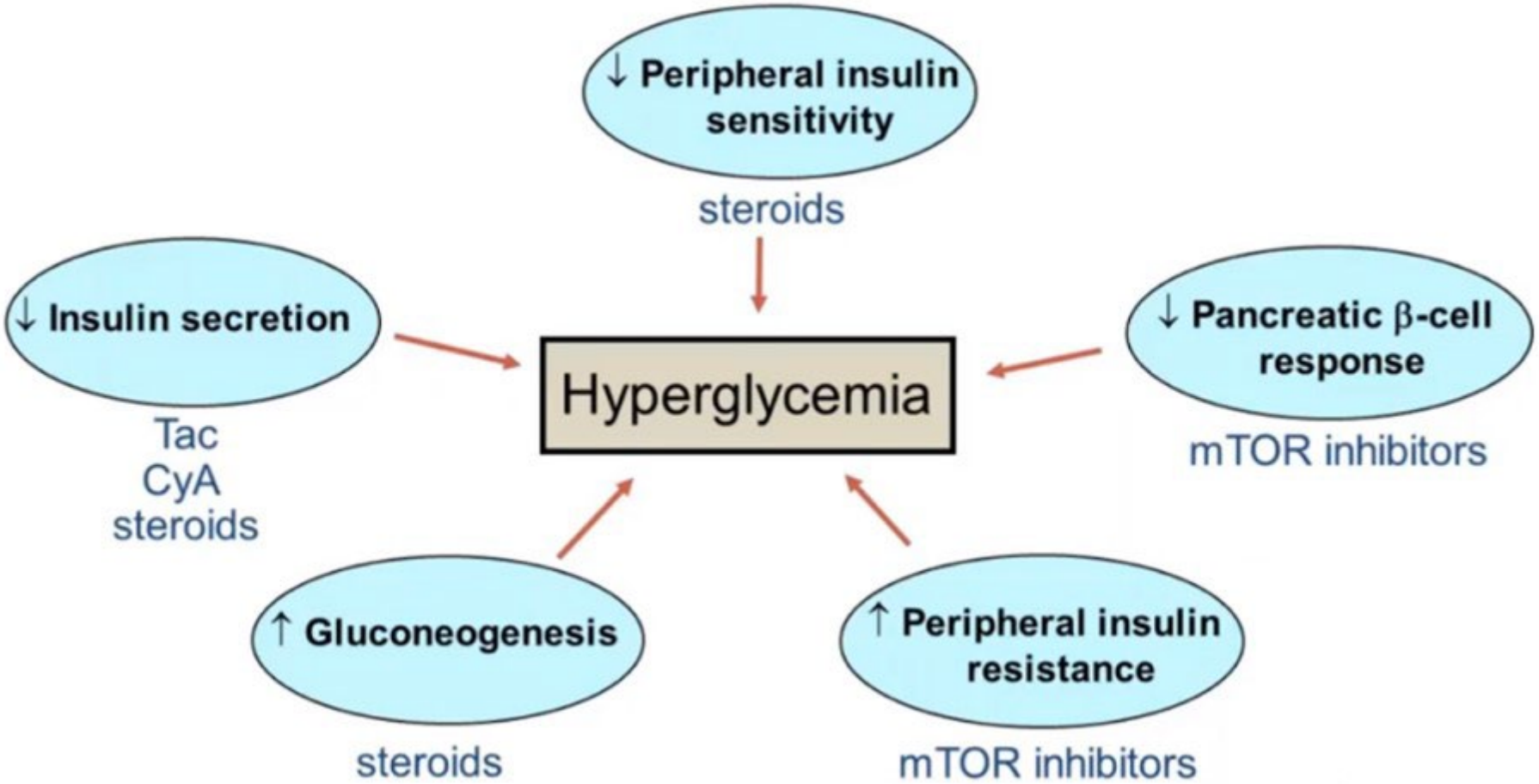
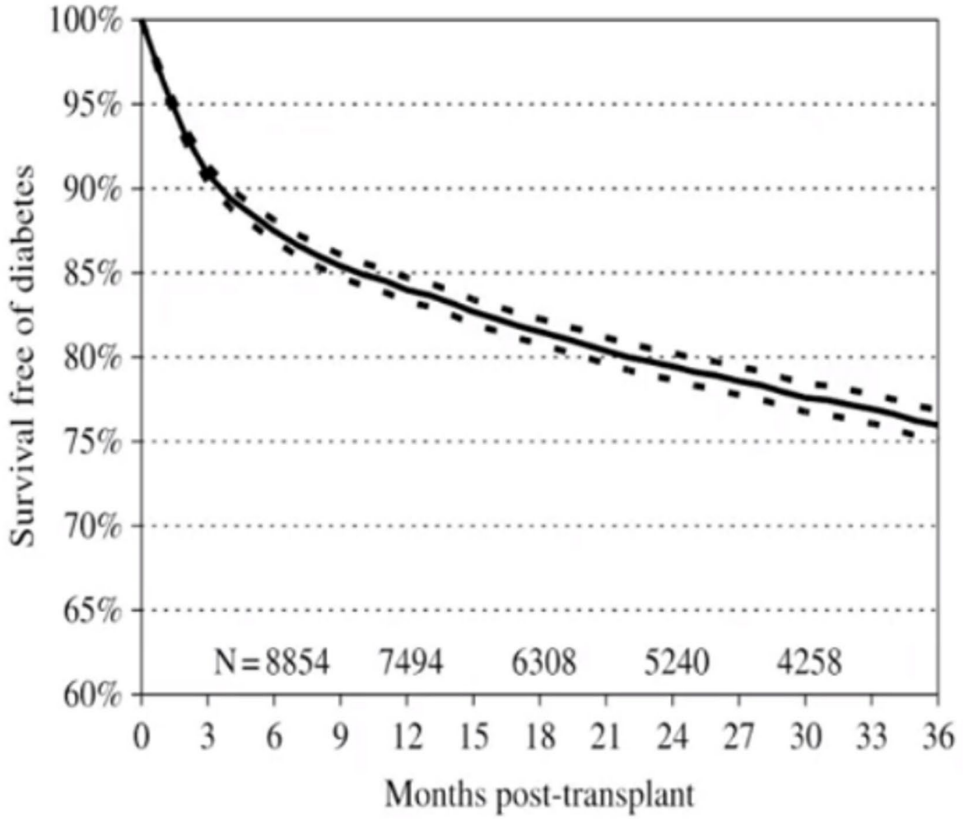
Immunosuppression and Glucose Intolerance



New Onset Diabetes After Transplant (NODAT)



Non modifiable	Potentially modifiable
Ancestry/ genetics	Immunosuppression - Tac (++) - CyA (+)
Family history	- Steroids (+) - mTOR inhibitors (++)
Older age	Viral infections - HCV/CMV/HIV
Male	Hypomagnesemia
	Pre-transplant IGT
ADPKD	Obesity

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Non-insulin Drugs for Diabetes After Transplant

Class	Mechanisms of Action	Example	Side Effects	Elimination/ Metabolism	CKD dose change
Sulfonylurea	Insulin secretagogue	Glipizide	Hypoglycemia	Liver	No
Glinides	Insulin secretagogue	Repaglinide	Hypoglycemia	CYP2C8/3A4	Yes
Biguanides	↓ liver glucose production	Metformin	Nausea, lactic acidosis	Kidney	Yes
Glitazones	↑ insulin sensitivity	Pioglitazone	Wt gain, edema bone loss	CYP2C9/3A4	No
α-glucosidase inhibitors	↓ intestinal glucose absorption	Acarbose	Nausea, Flatulence	Major-gut	Yes
GLP-1R agonists	↑ glucose med insulin secretion, ↓ gastric emptying, ↓ glucagon	Exenatide	Nausea, GI	Major-kidney	Yes
DPP-4 Inhibitors	↑ glucose med insulin secretion; ↓ glucagon	Sitagliptin	Minimal	Major-kidney CYP3A4/5/2C8	Yes
SGLT-2 inhibitors	Inhibit proximal tubule glucose reabsorption	Empagliflozin	UTI, ketosis, amputations,	Major-liver CYP3A4	No

???

- Several require eGFR dose adjustment
- Effects on immunosuppression are fairly limited
- CNIs (especially cyclosporine) can potentiate several of these

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Causes of Post-transplant Anemia

Common reasons for anemia in kidney transplant recipients	
Allograft dysfunction	Female sex
Iron deficiency	Blood loss/Hemolysis
Medications • mTOR inhibitors • MMF/MPA • Azathioprine • ACEI/ARBs • Antibiotics	Infections • CMV • Parvovirus B19 • Herpes viruses
Malignancy	Inflammation/Oxidative stress

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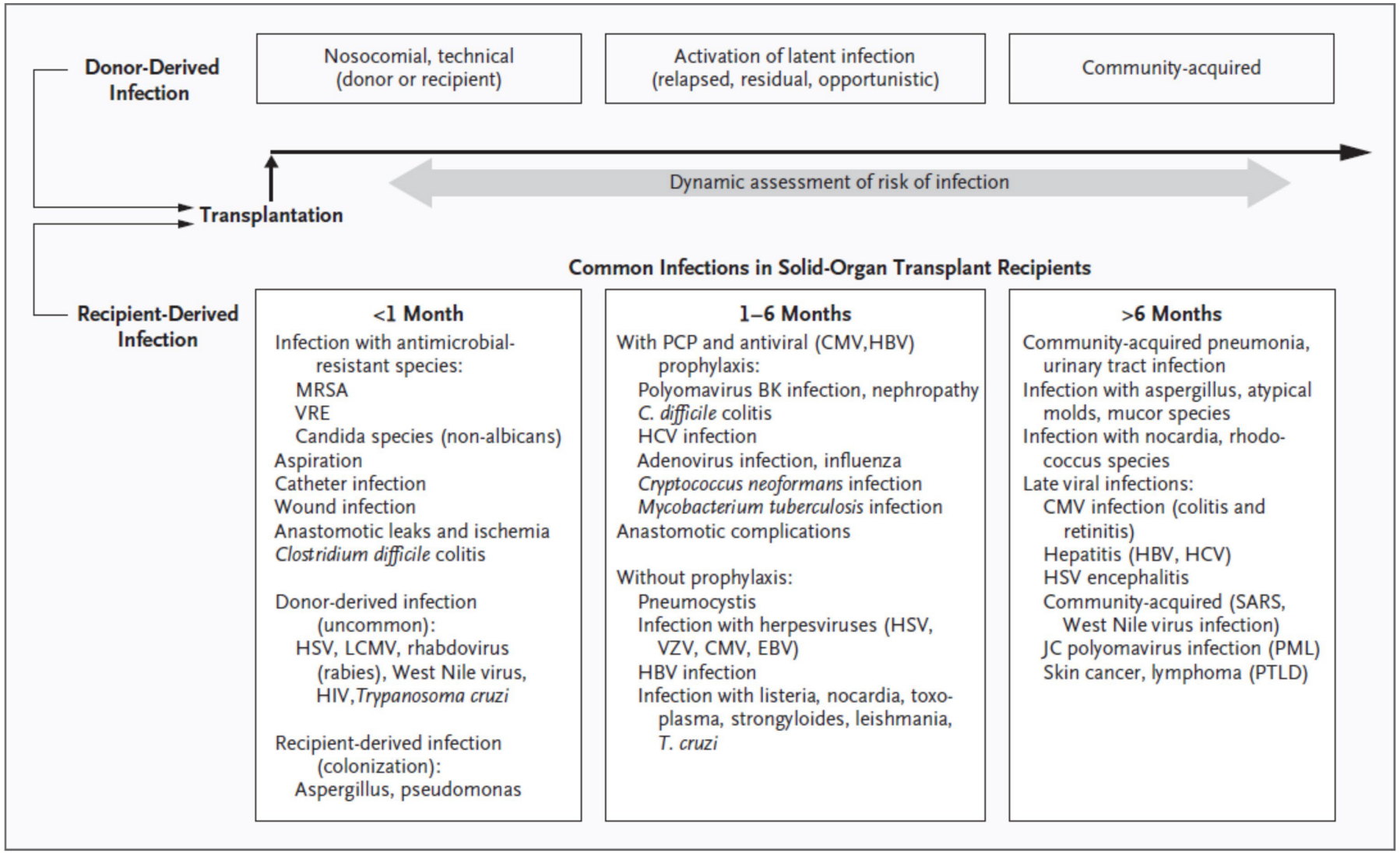
Infections are Very Common Post-transplant



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Fishman JA. *NEJM*. 2007;357:2601-14.

Malignancy After Transplant

- One of the most common late complications, incidence 2–4 times higher than general population
- Cancer after transplant tends to be more aggressive with increased mortality compared to general population
- Immunosuppression plays a central role in pathogenesis
- Non-melanoma skin cancer (NMSC) is most common
- Lymphomas account for 21% of cancers

Risk Factors for Malignancy After Transplant

- Immunosuppression
  - Direct effects
  - Suppress immune surveillance
  - Activate oncogenic viruses
- Underlying disease
- Type of transplant
- History of malignancy
- Established risk factors

Malignancy	Virus Associated
Cervical, vulvar, vaginal, and anal cancer	HPV-16 and -18
Hepatocellular carcinoma	HBV and HCV
PTLD	EBV
Leukemia and lymphoma	HTLV-1
Kaposi's sarcoma	HHV-8
	Suspected Viral Associations
Prostate cancer	Polyomavirus BK
Brain cancer	JCV
Brain, bone, and mesothelioma cance	SV-40

Abbreviations: EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papilloma virus; JCV, John Cunningham virus; PTLD, post-transplant lymphoproliferative disorder; HHV, human herpes virus; HTLV, human T-cell leukemia virus; SV, simian virus.

Asch et al. Adv CKD 2014; 21: 106-113

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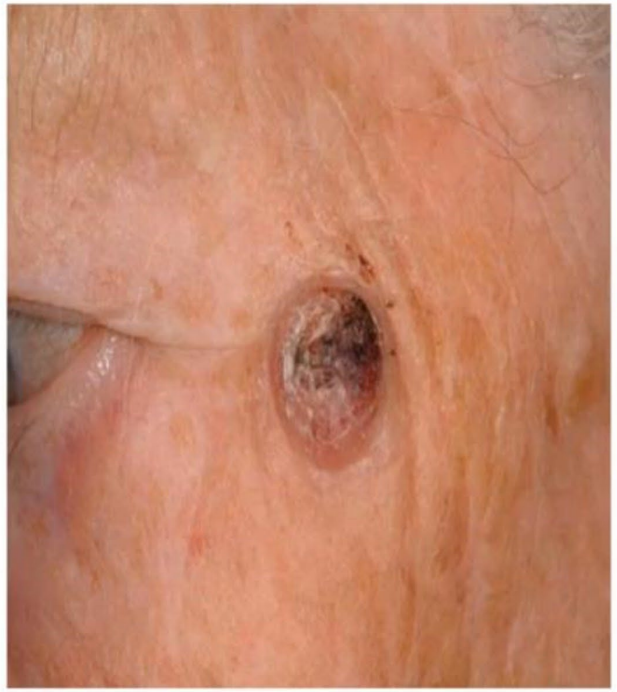
Skin Cancers After Transplant

Skin Cancers After Transplant

- Provide patient information
- Counsel about sun avoidance
- Use sun-protecting agents
- Monthly self exams
- Annual dermatology evaluation



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Post-transplant Lymphoproliferative Disorders (PTLD)

- 2nd most frequent tumors in adults and most frequent in kids
- 85% are of B-cell origin
- 80% associated with EBV
- Highest risk during 1st year
- 1-3% following KTx

WHO Classification of PTLD (2008)

I. Early lesions
  Plasmacytic hyperplasia
  Infectious mononucleosis-like
II. Polymorphic PTLD
III. Monomorphic PTLD (classify according to lymphoma they resemble)
 B-cell neoplasms
  Diffuse large B-cell lymphoma (DLBCL)
  Burkitt lymphoma
  Plasma cell myeloma
  Plasmocytoma-like lesion
  Other
 T-cell neoplasms
  Peripheral T-cell lymphoma, not otherwise specified
  Hepato-splenic lymphoma
  Other
IV. Classical Hodgkin lymphoma-type PTLD

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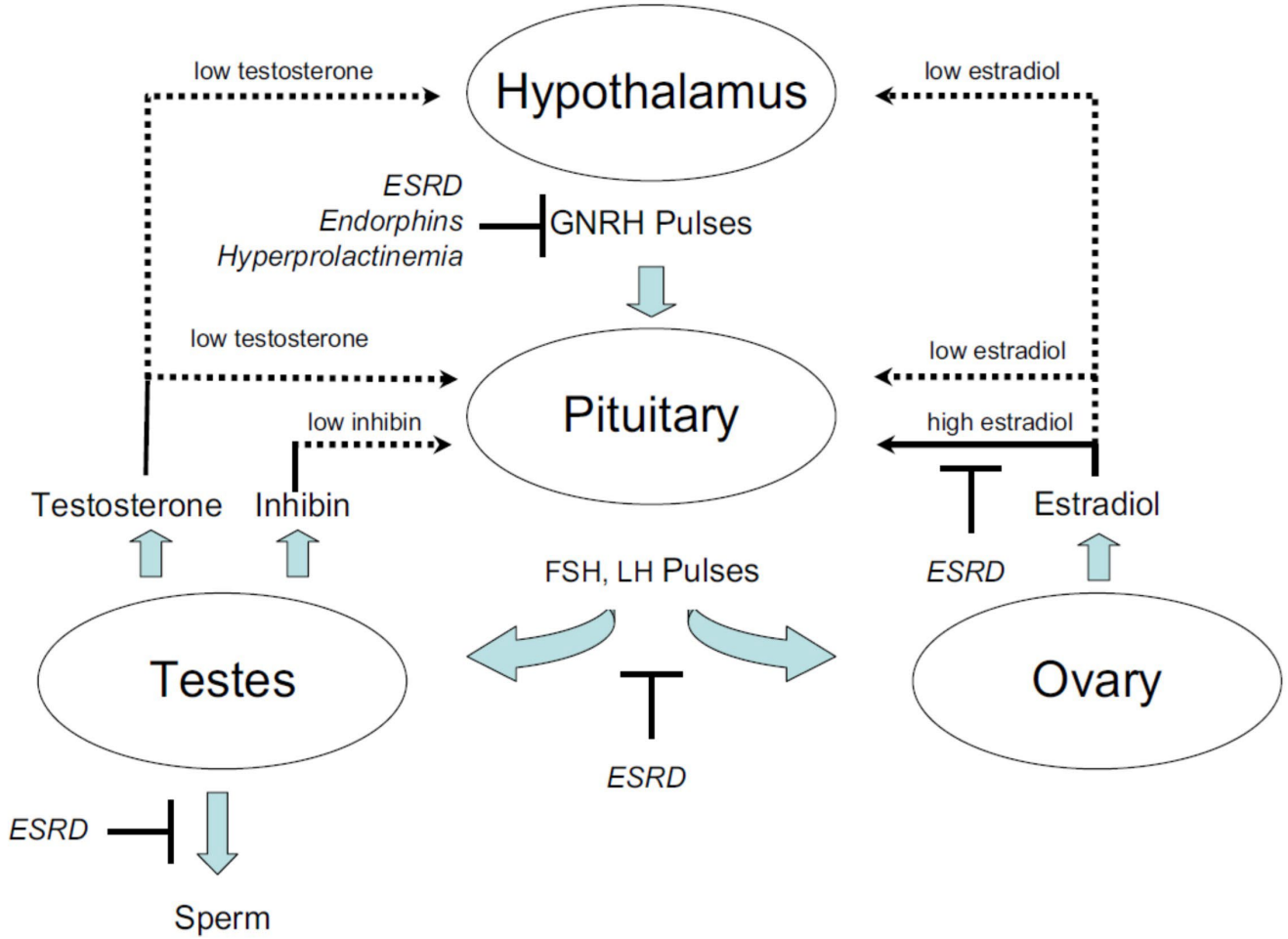
Reproductive Issues After Transplant

- Infertility in CKD is common
  - Sexual dysfunction
  - Loss of libido
  - Anovulation
  - Derangements in the hormonal control of fertility
- Fertility can be restored within a few months of transplant



Holley J. *Adv in CKD* 2013; 20: 240-245

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Reproductive Issues After Transplant (con't)

Counseling about contraception begins at the first pre-transplant evaluation

- Emphasis on need for continued IS therapy
- Need to plan pregnancy as medications need to be changed
- Discuss birth control options
- Recommend waiting 12–24 months post-transplant before considering pregnancy (plus no rejections in past year)

Hyperuricemia and Gout (KDIGO)

- Treat hyperuricemia when there are complications, such as gout, tophi, or uric acid stones. [2D]
- Use colchicine to treat acute gout, with appropriate dose reduction for decreased kidney function and concomitant CNI use. [2D]
- Avoid allopurinol in patients receiving azathioprine. [1B]
- Avoid NSAIDs and COX-2 inhibitors whenever possible. [2D]

Failed Kidney Transplant (Back on Dialysis): Signs and Symptoms of Graft Intolerance (Likely Need for Graft Nephrectomy)

Common Clinical Findings	Less Common Findings
• Fever • Gross hematuria • Allograft enlargement and localized edema • Allograft tenderness	• Malaise • Weight loss • ESA resistant anemia • Thrombocytopenia • High inflammatory markers: ferritin, CRP, ESR

Take Away Messages About the Long-term Care of Kidney Transplant Recipients

- Partner with the Transplant Center and Primary Nephrologist to recognize and identify problems early “in the field”
  - Graft dysfunction / possible rejection
  - Interactions between medications, potential non-adherence
  - Infections
  - Cancers
- IHS provider goal should be early detection, not treatment
- Transplant Center will help determine and coordinate treatment
- The Transplant Center needs the IHS providers as much as the IHS providers need the Transplant Center

Resources – Kidney Transplants

- https://esrdncc.org/en/patients/ (Transplant Section)
- https://kdigo.org/guidelines/ (Transplant Recipient Tile)
  - https://kdigo.org/wp-content/uploads/2017/02/Managing-Your-Adult-Patients-Who-Have-a-Kidney-Transplant-kdigo.pdf
  - https://kdigo.org/wp-content/uploads/2017/02/KDIGO_TX_NephsTool-Managing-Kidney-Transplant-Recipients.pdf
- https://www.myast.org/guidelines-post-kidney-transplant-management-community-setting

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