Non-Adherence

Definitions – Monitoring – Prevention/Maintenance

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Disclosures

I have financial relationships within the last 12 months with:

Clinical Research Grants

- Novartis, Onyx, GSK, Prolong, Bristol-Myers Squibb, Genzyme-Sanofi, and FDA

Advisory Board

- Genzyme-Sanofi

Speakers Bureau

- Genzyme-Sanofi, Veloxis

This presentation does not include discussion of off-label or investigational use of any drugs

Objectives

- Differentiate medication non-adherence and compliance
- Describe measures to quantitate medication non adherence
- Discuss efforts towards prevention and management of non adherence

Non-Adherence

- Age Old Problem
  - "Keep watch also on the fault of patients which makes them lie about taking of things prescribed."
    - Hippocrates, circa 500 B.C.
  - "Drugs don't work if people don't take them."
    - C. Everett Koop, 1985
- Transplantation can no longer accept the status quo
  - "The first shot is our best shot" for transplant success
  - Despite millions in investment, a "magic" drug or procedure to render adherence irrelevant is not on the horizon
  - Are federal mandates necessary to properly resource adherence initiatives if adherence continues to be neglected?

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Medication Adherence vs. Compliance

- Medication Adherence
  - The extent to which patients take medications as prescribed by health care providers.

- Compliance
  - Passive act of the patient to follow the providers orders

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England journal of medicine*, *353*(5), 487-97.

Medication Adherence

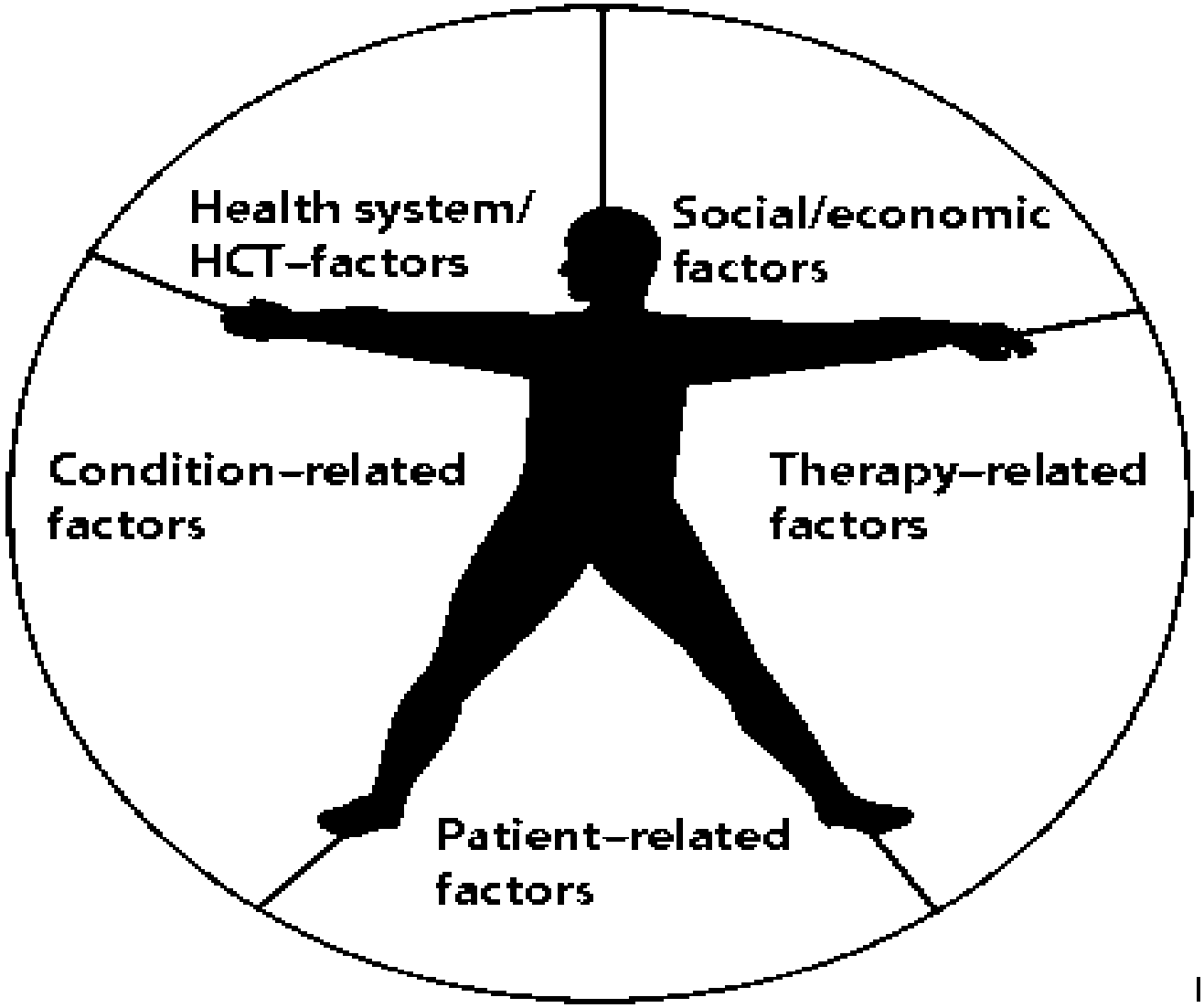
- A behavioral process that is influenced by many factors
- Assumes the patient has the knowledge, motivation, skills and resources to follow the health care providers prescription

Medication Non-Adherence

- Intentional medication non-adherence
  - "Active process whereby the patient chooses to deviate from the treatment regimen."
- Unintentional medication non-adherence
  - "Passive process in which the patient may be careless or forgetful about adhering to treatment regimen."

Ho, P., Bryson, C., , & Rumsfeld, J. (2009). Medication adherence: Its importance in Cardiovascular Outcomes. *Circulation*, *119*(23), 3031.

Five Dimensions of Adherence



Transplantation 2007:83:858-873
American College of Preventative Medicine

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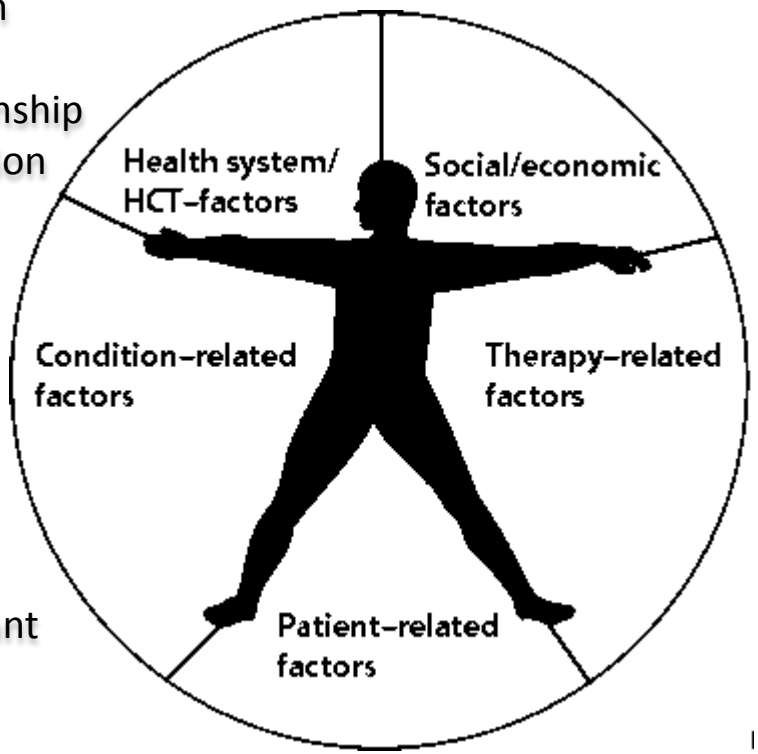
Transplant Specific Risk Factors for Nonadherence

Medication costs
Poor access to medication
Poor aftercare planning
Poor physician-patient relationship
Poor physician communication

Younger Patient
Male Gender
Non Caucasian
Non US resident
Poor social support
Poor transportation
Literacy



Complex Medical Regimens
Higher Medication Toxicity
Lack of medication education
No pillbox/reminder system

High Symptom Distress
Development of NODAT
Increased time post transplant

History of non-adherence
Adolescence
Psychologic disorder (depression)
Cognitive impairment
Substance abuse
Negative beliefs in medication

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Which Factors are MODIFIABLE??

Medication costs
Poor access to medication
Poor aftercare planning
Poor physician-patient relationship
Poor physician communication

Younger Patient
Male Gender
Non Caucasian
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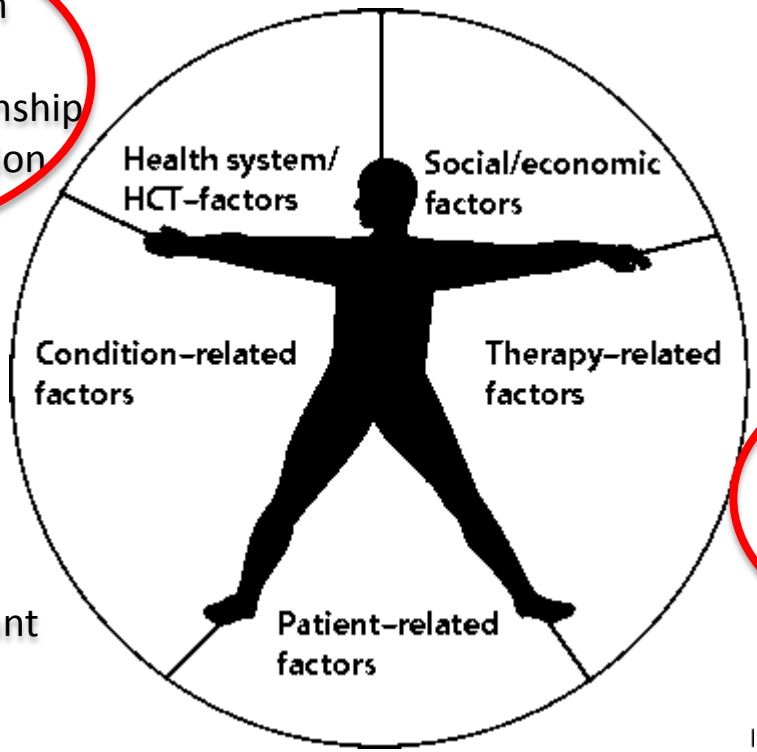

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Medication Adherence Measures

- Objective measures
  - Direct measures
    - Provide evidence that medication has been consumed or taken (example: Direct observation, ie Belatacept)
  - Indirect measures
    - Provide evidence suggesting that medication has been consumed or taken (example: Pill counts, tacrolimus drug levels, pharmacy refill records, medication possession ratio)
- Subjective measures
  - Provide testimony that medication has or has not been taken (example: Self report, assessment by others)

Direct Observation Options in Transplantation

- Advantages
  - Objective
  - Highly specific
  - Not invasive
- Disadvantages
  - Feasibility issues
  - Labor intensive (e.g., training observers)
  - Not practical
  - Expensive
  - Not an option for all transplant recipients

Bennet Johnson S. *Diabetes Care* 1992;15:1658-67; Farmer KC. *Clin Ther* 1999;21:1074-90; Hill J. *Musculoskeletal Care* 2005;3:143-56; Partridge AH, et al. *J Natl Cancer Inst* 2002;94:652-61.

Drug Concentration Monitoring

- Advantages
  - Objective
  - May be part of standard care
  - Direct assessment of whether patient has taken medication

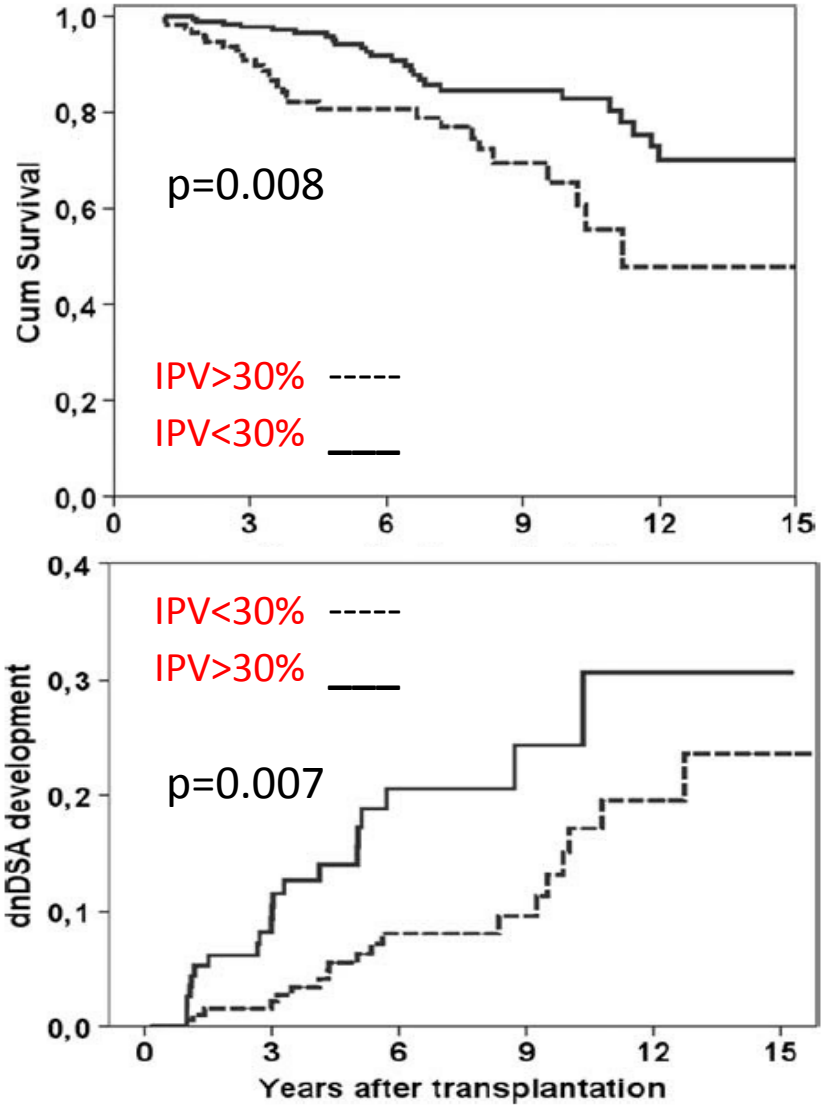
- Disadvantages
  - Snapshot of behavior
  - Affected by factors other than medication adherence (e.g., metabolism, drug-drug/drug-food interactions, poor absorption)
  - Cost
  - Invasive

Butler et al. *Transplantation* 2004;77:786-89; Chisholm MA, et al. *Transplantation* 2001;70:1240-44; Chisholm MA, et al. *Clin Transplant* 2001;15:330-36; Chisholm MA, et al. *Nephrol Dial Transplant* 2005;20:181-88; Chisholm MA, et al. *Clin Transplant* 2005;19:77-82; Chisholm MA, et al. *Am J Health-Syst Pharm* 2005;68:1775-81; Chisholm MA, et al. *Patient Educ Couns* 2005;59:13-20.

Tacrolimus Intrapatient Variability (IPV) Impact on Graft Loss and DSA development

Study Design

- 310 renal transplants receiving tacrolimus
- Tacrolimus IPV analyzed from 4-12 months post transplant and categorized as < or > 30% IPV
  - >30% IPV = 37.4%
  - <30% IPV = 62.6%
- DSA testing was performed at 1, 3, and 5 yrs
- 53 (17.1%) lost their graft
- 39 (12.6%) developed dnDSA
- Primary outcomes
  - Death censored graft survival
  - dnDSA development



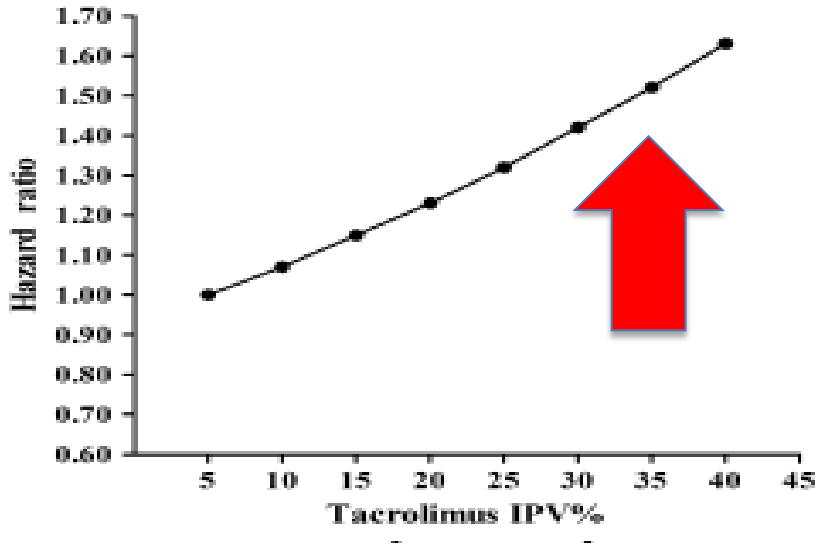
Transplantation Nov 2016, Volume 100, Number 11. 2479-2485

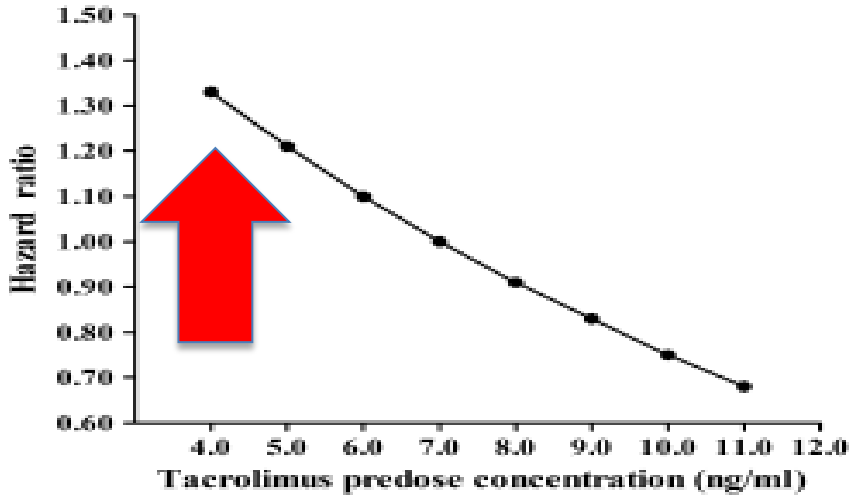
Tacrolimus Intrapatient Variability (IPV) Impact on Late Outcomes

Composite endpoint

Graft failure, late biopsy-proven acute rejection and transplant glomerulopathy or doubling of serum creatinine censored for death.

	Hazard ratio (95% CI)	*P*-value
Recipient age at transplantation (year)	0.980 (0.970–0.991)	<0.001
eGFR at 6 months (ml/min)	0.985 (0.976–0.995)	0.002
Tac IPV% (high)	1.420 (1.059–1.903)	0.019
Transplant number (>1)	1.505 (1.066–2.125)	0.020
Mean Tac concentration (ng/ml)	0.913 (0.839–0.994)	0.036
HLA mismatch (none)	1.087 (0.989–1.194)	0.084
DGF	0.736 (0.473–1.146)	0.175
Donor type (deceased)	0.791 (0.555–1.127)	0.194



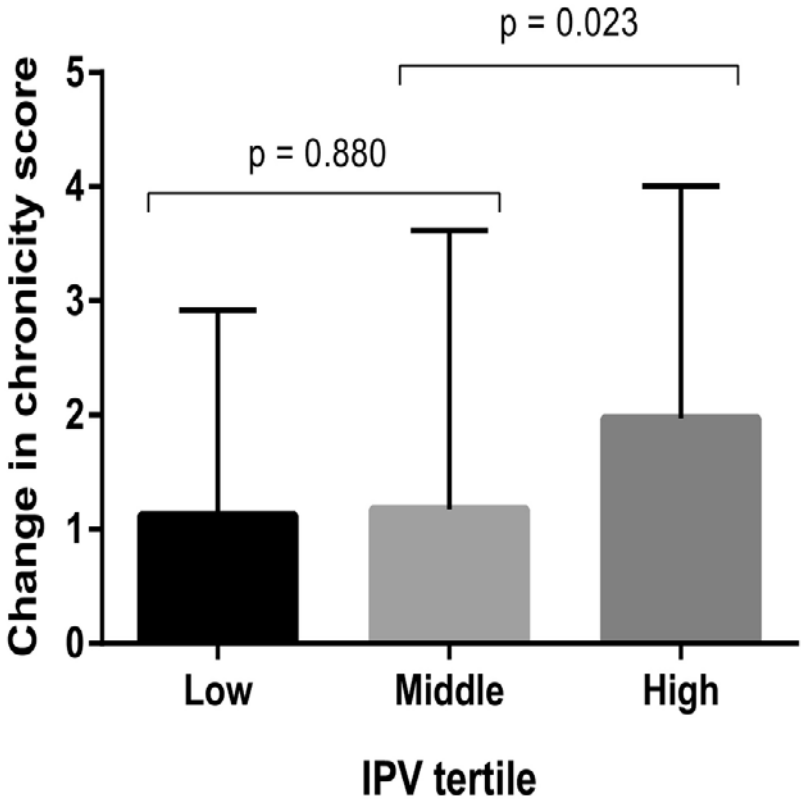


Transplant International 2016;29:1158-1167

Tacrolimus Intrapatient Variability (IPV) Impact on Chronic Histologic Lesions

Study Design

- 220 renal transplants receiving tacrolimus
- Tacrolimus IPV analyzed from 6-12 months post transplant
  - Lowest IPV tertile – 9.8 ± 3.3
  - Middle IPV tertile – 18.3 ± 2.4
  - Highest IPV tertile – 31.1 ± 7.8
- Protocol biopsies at 3 mos and 2 year were utilized to calculate a change in chronicity score
- Recipients with the highest IPV had an increased risk of moderate to severe fibrosis and tubular atrophy at 2 years compared with the low IPV



AJT 2016: 16: 2954-2963

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Electronic Monitoring

- Advantages
  - Objective
  - Indicate time/date of bottle opening (real-time tracking; detects poor adherence to dosing schedule, pill box versions now available)
  - Detects pill dumping when used in correlation with pill counts
  - Not invasive
- Disadvantages
  - Cost
  - Not effective with liquid medications
  - Can malfunction, lose data
  - Device may be bulky/inconvenient
  - May cause distress to patient (being monitored)
  - Assumes medication removed from bottle/box is taken

Blowey DL, et al. *Pediatr Nephrol* 1997;11:547-51; Butler et al. *Transplantation* 2004;77:786-89; DeGeest S, et al. *Clin Transplant* 2006;20:359-68; DeGeest S, et al. *J Cardiovasc Nurs* 2001;16:1-14; Feldman HI, et al. *Pharmacoepidemiol Drug Saf* 1999;8:1-14; Hardstaff R, et al. *Transplant Proc* 2003;35:796-97; Russell CL, et al. *Clin Nurs Res* 2007;16:153-63; Russell CL, et al. *Res Nurs Health* 2006;29:521-32.

Strategies to Impact Non-Adherence

- Electronic Medication Monitors (MEMS) predict patterns of early medication adherence
  - Tested with MMF, sirolimus and azathioprine in 195 kidney transplant recipients
  - Adherence between month 1-2 predicted adherence for 6mo and 12mo
  - Non-adherent patients more frequent, earlier AR and death censored graft loss
  - During month 1-3 – Adherence QID 84%, BID 91%, and QD 94%

Transplantation 2014;98:878-884

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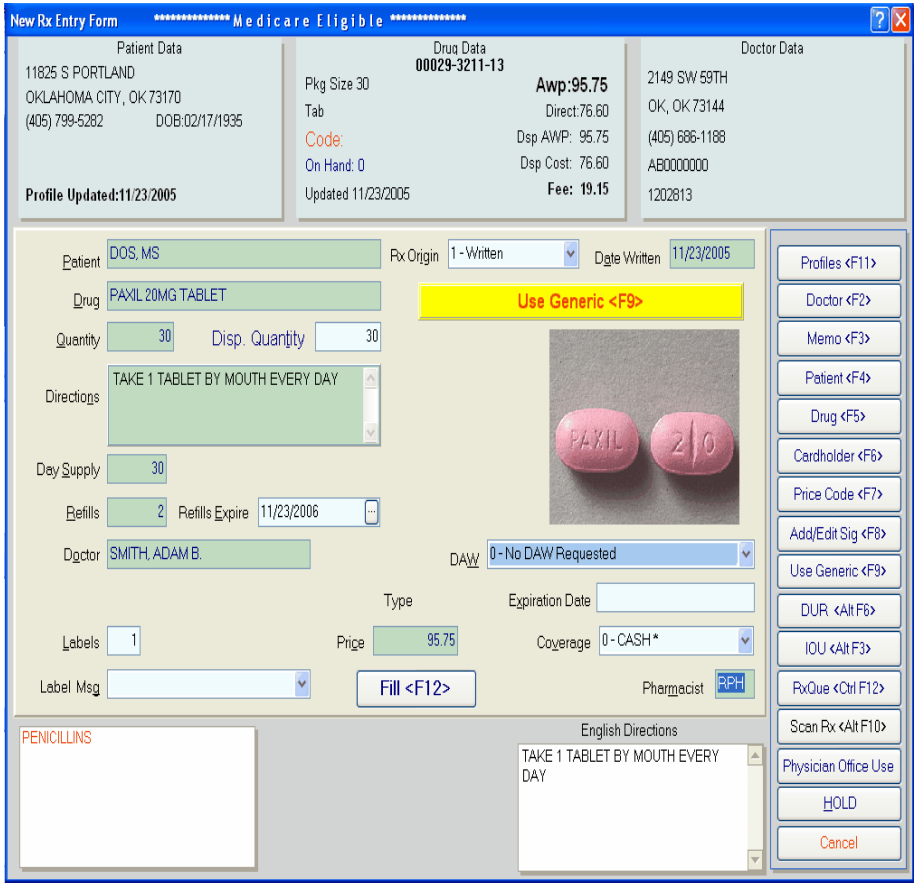
Refill Records

- Advantages
  - Objective
  - Standardized data
  - Identify patients who fail to refill medication
  - Not invasive
  - Inexpensive
- Disadvantages
  - Possible misinterpretation of use when changes made to dosage
  - Assumes filled prescriptions are taken
  - Assumes all sources of medication are captured
  - Only useful for long-term medication
  - Increased complexity when using records from multiple pharmacies



Chisholm et al. *Transplantation* 2000;70:1240-44; Chisholm et al. *Clin Transplant* 2001;15:330-36; Chisholm et al. *Patient Educ Couns* 2005;59:13-20; Hill J. *Musculoskeletal Care* 2005;3:143-56; Liu H, et al. *Ann Intern Med* 2001;134:968-77; Modi AC, et al. *Diabet Med* 2006;5:177-85; Partridge AH, et al. *J Natl Cancer Inst* 2002;94:652-61.

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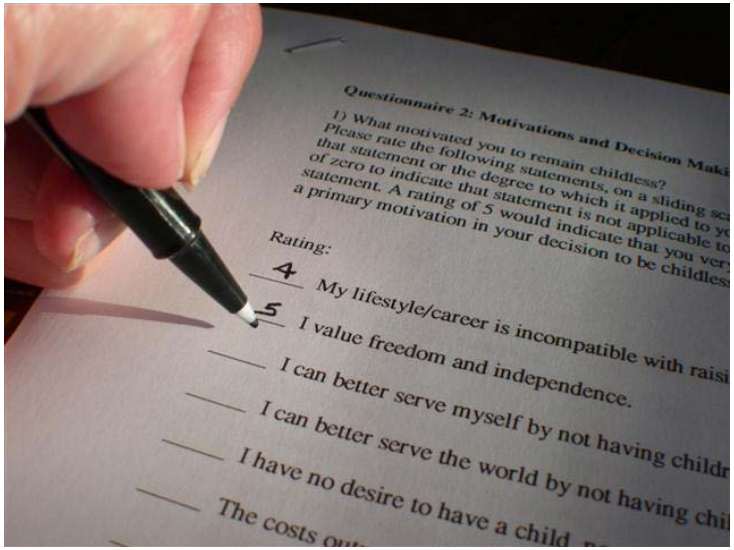
Medication Possession Ratio or Proportion of Days Covered

- **Medication Possession Ratio (MPR)** and **Proportion of Days Covered (PDC)** are the two most common formulas used to estimate patients' adherence to chronic medications. Both formulas use prescription fill data to calculate the percentage of days for which the patient has medication on-hand to take for their chronic conditions.
- Examples of adherence measures for diabetes and cardiovascular medications can be obtained from the Pharmacy Quality Alliance (PQA) at: www.PQAalliance.org
- Optimal MPR for any immunosuppressant is not known.

Self Reports

- Advantages
  - Simple
  - Quick
  - Inexpensive
  - May provide information that explains variability in pharmacoadherence patterns and/or clinical response to medication
- Disadvantages
  - Overestimate pharmacoadherence
  - Patients may provide socially acceptable responses
  - Limited patient recall (impact of time)
  - Diaries may be burdensome/not returned/not completed
  - Tend to be done at time of clinic visit when pharmacoadherence generally increases (bias)



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Clinician Reports

- Advantages
  - Simple
  - Quick
  - Inexpensive
- Disadvantages
  - May be influenced by interactions with patients and by patient therapeutic outcomes
  - Tends to underestimate non-adherence

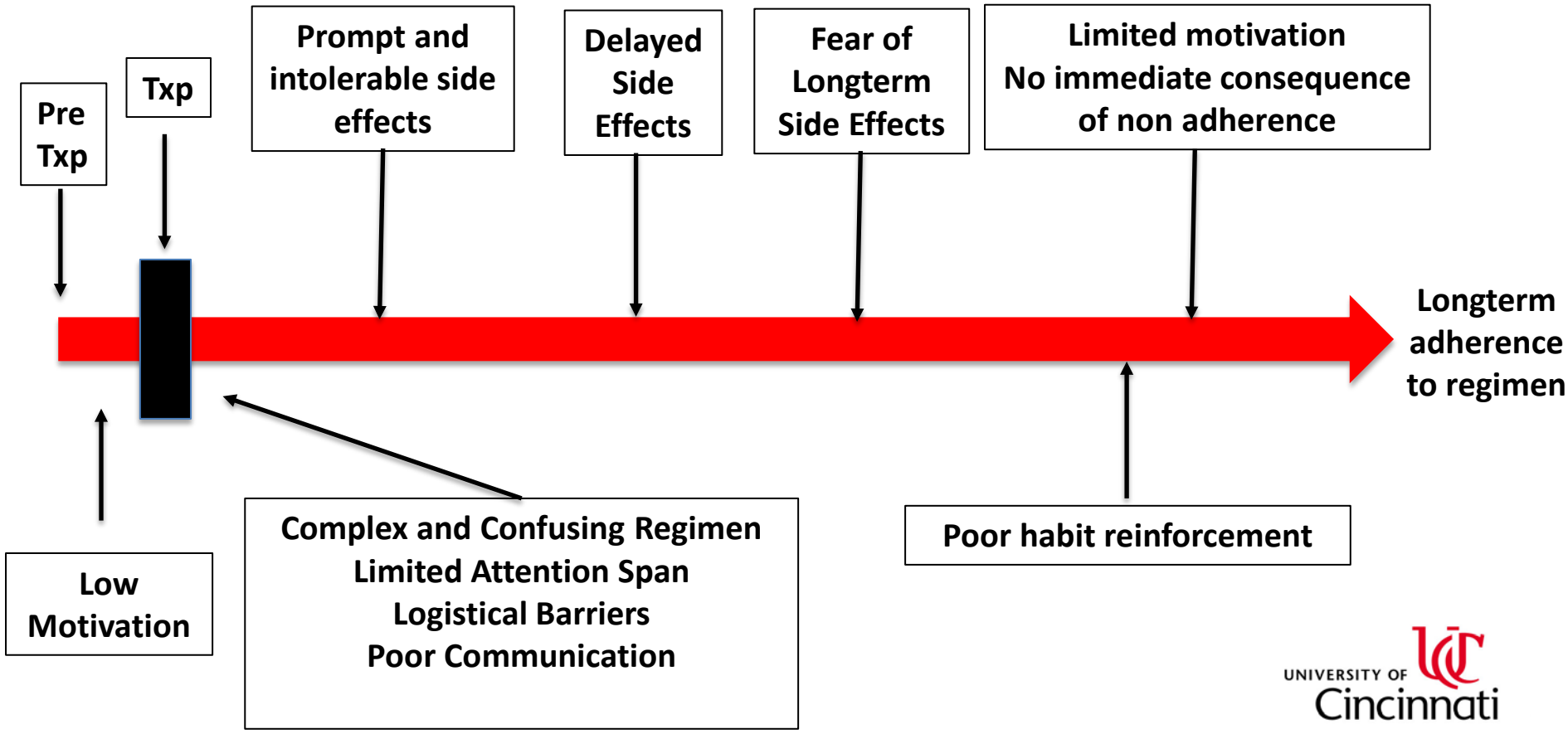
Bennett Johnson S. *Diabetes Care* 1992;15:1658-67; Byerly MJ, et al. *Psychiatr Serv* 2007;58:844-47; Chisholm MA, et al. *Transplantation* 2007;84:1145-50; Miller LG, Hays RD. *HIV Clin Trials* 2000;1:36-46; Rand CS, Wise RA. *Am J Respir Crit Care Med* 1994;149:569-76.

Table 1. Methods to monitor immunosuppressant adherence in transplant recipients (7,17-18).			
		Advantages	Disadvantages
DIRECT	Observation	• Accurate	• Patient able to alter data (e.g., pill cheeking) • Routine use in clinical practice is impractical
	Measurement (i.e., blood, urine) of drug, metabolite, or biological marker	• Objective	• Increased costs • Patient factors may impact results (e.g., metabolism)
	Ingestible Sensor System	• Objective • Accurate • Confirms medication ingestion • Able to track ingestion of multiple medications taken at the same time	• Increased costs • System usability requires mobile telephone service • Need for sensor applied to the skin • Potential for skin reactions
INDIRECT	Patient questionnaires, interviews, self-reports	• Easy to use • Low costs	• Subjective • Relies on patient recall • Patient able to alter data
	Patient diaries	• Simple • Inexpensive	• Subjective • Relies on patient recall • Patient able to alter data
	Pill counts	• Objective • Easy to perform	• Does not confirm medication ingestion • Patient able to alter data • Does not provide information on dose, timing, or drug holidays
	Rate of prescription refills	• Objective • Easy to obtain data	• Refill rate does not necessarily equal ingestion rate • Difficult to perform when patient uses multiple pharmacies
	Electronic monitoring	• Objective • Precise • Effective in controlled research setting	• Increased costs • Data download required • Does not confirm medication ingestion • Interventions in real time unlikely • Selection bias • Routine use in clinical practice is impractical

Adapted from Kaiser T and Alloway R. Clinical Transplants 2015, Chapter 27 p275-284

Interventions to Promote Adherence: When, Where, and How

What is the optimal intervention time to promote adherence?



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Interventions to Promote Adherence: When, Where, and How

Modes of Interventions

- Face to Face
- Telephone
- Smartphone Apps
- Computer

Types of Interventions

- Educational - multidisciplinary
- Behavioral (ex. Contracting, mentor/support groups, problem solving therapy)
- Psychosocial/Affective
- Technology-based
- Simplified regimens (ex. Once daily tacrolimus)
- Multicomponent

Intervention Randomized Controlled Trials

- Automated reminders and physician notification to promote IS adherence among Kidney Transplant Recipients: A Randomized Trial. Am J Kidney Dis 2017:69(3): 400-409
- Telemedically supported case management of living-donor renal transplant recipients to optimize routine evidence based aftercare: A single center randomized controlled trial. AJT 2017 doi: 10.1111/ajt.14138
- A pilot randomized controlled trial to promote immunosuppressant adherence in adult kidney transplant recipients. Nephron 2017;135:6-14 (cognitive behavioral program)
- Randomized controlled trial of a computer based education program in the home for solid organ transplant recipients: Impact on medication knowledge, satisfaction, and adherence. Transplantation 2016; 00:1-8
- Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study. Nephrol Dial Transplant 2014 29:1597-1607 (MEMs)
- Improving outcomes of renal transplant recipients with behavioral adherence contracts: A randomized controlled trial. AJT 2013;13: 2364-2373 (pharmacy refill records)
- Improved adherence to tacrolimus once daily formulation in renal recipients : A randomized controlled trial using electronic monitoring. Transplantation Vol 95, No.

FACTS

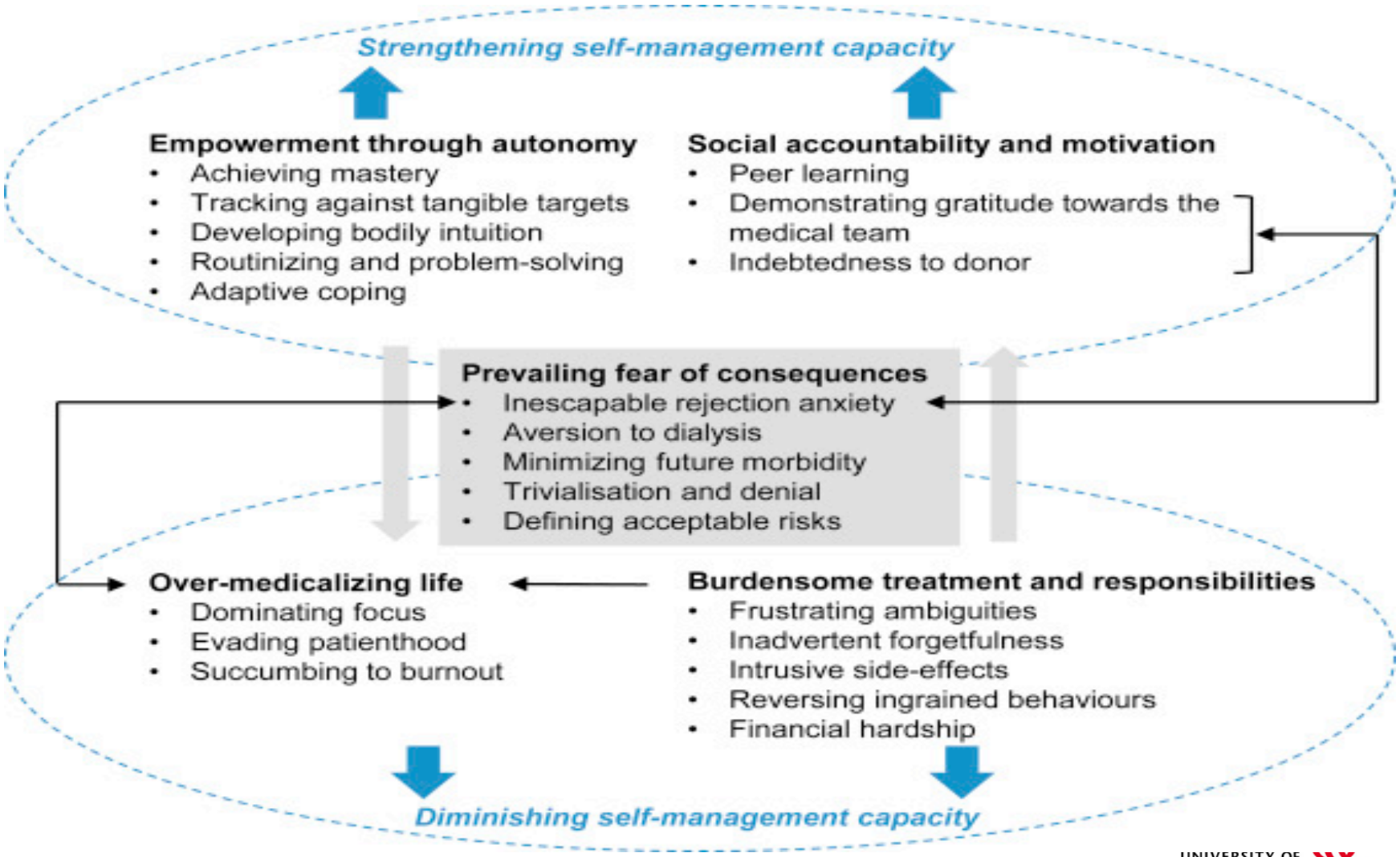
- The scientific rigor of adherence intervention testing has increased with RCT
- Types of interventions tested are heterogeneous
- Multicomponent interventions appear most effective
- Intervention effectiveness appears to be increased by tailoring (e.g., based on patient needs and dynamic information on patient adherence over time)
- Degree of intervention impact is variable and often trials did not evaluate clinical outcomes
- Whether interventions improve longterm clinical outcomes remain unclear

Study of Non adherence
New Paradigm

- Quantitative Measurements
- **Qualitative Measurements**
  - Provide insight into patients values, knowledge, beliefs that influence behaviors and choices in transplantation self management.
  - Self Management – the tasks that individuals must undertake to live with chronic conditions, having confidence to deal with medical management, role management and emotional management of chronic conditions

Jamieson et al. Am J Kidney Dis 2016;67(3): 461-478

Self Management in Kidney Transplantation



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Self Management in Kidney Transplantation

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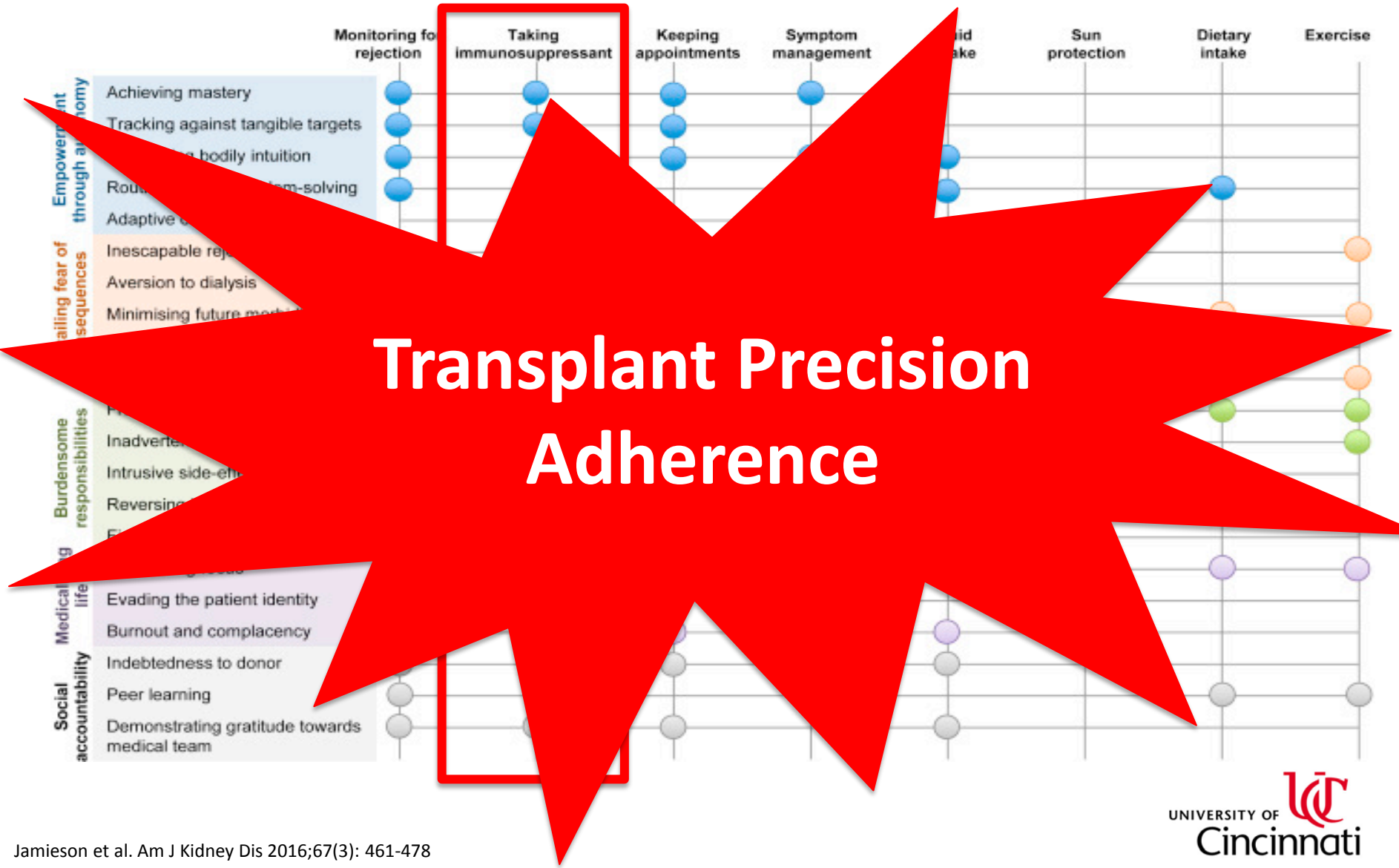
Self Management in Kidney Transplantation



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THANK YOU