Database & Methods Cyberseminar Series

Session #8. Pharmacoepidemiological Designs: Using CDW lab data for drug effectiveness research

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VIReC
RESEARCHERS' GUIDE TO VA DATA

The objectives of this cyberseminar are to:

- Provide overview of laboratory data in VA Corporate Data Warehouse (CDW).
- Review how to find drug information in the CDW.
- Share examples of studies using pharmacoepidemiological designs and pharmacogenomics designs.
- Describe use of creatinine and CDW pharmacy data for pharmacogenomics in the Million Veteran Program.

Session roadmap

- Provide overview of laboratory data in Corporate Data Warehouse (CDW).

  → Serum creatinine and HbA1c

- Review how to find drug information in CDW.
- → Including date of fill, the number of pills per day, the strength of the pill, refill data, exposure window
- Share examples of studies with pharmacoepidemiological designs & pharmacogenomics designs.

  → Studies relate to metformin exposure and kidney function

- Describe use of creatinine and CDW pharmacy data for pharmacogenomics in the Million Veteran Program.

Poll Question #1

What is your primary role at the VA?

a. Primary Care/Specialty Provider
b. Mental Health Provider
c. Nurse
d. Researcher
e. Administrator

Poll Question #2

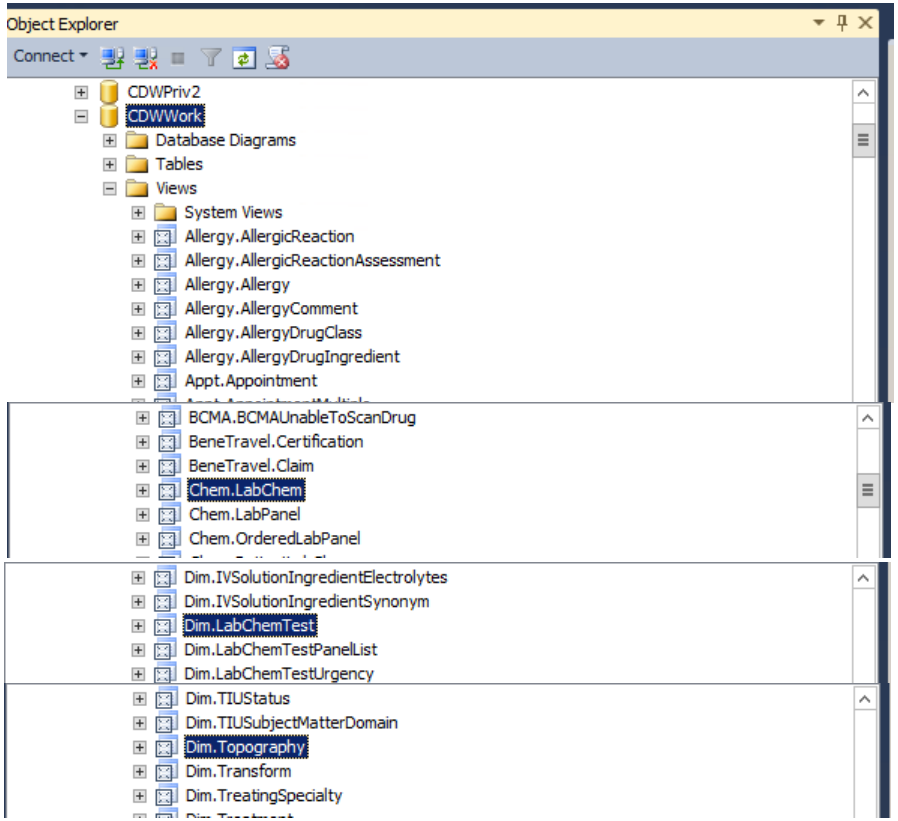
What is your experience with using lab data and pharmacy data?

a. Heard of it, but no experience using it
b. I have experience using it
c. Not heard of it/no experience using it

Lab data CDW

- CDW lab Data is derived from VistA at individual medical centers
- CDW back to FY 1999
- CDW includes all lab tests
- Disadvantage is that it follows VistA test format at each medical center. An example is BUNpost BUNpre a name created by us in my station for dialysis purposes and it will show that way in VistA.
- It also introduces variability in the way that the test are reported (units, comments, etc)
- Contains LOINC code (we have not use LOINC code)

Lab data CDW: How to access creatinine or HbA1c or any other Labs?

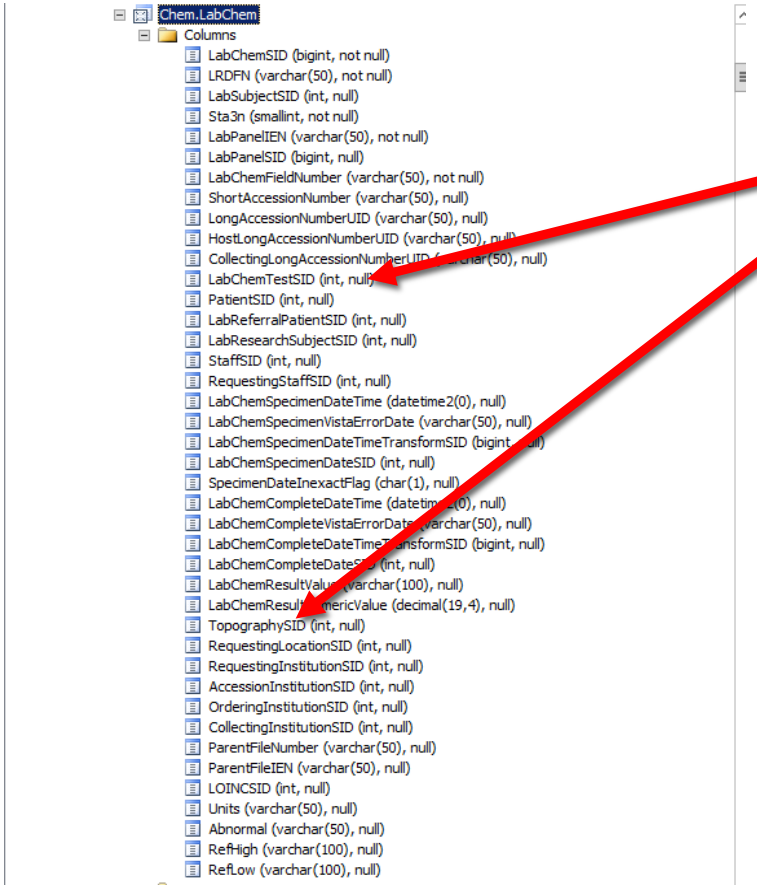


1. Locate database i.e. "ORD_Hung_2012XXXXX".

2. Inside "CDWWORK", find "Views" folder

3. Inside "Views", locate views
"Chem.LabChem"
"Dim.LabChemTest"
"Dim.Topography"

Location for all labs and topography
(specimen type)



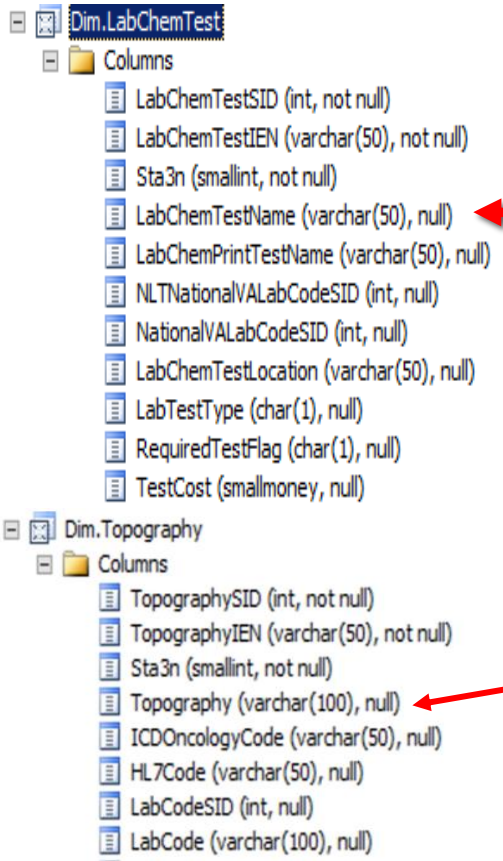
Inside view “Chem.LabChem”

- **LabChemTestSID**
- **TopographySID**

The LabchemTestSID is used to reference the Creatinine lab inside Dim.LabChemTest.

The TopographySID is used to reference the specimen collected for the Creatinine results

Full lab test names for all tests by facility



The Dim.LabChemTest view is a data dictionary for all labs within a given VA facility. The LabchemTestSID

Topography

The Dim.Topography view is a data dictionary for all lab specimens within a given VA facility.

The TopographySID is used to pull the full specimen name from the patient's lab record.

Tips for using creatinine from the CDW

- Always make sure that you are using the correct specimen –we use blood, serum and plasma for serum creatinine
- Check for multiple creatinines in the same day for the patient –most commonly they are exact duplicates but in some instances they are different—The approach at this point depends in each researcher.
- Define your limits (we use >=0.4 to =<20 mg/dl.
- Remove the reciprocal.

Creatinine values in MVP at enrollment and per year since 1999

Baseline Creatinine By Enrollment Year MVP	
Enrollment Year	Patient count
2011	15,481
2012	89,135
2013	100,427
2014	93,253
2015	93,617
2016	66,870
Total	**458,783**

90%
N=510,348

MVP Patients with Creatinine per Year	
Year	Patient Count
1999	31,457
2000	92,559
2001	114,872
2002	137,634
2003	160,729
2004	183,130
2005	201,506
2006	220,572
2007	240,139
2008	263,662
2009	291,677
2010	316,792
2011	341,744
2012	367,938
2013	395,293
2014	411,422
2015	411,953
2016	397,284
2017	354,468

Outpatient Creatinine Lab by Year MVP	
Year	Creatinine Lab Count
1999	38,205
2000	185,361
2001	235,103
2002	284,822
2003	342,177
2004	397,626
2005	446,326
2006	501,073
2007	549,980
2008	623,840
2009	709,200
2010	772,857
2011	846,230
2012	1,013,361
2013	1,456,201
2014	1,607,526
2015	1,653,570
2016	1,618,123
2017	1,232,321
Total	**14,513,902**

VA Serum Creatinine from OMOP

Counts	Type		
Year	Serum Creatinine	Blood Creatinine	Grand Total
1999	1,060,649		1,060,649
2000	4,975,887		4,975,887
2001	6,351,601		6,351,601
2002	7,369,397		7,369,397
2003	8,045,428		8,045,428
2004	8,084,417		8,084,417
2005	8,648,522		8,648,522
2006	9,167,060	181	9,167,241
2007	9,022,042	746	9,022,788
2008	9,811,005	44,083	9,855,088
2009	10,580,908	121,216	10,702,124
2010	10,555,814	92,331	10,648,145
2011	10,797,144	87,893	10,885,037
2012	10,756,478	100,225	10,856,703
2013	10,365,237	188,794	10,554,031
2014	10,839,796	271,888	11,111,684
2015	10,749,461	281,533	11,030,994
2016	10,913,168	148,125	11,061,293

Courtesy Of Michael's Matheny's Lab

*OMOP: Observational Medical Outcomes Partnership (**OMOP**) Common Data Model

Creatinine base Glomerular filtration rate by age and race

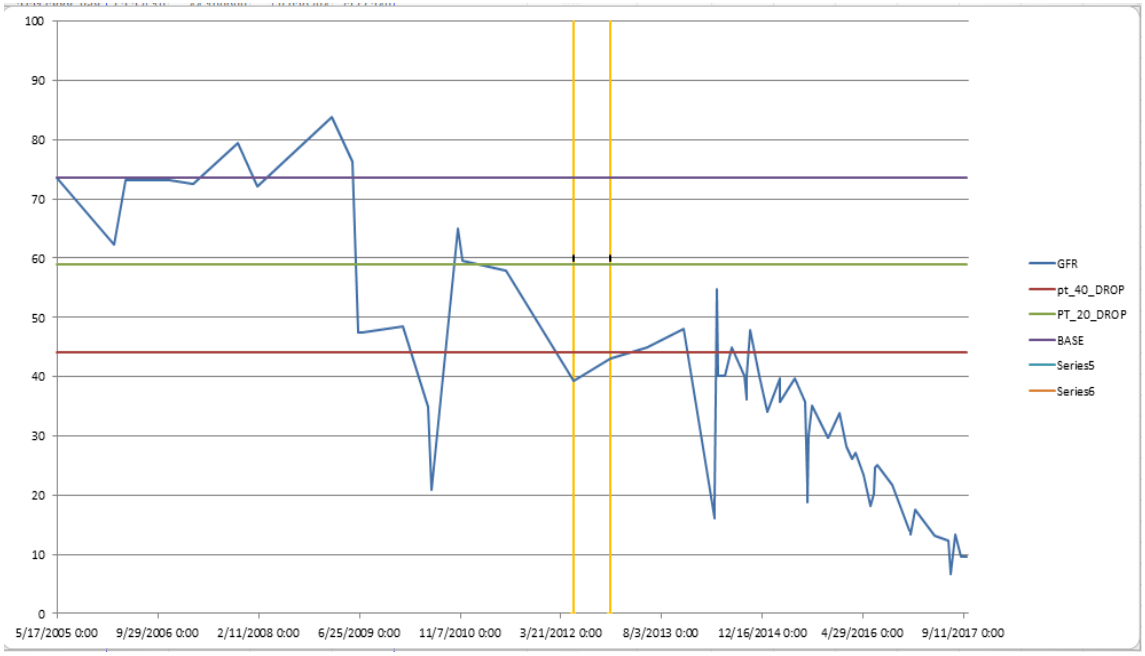
Calculated using the CKD-EPI equation using creatinine, age, race and gender

	Race											
	Sum of Count					% of Total					Total Sum of Count	Total % of Total
eGFR	Native	Asian	AA	Unknown	White	Native	Asian	AA	Unknown	White		
0	403	309	16,938	3,957	34,671	0.24%	0.28%	0.44%	0.33%	0.24%	56,278	0.29%
1-14	4,520	3,968	182,338	21,873	219,235	2.69%	3.56%	4.72%	1.84%	1.54%	431,934	2.21%
15-29	5,512	3,473	157,528	39,572	461,928	3.28%	3.11%	4.08%	3.33%	3.25%	668,013	3.42%
30-59	31,435	20,054	627,393	288,319	3,362,062	18.71%	17.98%	16.25%	24.23%	23.67%	4,329,263	22.16%
60-89	76,676	51,956	1,517,931	557,231	6,645,177	45.63%	46.57%	39.31%	46.83%	46.78%	8,848,971	45.30%
>= 90	49,490	31,794	1,359,322	278,846	3,480,823	29.45%	28.50%	35.20%	23.44%	24.51%	5,200,275	26.62%
Grand Total	**168,036**	**111,554**	**3,861,450**	**1,189,798**	**14,203,896**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**19,534,734**	**100.00%**

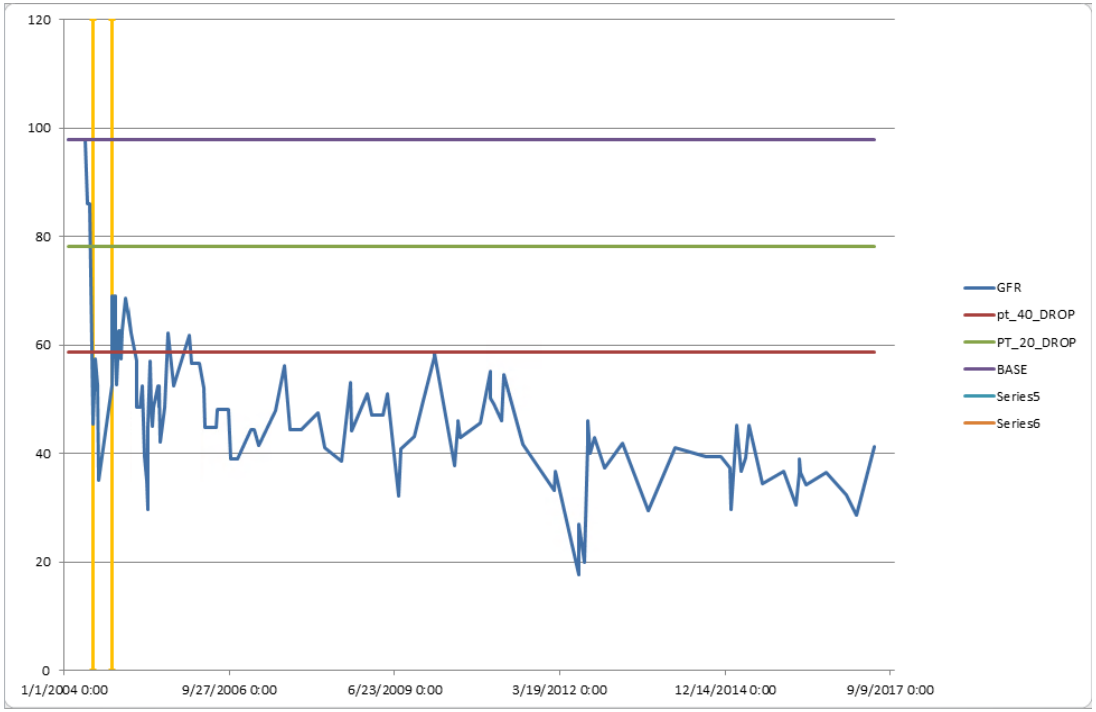
% of Total																Total Sum of Count	Total % of Total	
< 18	18-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>= 85	Other			eGFR
9.35%	0.28%	0.29%	0.30%	0.26%	0.25%	0.27%	0.31%	0.32%	0.27%	0.27%	0.26%	0.28%	0.31%	0.36%	100.00%	56,278	0.29%	0
0.00%	0.26%	0.33%	0.34%	0.53%	1.05%	1.47%	1.93%	2.67%	2.64%	2.45%	2.35%	2.21%	2.22%	1.81%	0.00%	431,934	2.21%	1-14
0.00%	0.44%	0.24%	0.28%	0.39%	0.81%	1.07%	1.57%	2.51%	2.90%	3.35%	4.14%	5.01%	5.72%	7.25%	0.00%	668,013	3.42%	15-29
0.00%	1.04%	1.44%	2.11%	3.15%	5.13%	7.65%	9.66%	12.46%	16.70%	20.92%	29.93%	36.25%	41.42%	46.51%	0.00%	4,329,263	22.16%	30-59
1.87%	26.16%	37.10%	42.81%	46.05%	48.21%	48.33%	49.21%	46.36%	47.53%	49.35%	44.54%	41.07%	37.78%	33.75%	0.00%	8,848,971	45.30%	60-89
88.79%	71.82%	60.60%	54.16%	49.62%	44.55%	41.21%	37.32%	35.67%	29.97%	23.66%	18.77%	15.18%	12.55%	10.31%	0.00%	5,200,275	26.62%	>= 90
100.00%	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**19,534,734**	**100.00%**	All

Courtesy Of Michael's Matheny's Lab

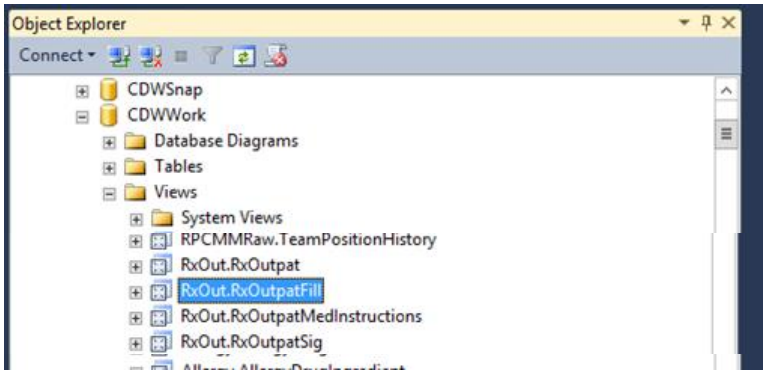
GFR trajectories –incident CKD and progression



GFR trajectory-incident CKD without progression

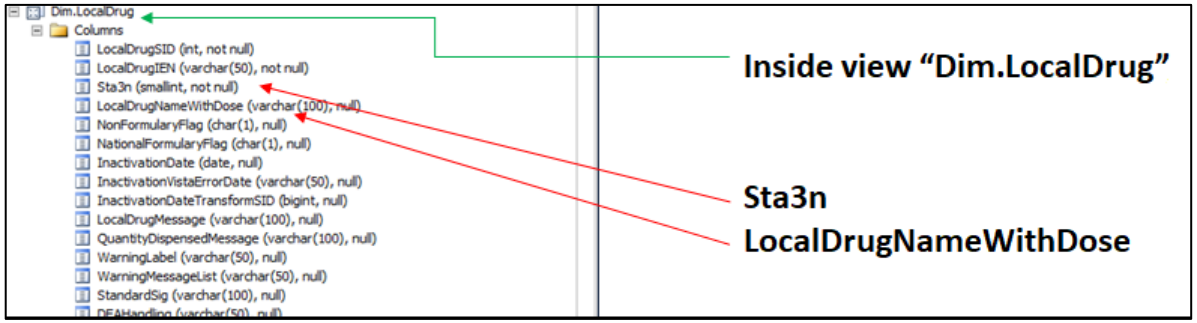


How to access outpatient pharmacy data file?

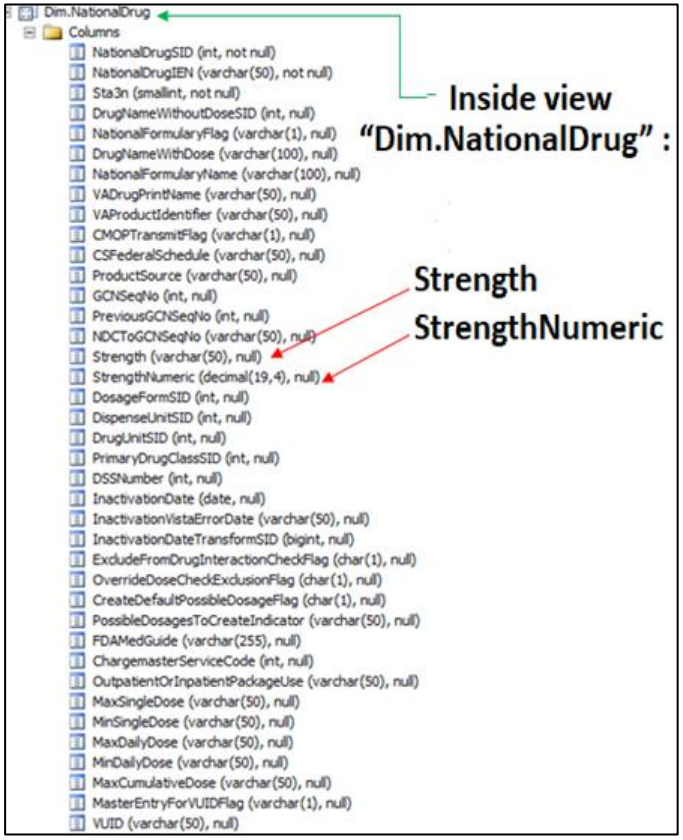


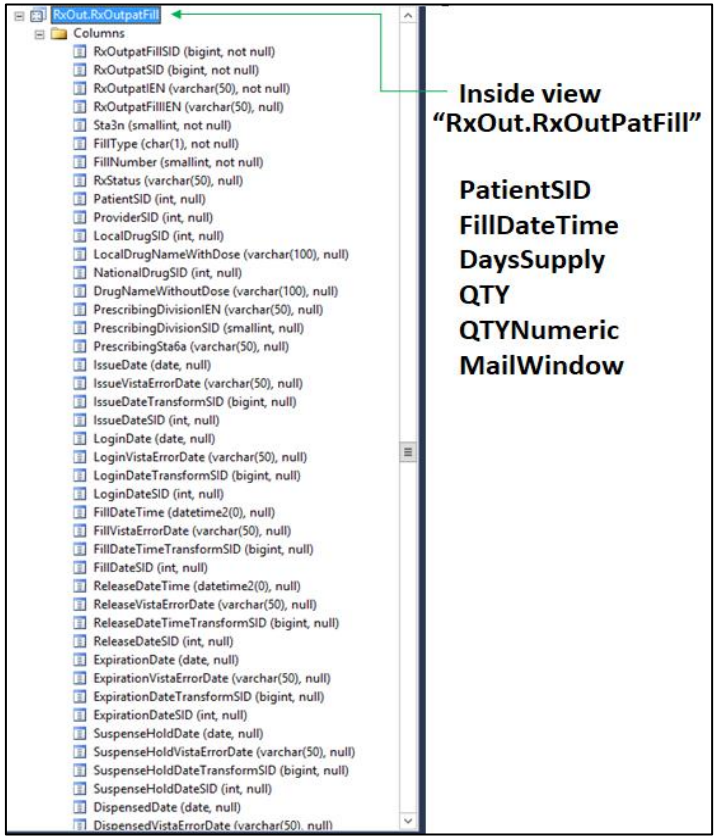
1. Locate database i.e. "ORD_Hung_2012XXXXX".

2. Inside "Views", locate views
"Dim.LocalDrug"
"Dim.NationalDrug"
"Dim.Drugnamewithoutdose"
"RxOut.RxOutPatFill"



Specific characteristics of the prescription





Metformin Fill data from the CDW

Results | Messages

	LocalDrugSID	LocalDrugNameWithDose	filldatesid	FillDateTime	qty	QtyNumeric	DaysSupply	MailWindow	Strength	StrengthNu
1	513287	METFORMIN HCL 500MG TAB	20120920	2012-09-20 00:00:00	180	180.00	90	M	500	500.0000
2	800196780	METFORMIN HCL 500MG TAB	20120907	2012-09-07 00:00:00	28	28.00	7	W	500	500.0000
3	800196780	METFORMIN HCL 500MG TAB	20120914	2012-09-14 00:00:00	28	28.00	7	W	500	500.0000
4	800064148	METFORMIN HCL 1000MG TAB	20120921	2012-09-21 00:00:00	180	180.00	90	M	1000	1000.0000
5	634457	METFORMIN HCL 500MG TAB	20120625	2012-06-25 00:00:00	90	90.00	90	M	500	500.0000
6	578612	METFORMIN HCL 1000MG TAB	20120622	2012-06-22 00:00:00	90	90.00	90	M	1000	1000.0000
7	297309	metFORMIN HCL 500MG TAB	20120422	2012-04-22 00:00:00	90	90.00	90	M	500	500.0000
8	800046837	MetFORMIN HCL 500MG TAB	20120325	2012-03-25 00:00:00	360	360.00	90	M	500	500.0000
9	583435	METFORMIN HCL 1000MG TAB	20120710	2012-07-10 00:00:00	180	180.00	90	M	1000	1000.0000
10	211482	METFORMIN HCL 500MG TAB	20111228	2011-12-28 00:00:00	180	180.00	90	M	500	500.0000
11	297309	metFORMIN HCL 500MG TAB	20110627	2011-06-27 00:00:00	270	270.00	90	M	500	500.0000
12	800038489	METFORMIN HCL 500MG 24HR SA TAB	20111216	2011-12-16 00:00:00	360	360.00	90	M	500	500.0000
13	358990	METFORMIN HCL 500MG TAB	20120418	2012-04-18 00:00:00	360	360.00	90	M	500	500.0000

Estimating Daily Dose and drug exposure window

Results | Messages

LocalDrugSID	LocalDrugNameWithDose	filldatesid	FillDateTime	qty	QtyNumeric	DaysSupply	MailWindow	Strength	StrengthNumeric
358990	METFORMIN HCL 500MG TAB	20120418	2012-04-18 00:00:00	360	360.00	90	M	500	500.0000
358990	METFORMIN HCL 500MG TAB	20120316	2012-03-16 00:00:00	360	360.00	90	M	500	500.0000
698640	METFORMIN HCL TAB 500 MG	20120622	2012-06-22 00:00:00	270	270.00	90	M	500	500.0000
708188	METFORMIN HCL 850MG TAB	20120419	2012-04-19 00:00:00	270	270.00	90	M	850	850.0000

DDD (Drug Daily Dose): 360/90=4 tablets a day= 500x4= 2000

fill date was 4-18=-2012 + 90 -> end of drug supply July 11-2012

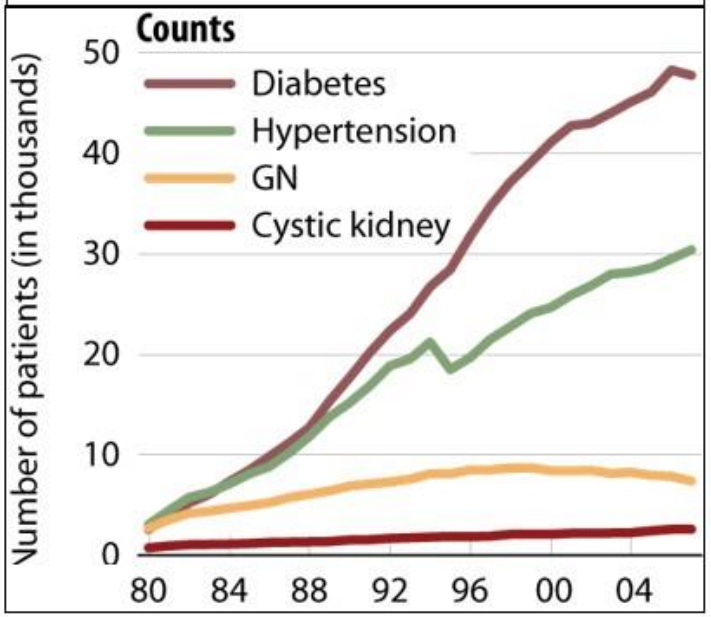
Pharmaco-epidemiology to calculate continues exposure you allow a gap to account for stock pilling

+Gap (14,30,60,90) than next refill date should be within the desire period. (i.e. 90 days 9/26/2012)

CKD is a major public health problem

- CKD affects 850 million worldwide.
- For the VA is the 4th most common diagnosis, affecting 36% of the population.
- The number one cause of kidney failure is diabetes.
- Diabetes prevention and management are key to prevent and slow down the progression of chronic kidney disease.

Diabetes & Hypertension are the two most common causes of ESRD, incident counts.



original article

http://www.kidney-international.org

Open

Comparative effectiveness of incident oral antidiabetic drugs on kidney function

Adriana M. Hung[1,2,3], Christianne L. Roumie[1,2], Robert A. Greevy[1,4], Xulei Liu[1,4], Carlos G. Grijalva[5], Harvey J. Murff[1,2], T. Alp Ikizler[1,2,3] and Marie R. Griffin[1,2,5]

[1]VA Tennessee Valley, Clinical Science Research and Development, Geriatric Research Education Clinical Center (GRECC), Department of Medicine, Nashville, Tennessee, USA; [2]Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA; [3]Division of Nephrology, Vanderbilt University, Nashville, Tennessee, USA; [4]Department of Biostatistics, Vanderbilt University, Nashville, Tennessee, USA and [5]Department of Preventive Medicine, Vanderbilt University, Nashville, Tennessee, USA

- Metformin is the first line therapy for diabetes and one of the most heavily prescribed drugs in the world.
- Metformin has many pleiotropic actions including anti-inflammatory and anti-oxidant properties.
- We hypothesize that it could be renoprotective independently of its glucose lowering capacity.

Hung et al. Kidney Int. 2012 Apr;81(7):698-706. doi: 10.1038/ki.2011.444. Epub 2012 Jan 18.

Exposure Groups

- ***Incident monotherapies:***
  - Metformin (reference-most common prescription)
  - Sulfonylureas (Glyburide and Glipizide)
  - Rosiglitazone (Pioglitazone was non-formulary in the VA system).

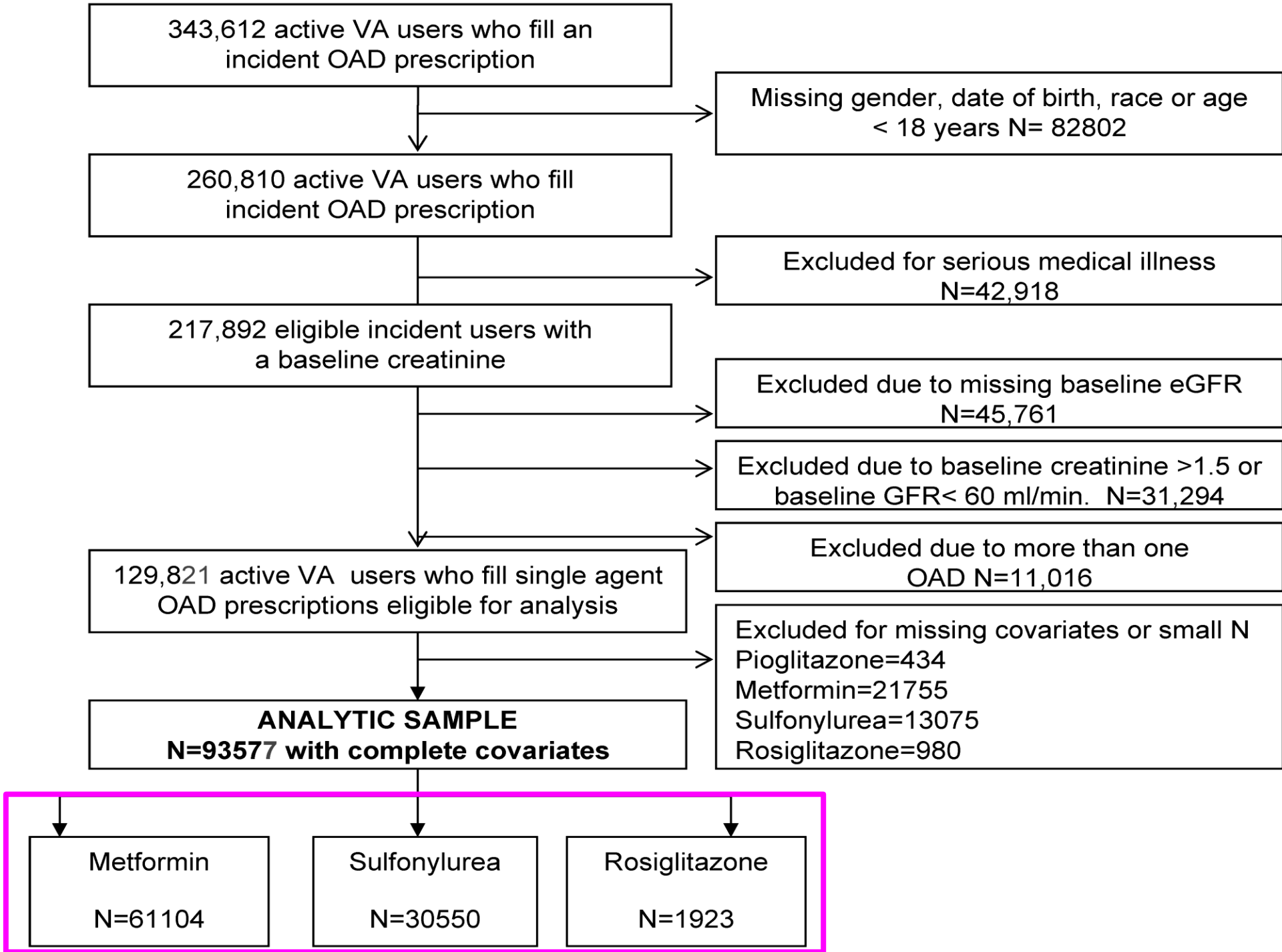
Study Outcomes

Kidney Outcomes (Primary)	**Composite of eGFR event or ESRD**
Secondary Outcome	**Composite of eGFR event , ESRD or death of any cause**

** eGFR was calculated using the MDRD equation a serum creatinine based equation

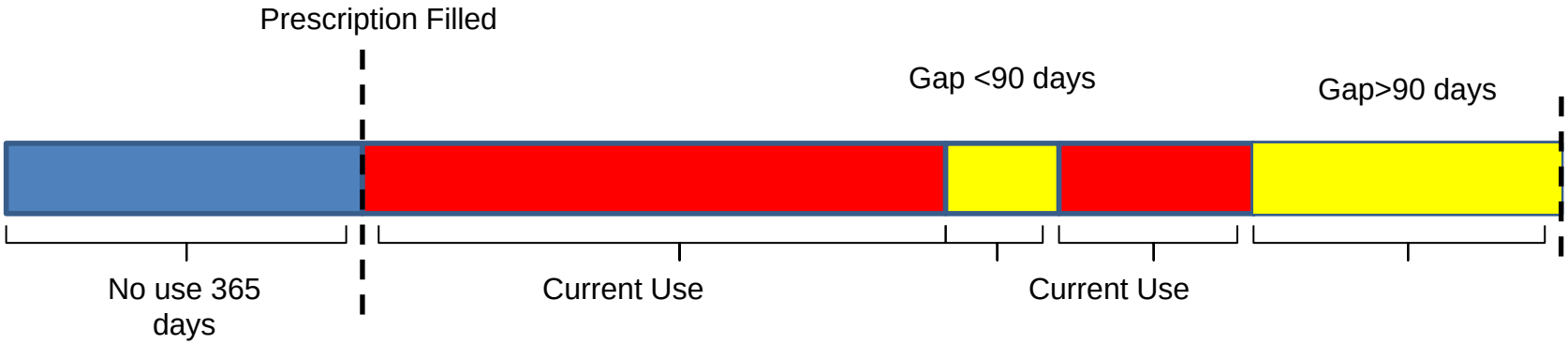
GFR events	1) A sustain 25% decrease in eGFR (~30 mL/min/1.73 m^2) from baseline value.
ESRD	•An outpatient eGFR <15 ml/min/1.73 m^2 or •a dialysis code (ICD-9 or CPT-code) or •renal transplant

**GFR events & ESRD diagnosis needed to be confirmed between 3-12 month from the qualifying GFR or code.


343,612 active VA users who fill an incident OAD prescription
Missing gender, date of birth, race or age < 18 years N= 82802
260,810 active VA users who fill incident OAD prescription
Excluded for serious medical illness N=42,918
217,892 eligible incident users with a baseline creatinine
Excluded due to missing baseline eGFR N=45,761
Excluded due to baseline creatinine >1.5 or baseline GFR< 60 ml/min. N=31,294
Excluded due to more than one OAD N=11,016
129,821 active VA users who fill single agent OAD prescriptions eligible for analysis
Excluded for missing covariates or small N
Pioglitazone=434
Metformin=21755
Sulfonylurea=13075
Rosiglitazone=980
ANALYTIC SAMPLE
N=93577 with complete covariates
Metformin
N=61104
Sulfonylurea
N=30550
Rosiglitazone
N=1923

Primary Analysis

Persistent exposure required (PER)



Exposure ends if: the patient experience and outcome or is censored.

Censoring events:

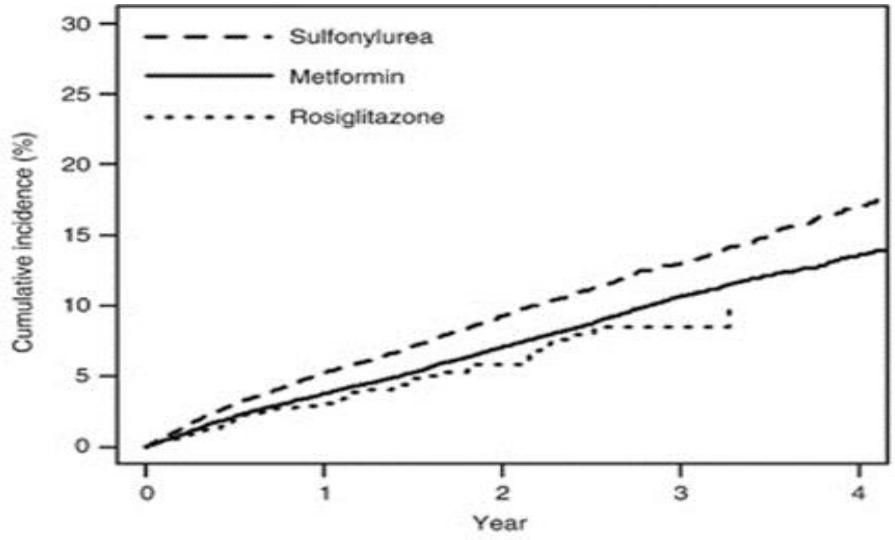
- Gap> 90 days, switch regimen or add any other OAD or insulin to your regimen.
- End of study (September 30th , 2008)
- Lost to follow up (no contact with the VA in 181 days)

Days with drug supply in hand : which was calculated using **refill data** (how many pills a patient had in hand in each follow up day).

Baseline Characteristics by Exposure Group

Characteristics	**Metformin N=61104**	**Sulfonylurea N=30550**	**Rosiglitazone N=1923**
Age, median (IQR) *	60 (55, 69)	62 (56, 72)	64 (57,72)
Male, %	95	97	97
Race, %			
Non African Americans	84	82	84
African Americans	16	18	16
Glomerular Filtration Rate, ml/min	81 (72, 93)	80 (70, 93)	79 (69, 91)
Microalbuminuria present, %	3	3	4
HbA1c, median (IQR)	7.1 (6.5, 7.9)	7.3 (6.6, 8.4)	6.8 (6.2, 7.6)
Systolic blood pressure, median(IQR)	134 (124, 144)	135 (124, 146)	133 (122, 143)
Diastolic blood pressure, median(IQR)	77 (70, 84)	76 (69, 84)	74 (67,81)
Body mass index (kg/m^2), median (IQR)	32.3 (28.8, 36.7)	30.7 (27.3, 34.7)	30.9 (27.5, 34.7)
ACEI or ARBs, % †	57	56	57
Loop diuretics, %	8	12	10
Coronary artery disease, %	21	23	23
Hospitalized in the prior year, %	8	10	8

Crude cumulative incidence of the composite outcome



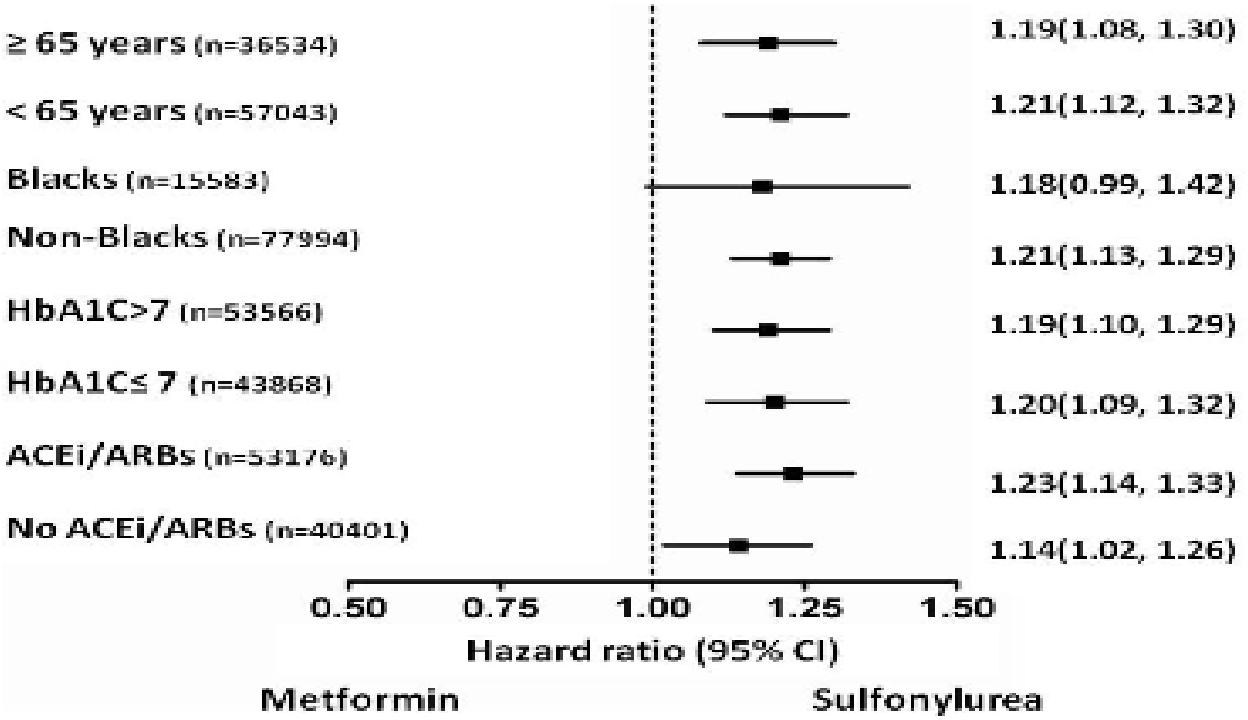
Total at risk (%)	93,577 (100)	41,414 (44)	19,536 (21)	8564 (9)	3054 (3)
Metformin	61,104 (100)	27,855 (46)	13,069 (21)	5669 (9)	2019 (3)
Sulfonylurea	30,550 (100)	12,896 (42)	6160 (20)	2768 (9)	1012 (3)
Rosiglitazone	1923 (100)	737 (38)	307 (16)	127 (7)	23 (1)

Proportion of patients on renin-angiotenin–aldosterone system blockade at each point in time.

Overall (%)	53,172 (57)	27,319 (66)	13,783 (71)	6106 (74)	2267 (74)
Metformin	35,007 (57)	18,396 (66)	9258 (71)	4191 (74)	1501 (75)
Sulfonylurea	17,075 (56)	8434 (66)	4307 (70)	2025 (73)	751 (74)
Rosiglitazone	1094 (57)	486 (66)	218 (71)	99 (78)	15 (68)

Hung et al. Kidney Int. 2012 Apr;81(7):698-706. doi: 10.1038/ki.2011.444. Epub 2012 Jan 18.

Adjusted Hazard ratios for the composite outcome of GFR event or ESRD Among age, race, HbA1c, and RAAS blockade subgroups



Hung et al. Kidney Int. 2012 Apr;81(7):698-706. doi: 10.1038/ki.2011.444. Epub 2012 Jan 18.

Conclusion

- Initiation of sulfonylureas compared with metformin was associated with a 20% increased risk of the composite outcome of an eGFR event or ESRD.
- This association was consistently observed across all planned sensitivity, including a supplemental propensity match analyses and we consider our findings robust.

New User of Second Line Therapy

Comparative effectiveness of adding either insulin or sulfonylurea to metformin in preventing kidney function decline among patients with diabetes

Adriana M. Hung, MD MPH[1,2,3], Christianne L. Roumie, MD MPH [1,2,3]; Robert A. Greevy, PhD[1,4]; Carlos G. Grijalva, MD MPH [1,5]; Xulei Liu, MD MS[1,4]; Harvey J. Murff, MD MPH[1,3]; T. Alp Ikizler, MD MPH[2,3]; Marie R. Griffin, MD MPH[1,3,5]

Hung et al. Clin J Am Soc Nephrol. 2016 Dec 7;11(12):2177-2185. Epub 2016 Nov 8.

Original Investigation | June 11, 2014

Association Between Intensification of Metformin Treatment With Insulin vs Sulfonylureas and Cardiovascular Events and All-Cause Mortality Among Patients With Diabetes

Christianne L. Roumie, MD, MPH[1,2]; Robert A. Greevy, PhD[1,3]; Carlos G. Grijalva, MD, MPH[1,4]; Adriana M. Hung, MD, MPH[1,2]; Xulei Liu, MD, MS[1,3]; Harvey J. Murff, MD, MPH[1,2]; Tom A. Elasy, MD, MPH[1,2]; Marie R. Griffin, MD, MPH[1,2,4]

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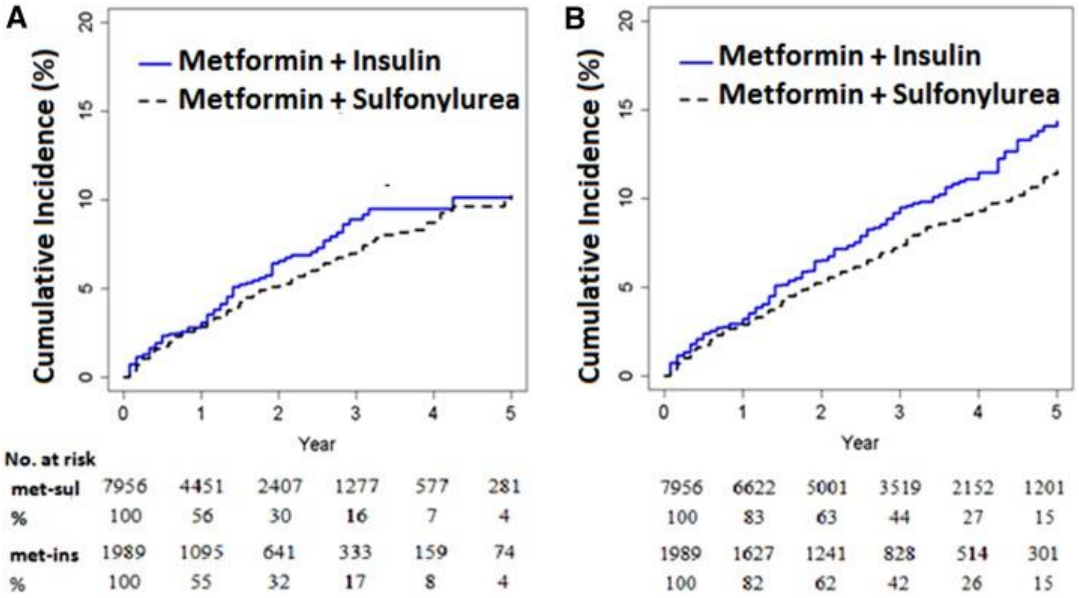
JAMA. 2014;311(22):2288-2296. doi:10.1001/jama.2014.4312.

Crude cumulative incidence of GFR events or ESRD by drug combination groups. (A) Propensity score–matched cohort with persistent exposure required in the intensified regimen. (B) PS matched with persistent exposure not required: patients remain in their exposure group, regardless of persistence with the intensified regimen. met-ins, Metformin and insulin; met-sul, metformin and sulfonylurea.

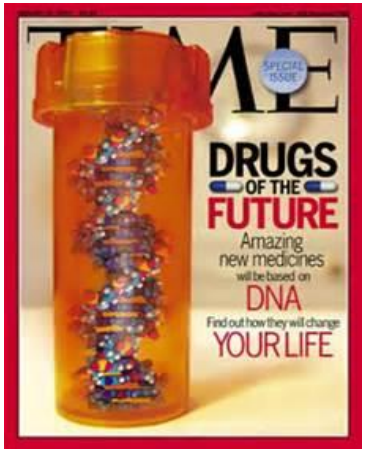


Follow-up began 180 days after the intensified prescription
To prevent misclassifying a switcher with and Add-on therapy

Hung et al. Clin J Am Soc Nephrol. 2016 Dec 7;11(12):2177-2185. Epub 2016 Nov 8.

Pharmacogenomics of Metformin

Metformin is the first line therapy for T2DM and for the prevention of diabetes.
It is the most heavily prescribed drug in the world with more than 100 million users.



Metformin response is heritable ~ 40% and highly variable.

Ewan Pearson -www.thelancet.com/diabetes-endocrinology Vol 2 June 2014

What we know from the Metformin Genetics Consortium (MetGen).

Non Responders: In the DPP trial (***MATE1*** rs8065082 =CC homozygous)

Jablonski *et al., Diabetes*
2010;59:2672-2681

Enhanced responders: GWAS GoDARTS & UKPDS ->ATM locus

- *Ewan Person: Nature Genetics 43,117–120 (2011) doi:10.1038/ng.735*

Tolerability/ AE -> GoDARTS: ***OCT1*** (stopping metformin short after initiation)

- *Ewan Pearson Diabetes 2015;64:1786-1793|DOI 10.2337/db14-1388*

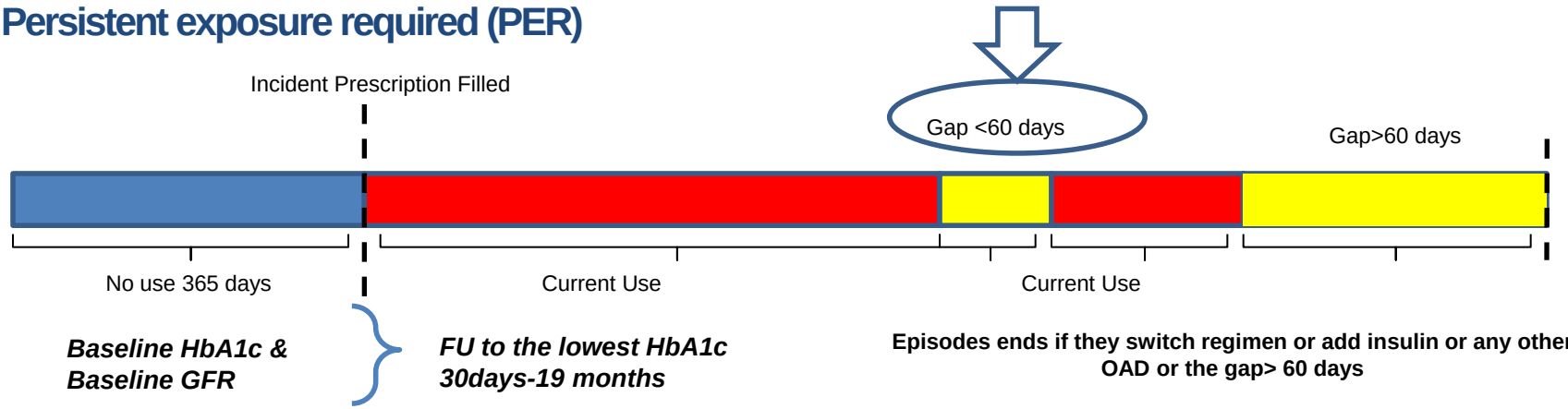
Stronger response to metformin: common variant in the SLC2A2 gene, which reduces GLUT2.

- *Nature Genetics on August 8, 201648,1055–1059(2016) doi:10.1038/ng.3632*

Safety: Lactic acid? My CSRD merit-metformin RCT in CKD "Hyperlactenemia of unknown significance".

Drug exposure phenotype: Incident User of Metformin persistently exposed

Primary Analysis
Persistent exposure required (PER)



Days with drug supply in hands : which was calculated using refill data (how many pills a patient had in hand in each follow up day). Average daily dose: is calculated using the strength of the pill. Can be validated with printed bottle instructions. Average of the 90 days prior to the lowest HbA1c.

Outcomes

- Three outcomes of interest:
  - HgbA1c lowest levels after metformin
  - HgbA1c absolute reduction (baseline HgbA1c – HgbA1c after metformin)
  - HgbA1c relative reduction (HgbA1c absolute reduction/baseline HgbA1c)
- Key covariates: closest HgbA1c 1-year prior + adjusted daily drug dose + eGFR 1-year prior + Number of HgbA1c measurements + Days to lowest HgbA1c + 5 principal components

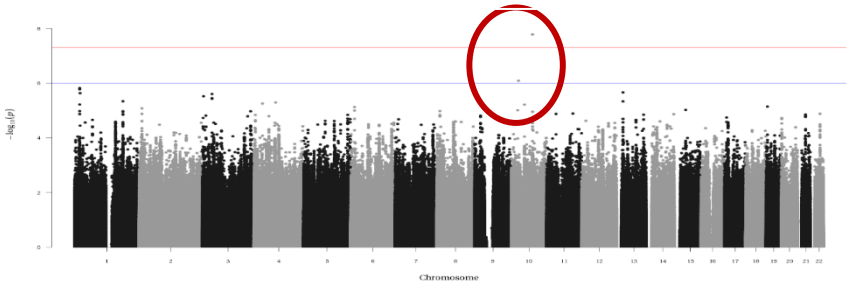
Clinical characteristics by group

	Non Hispanic Whites (n=6553)	Non Hispanic Blacks (n=1729)	Not used lack SIRE (n=4689)
Gender, male % (n)	92%	92%	92%
Baseline HbA1c (%)	7.2±1.21	7.4±1.5	7.4±1.6
GFR year prior, ml/min/year	81±15	90±18	87± 18
Adjusted drug daily dose, mg	1035±489.4	997±	1064±510
# HbA1c prior to the lowest HbA1c	2.5±1.2	2.4±1.3	2.3 ±1.3
Days to the Lowest A1c	255±	242±129	210±137
SGOT 1 year prior, mg/dl	29±18	28±14	
Lowest HbA1c (%)	6.29±0.59	6.35±0.6	6.5±0.9
Absolute reduction (%)	0.9±1.2	1.1±1.5	1.0 ±1.4
Relative reduction (%)	0.11±0.12	0.12±0.14	0.11 ±0.13

Two common variants were associated with the glycemic response to metformin in the MVP GWAS (n=8282)

European Americans for the lowest HbA1c adjusted for baseline HbA1c

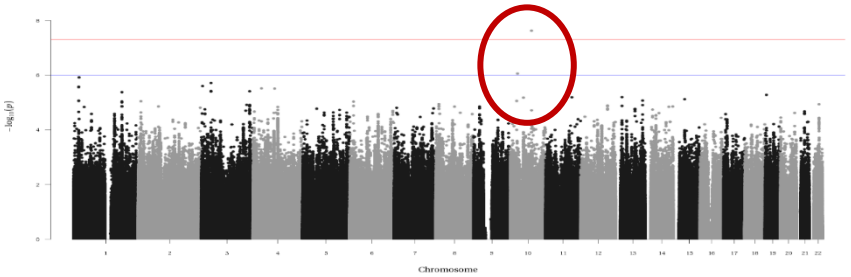
rs55755349: intron in *FAM107B*, 0.39% reduction for allele T, P=1.4x10^{-9}



FAM107B gene have been associated with cancer

Transethnic Metanalysis
For the absolute HbA1c redudtion

rs4253564; 0.17 unit reduction for allele GT; P=2.4x10^{-8}



Rs4253564 lies within 500KB of well-known type-2 diabetes associated gene, *ZMIZ1*

Regional Significance

For the Index SNPs for top loci (P < 5e-7)

European Americans

SNP	Nearby Genes	Regional significance
Rs55755349	FAM107B*	Cancer top loci for (P < 5e-8)
rs576213441	SPATA13, PARP4	HbA1c , DM nephropathy
rs74332025	CRACR2A*, PARP11	HbA1c, NAFLD
rs35053501	PARP4*	HbA1c, DM nephropathy

African Americans

SNP	Nearby Genes	Regional Significance
rs12305233	ETNK1, SOX5, KCNJ8	Diabetic Nephropathy
rs80281848	ABR*	HbA1c, T2DM
rs73033976	IRX4, IRX2	
rs58767041	LINC01492*, CYLC2	
rs36104830	DYNC1I1*, SLC25A13	

Comparison with previously reported locus: rs8192675

Variation in the glucose transporter gene SLC2A2 that is associated with glycemic response to metformin

rs8192675 C:T (Effect:Ref)	BETA	P	Effect Allele Frequency
PMC5007158*	0.08% greater reduction		-
MVP whites lowest-met	-0.017	0.334	29.9%
			68.5%

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5007158/
- *Nature Genetics on August 8, 201648,1055–1059(2016) doi:10.1038/ng.3632*

Summary

- Two genome-wide significant loci (one link to cancer and another one to T2DM).
- Several suggestive loci @ 10-7,with previous ties to HgbA1c levels, DKD and NAFLD
- Nominal Replication of the GLUT2 variant --rs8192675 in blacks, identified another SNP rs11309000 that is < 500 KB downstream.
- Further nominal replication of association by strata of BMI. Larger association found in BMI >= 30 for rs8192675 than in BMI < 30. Important because metformin response is enhanced.

	Genetic determinants of glycemic response ...	POSTER Statistical Genetics and Genetic Epidemiology	**2782W**	Wednesday, Oct. 18 Exhibit Hall, Level 1	3:00pm-4:00pm

Genetic Determinants of kidney function in the MVP

GWAS of eGFR traits (to recognize genes involved in disease initiation):

GFR was estimated using a creatinine based formula : CKD-EPI

1) Genetic determinants of eGFR stratified by T2DM –oral presentation at the ASN

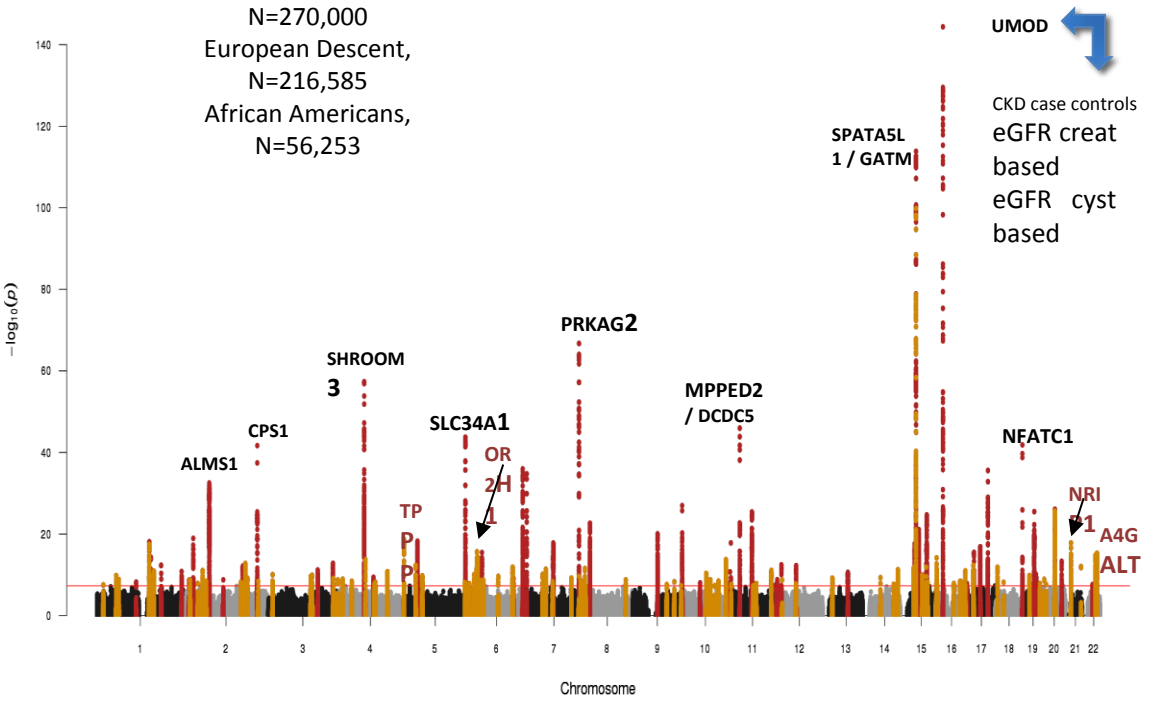
dm_overall	is_genotyped	omop_race	n	min	p1	p5	p10	p25	p50	p75	p90	p99
0	Y	Black or African American	41660	3.4423	33.8555	53.7388	62.0834	74.9579	89.6906	105.2496	116.4672	136.5357
1	Y	Black or African American	24308	3.3308	19.3854	37.1219	47.5231	64.0137	80.9756	98.8749	111.4920	128.4440
0	Y	Unknown	21833	5.2404	31.0371	45.9831	54.0715	67.2159	81.1256	93.2460	103.8680	121.6800
1	Y	Unknown	7585	4.8147	23.4980	36.2903	44.5165	58.7199	74.7562	89.9580	98.9228	115.6900
0	Y	White	171268	2.5017	32.1790	47.7282	55.6371	68.4397	81.8893	93.6800	103.3445	121.0417
1	Y	White	79727	4.2345	23.1307	36.6347	44.2514	58.1136	74.7724	89.2539	97.7142	112.7526

(non-T2DM (N = 181,315) & T2DM veterans (N = 91,523)—the last T2DM GWAS 16,000 .

2) Transethnic eGFR GWAS –(n=270000) ASHG Top 10% poster (101 new +56 known loci)

3) GWAS eGFR in African Americans –ASHG (n=56,253-the largest GWAS in AA to the date)

Kidney function traits (eGFR) transethnic
101 New (orange) + 56 known Loci (red) detected



Summary

- The laboratory data at the VA is extensive
- One of the few electronic health record that offers pharmacy files and allows comparative effectiveness research
- Because the VA is a close system the VA CDW offers the opportunity to study longitudinal outcomes “CKD progression and end stage renal disease” and many other hard outcomes.
- Potential for genetic studies through the Million Veteran Program (several ongoing projects)

Additional Resources

VIReC Options for Specific Questions

HSRData Listserv

- Community knowledge sharing
- ~1,300 VA data users
- Researchers, operations, data stewards, managers
- Subscribe by visiting http://vaww.virec.research.va.gov/Support/HSRData-L.htm (VA Intranet)

HelpDesk

- Individualized support

virec@va.gov

(708) 202-2413

VIReC RESEARCHERS' GUIDE TO VA DATA

Quick links for VA data resources

Quick Guide: Resources for Using VA Data
http://vaww.virec.research.va.gov/Toolkit/QG-Resources-for-Using-VA-Data.pdf (VA Intranet)

VIReC: http://vaww.virec.research.va.gov/Index.htm (VA Intranet)

VIReC Cyberseminars: http://www.virec.research.va.gov/Resources/Cyberseminars.asp

VHA Data Portal: http://vaww.vhadataportal.med.va.gov/Home.aspx (VA Intranet)

VINCI: http://vaww.vinci.med.va.gov/vincicentral/ (VA Intranet)

Health Economics Resource Center (HERC): http://vaww.herc.research.va.gov (VA Intranet)

CDW: https://vaww.cdw.va.gov/Pages/CDWHome.aspx (VA Intranet)

Archived cyberseminar: What can the HSR&D Resource Centers do for you?
http://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/video_archive.cfm?SessionID=101

Contact information

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virec@va.gov
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Next session:
Monday, June 4th at 1pm ET

Database & Methods Cyberseminar Series

Working with EHR Data Using VistAWeb, VINCI ChartReview Tool, and Joint Legacy Viewer

Susan Nicole (Nicki) Hastings, MD, MHS
Durham VA Medical Center

Elizabeth Mahanna, MPH
Durham VA Medical Center

Daniel Denhalter, MSPH
VINCI

VIReC
RESEARCHERS' GUIDE TO VA DATA