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OHDSI SOS Challenge: Intravitreal Anti-VEGF and Kidney Failure

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3/7/2023

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~596 million people have vision impairment worldwide

Quality of life
Loss of independence & mobility
Unable to work

Burton, M. J. *et al.* The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. *Lancet Global Heal* **9**, e489–e551 (2021).
Fenwick, E. *et al.* Social and emotional impact of diabetic retinopathy: a review. *Clinical & Experimental Ophthalmology* **40**, 27–38 (2012).
Coyne, K. S. *et al.* The impact of diabetic retinopathy: perspectives from patient focus groups. *Family practice* **21**, 447–453 (2004).
Sherrod, C. E., Vitale, S., Frick, K. D. & Ramulu, P. Y. Association of Vision Loss and Work Status in the United States. *JAMA Ophthalmology* **132**, 1239–4 (2014).

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Leading Causes of Vision Impairment/Blindness Worldwide	
Diabetic retinopathy (DR) / diabetic macular edema (DME)	120 million
Age-related macular degeneration (AMD)	196 million
Retinal vein occlusion (VO)	28 million

Combined Global Prevalence: 344 million

Collaborators, G. 2019 B. and V. I. *et al.* Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Global Heal* **9**, e144–e160 (2021).
Teo, Z. L. *et al.* Global Prevalence of Diabetic Retinopathy and Projection of Burden through 2045 Systematic Review and Meta-analysis. *Ophthalmology* **128**, 1580–1591 (2021).
Wong, W. L. *et al.* Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Global Heal* **2**, e106–e116 (2014).
Song, P., Xu, Y., Zha, M., Zhang, Y. & Rudan, I. Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health* **9**, 010427 (2019).

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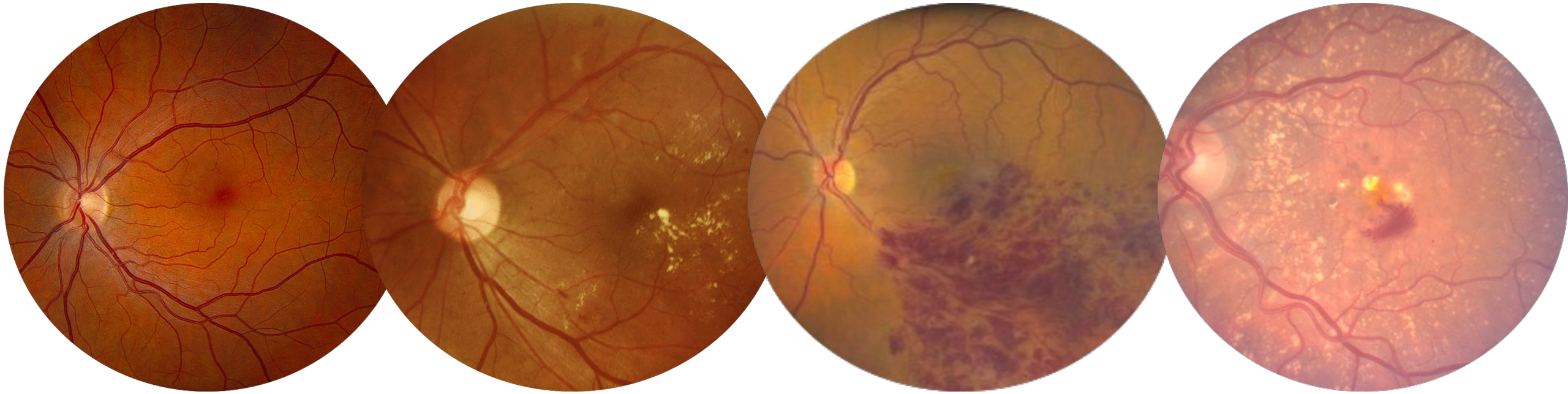
Leaking Blood Vessels in the Retina



Normal

Diabetic Retinopathy /
Diabetic Macular Edema

Vein Occlusion

Age-Related Macular
Degeneration

https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/normal-fundus.htm
https://link.springer.com/article/10.1007/s10916-021-01795-8/figures/1
http://eyerounds.org/atlas/photos/BRVO2005.jpg
https://webvision.med.utah.edu/imageswv/Hagerman.Fig34.jpg

Anti-vascular endothelial growth factor (anti-VEGF) medications

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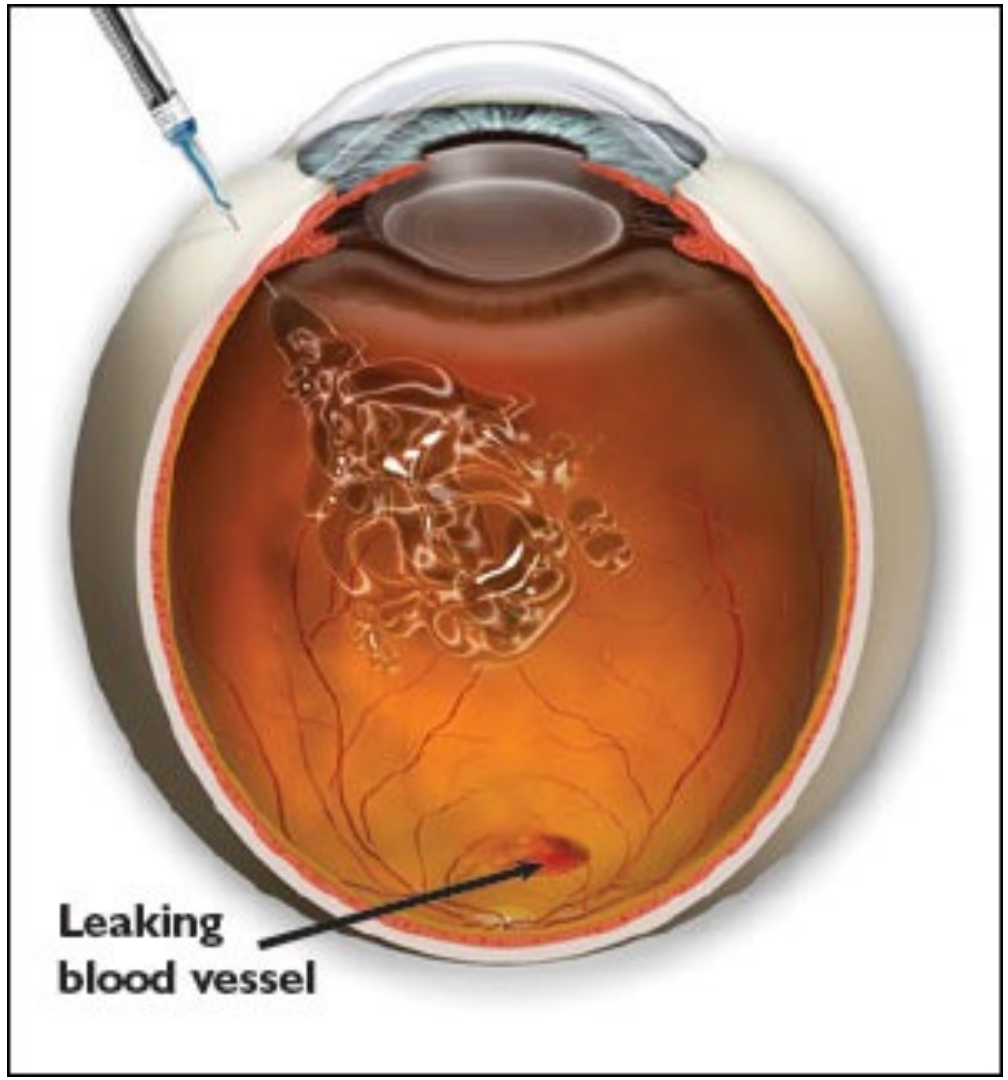
Aflibercept (Eylea)
Ranibizumab (Lucentis)
Bevacizumab (Avastin)

Typically given monthly



CPT Code 67028 *intravitreal injection of a pharmacologic agent*

>20 million intravitreal injections are given worldwide (estimate from 2016)

https://www.randeye.com/intravitreal-injection/

Martin, D. F. Evolution of Intravitreal Therapy for Retinal Diseases—From CMV to CNV: The LXXIV Edward Jackson Memorial Lecture. *Am J Ophthalmol* **191**, xli–lviii (2018).

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Intravitreal Anti-VEGF: Side Effects

- Ophthalmic
  - Cataract
  - Retinal detachment
  - Vitreous hemorrhage
  - Endophthalmitis
- Systemic
  - Wound healing complications
  - Hypertension
  - Adjudicated Anti-Platelet Trialists Collaboration defined Thromboembolic events
    - Nonfatal myocardial infarction
    - Nonfatal stroke
    - Vascular death
  - All cause mortality
  - Hospitalization
  - Serious adverse event

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Systemic Anti-VEGF and Kidneys

- Systemic administration of anti-VEGF agents have known adverse kidney side effects
  - Acute kidney injury
  - Worsening of proteinuria
  - Hypertension
  - Vascular clotting events
  - Glomerular disease
  - Kidney failure

Hanna RM, Barsoum M, Arman F, Selamet U, Hasnain H, Kurtz I. Nephrotoxicity Induced by Intravitreal Vascular Endothelial Growth Factor (VEGF) inhibitors: Emerging Evidence. *Kidney Int*. 2019;96(3):572-580. doi:10.1016/j.kint.2019.02.042
Gurevich F, Perazella MA. Renal Effects of Anti-angiogenesis Therapy: Update for the Internist. *Am J Medicine*. 2009;122(4):322-328. doi:10.1016/j.amjmed.2008.11.025
Izzedine H, Escudier B, Lhomme C, et al. Kidney Diseases Associated With Anti-Vascular Endothelial Growth Factor (VEGF). *Medicine*. 2014;93(24):333-339. doi:10.1097/md.0000000000000207

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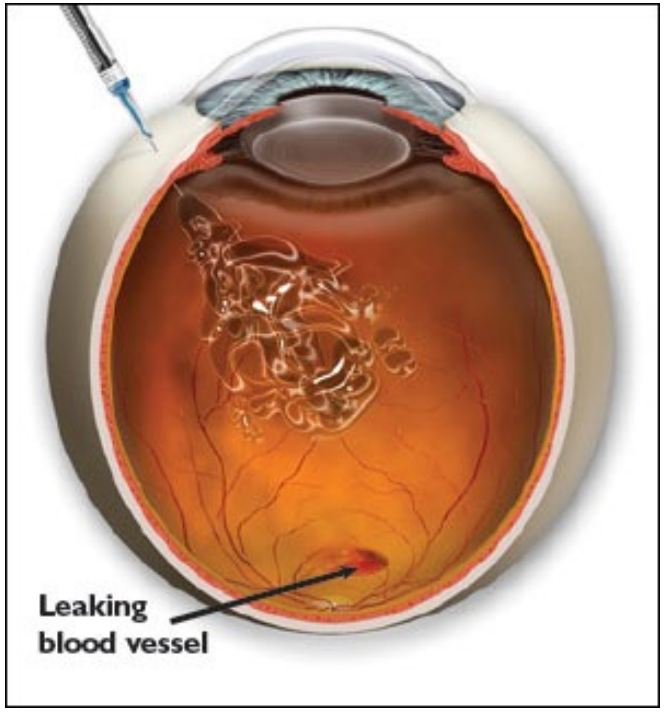
Intravitreal Anti-VEGF and Systemic Absorption



Detectable/elevated serum drug levels
Decreased plasma concentrations of free-VEGF

Aflibercept > bevacizumab >> ranibizumab

https://www.randeye.com/intravitreal-injection/

Avery RL, Castellarin AA, Steinle NC, et al. SYSTEMIC PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRAVITREAL AFLIBERCEPT, BEVACIZUMAB, AND RANIBIZUMAB. *Retin*. 2017;37(10):1847-1858. doi:10.1097/iae.0000000000001493

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We All Have That One Patient…

Hospitalized for acute kidney injury after intravitreal anti-VEGF → downward spiral → dialysis

ckj OXFORD era edta

Clinical Kidney Journal, 2020, vol. 13, no. 6, 969–980

doi: 10.1093/ckj/sfaa049
Advance Access Publication Date: 28 June 2020
CKJ Review

CKJ REVIEW

Worsening proteinuria and renal function after intravitreal vascular endothelial growth factor blockade for diabetic proliferative retinopathy

Michael Shye[1,*], Ramy M. Hanna[1,2,*], Sapna S. Patel[3], Ngoc Tram-Tran[3], Jean Hou[4], Collin Mccannel[5], Maham Khalid[2], Mina Hanna[6], Lama Abdelnour[1] and Ira Kurtz[1,7]

Original Clinical Science—General

Transplantation ■ November 2015 ■ Volume 99 ■ Number 11

Intravitreal Antivascular Endothelial Growth Factor Therapy May Induce Proteinuria and Antibody Mediated Injury in Renal Allografts

Wisit Cheungpasitporn, MD,[1] Fouad T. Chebib, MD,[1] Lynn D. Cornell, MD,[2] Michelle L. Brodin, Pharm D,[3] Samih H. Nasr, MD,[2] Carrie A. Schinstock, MD,[1,3] Mark D Stegall, MD,[3] and Hatem Amer, MD[1,3]

NEFROLOGIA. 2017;37(6):646–668

José Ruiz[a,b], Antonio Ríos[a,b,c,*], José Manuel Rodríguez[a,b,c], Santiago Llorente[d], Luisa Jimeno[d], Pascual Parrilla[a,b,c]

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http://dx.doi.org/10.1016/j.nefroe.2017.10.008

Renal damage associated to intravitreal administration of ranibizumab☆

Cheungpasitporn W, Chebib FT, Cornell LD, et al. Intravitreal Antivascular Endothelial Growth Factor Therapy May Induce Proteinuria and Antibody Mediated Injury in Renal Allografts. *Transplantation*. 2015;99(11):2382-2386. doi:10.1097/tp.0000000000000750
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Shye M, Hanna RM, Patel SS, et al. Worsening proteinuria and renal function after intravitreal vascular endothelial growth factor blockade for diabetic proliferative retinopathy. *Clin Kidney J*. 2020;13(6):sfaa049-. doi:10.1093/ckj/sfaa049

Side Effect: Kidney Failure or End Stage Kidney Disease

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- ESKD: kidney transplant recipients and patients treated by dialysis
  - **Prevalent**: ~2.5 million doubling to 5.4 million by 2030
  - **Costly**: $20-100K per person
  - **Deadly**: 2.3-7.1 million adults died prematurely from lack of access to treatment

Collaboration, G. C. K. D. *et al.* Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **395**, 709–733 (2020).
Wang, V., Vilme, H., Maciejewski, M. L. & Boulware, L. E. The Economic Burden of Chronic Kidney Disease and End-Stage Renal Disease. *Semin Nephrol* **36**, 319–330 (2016).
Elshahat, S. *et al.* The impact of chronic kidney disease on developed countries from a health economics perspective: A systematic scoping review. *Plos One* **15**, e0230512 (2020).

Gap in Knowledge: Intravitreal anti-VEGF and Kidney Failure

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- Not adequately assessed in clinical trials: often lumped under "serious adverse events"
- Existing studies have largely focused on kidney function not the more severe kidney failure
- Kidney failure requires longer follow-up (clinical trials 1-2 years)
- Studies have limited sample size (largest one ~600 patients)

Kameda Y, Babazono T, Uchigata Y, Kitano S. Renal function after intravitreal administration of vascular endothelial growth factor inhibitors in patients with diabetes and chronic kidney disease. *J Diabetes Invest*. 2018;9(4):937-939. doi:10.1111/jdi.12771
O'Neill RA, Gallagher P, Douglas T, et al. Evaluation of long-term intravitreal anti-vascular endothelial growth factor injections on renal function in patients with and without diabetic kidney disease. *Bmc Nephrol*. 2019;20(1):478. doi:10.1186/s12882-019-1650-1
Glassman AR, Liu D, Jampol LM, Sun JK, Network DRCR. Changes in Blood Pressure and Urine Albumin-Creatinine Ratio in a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema. *Invest Ophth Vis Sci*. 2018;59(3):1199-1205. doi:10.1167/iovs.17-22853

Comparative Safety Study

Analytic use case	Type	Structure	Example
Clinical characterization	**Disease Natural History**	Amongst patients who are diagnosed with **<insert your favorite disease>**, what are the patient's characteristics from their medical history?	Amongst patients with **rheumatoid arthritis**, what are their demographics (age, gender), prior conditions, medications, and health service utilization behaviors?
	Treatment utilization	Amongst patients who have **<insert your favorite disease>**, which treatments were patients exposed to amongst **<list of treatments for disease>** and in which sequence?	Amongst patients with **depression**, which treatments were patients exposed to **SSRI, SNRI, TCA, bupropion, esketamine** and in which sequence?
	Outcome incidence	Amongst patients who are new users of **<insert your favorite drug>,** how many patients experienced **<insert your favorite known adverse event from the drug profile>** within **<time horizon following exposure start>**?	Amongst patients who are new users of **methylphenidate,** how many patients experienced **psychosis** within **1 year of initiating treatment**?
Population-level effect estimation	**Safety surveillance**	Does exposure to **<insert your favorite drug>** increase the risk of experiencing **<insert an adverse event>** within **<time horizon following exposure start>**?	Does exposure to **ACE inhibitor** increase the risk of experiencing **Angioedema** within **1 month after exposure start**?
	Comparative effectiveness	Does exposure to **<insert your favorite drug>** have a different risk of experiencing **<insert any outcome (safety or benefit) >** within **<time horizon following exposure start>**, relative to **<insert your comparator treatment>**?	Does exposure to **ACE inhibitor** have a different risk of experiencing **acute myocardial infarction** while **on treatment**, relative to **thiazide diuretic**?
Patient level prediction	**Disease onset and progression**	For a given patient who is diagnosed with **<insert your favorite disease>**, what is the probability that they will go on to have **<another disease or related complication>** within **<time horizon from diagnosis>**?	For a given patient who is **newly diagnosed with atrial fibrillation**, what is the probability that they will go onto to have **ischemic stroke** in **next 3 years**?
	Treatment response	For a given patient who is a new user of **<insert your favorite chronically-used drug>**, what is the probability that they will **<insert desired effect>** in **<time window>**?	For a given patient **with T2DM who start on metformin** , what is the probability that they will **maintain HbA1C<6.5%** after **3 years**?
	Treatment safety	For a given patient who is a new user of **<insert your favorite drug>,** what is the probability that they will experience **<insert adverse event >** within **<time horizon following exposure>**?	For a given patients who is a **new user of warfarin**, what is the probability that they will have **GI bleed** in **1 year**?

OHDSI Study: Intravitreal anti-VEGF and Kidney Failure

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- Estimating the **comparative risk of kidney failure** associated with intravitreal anti-vascular endothelial growth factor exposure in patients with blinding diseases (DR/DME, AMD, VO)
  - Amongst people with blinding diseases, does exposure to **ranibizumab** increase the risk of kidney failure, relative to **aflibercept**?
  - Amongst people with blinding diseases, does exposure to **bevacizumab** increase the risk of kidney failure, relative to **aflibercept**?
  - Amongst people with blinding diseases, does exposure to **bevacizumab** increase the risk of kidney failure, relative to **ranibizumab**?

Hypothesis: in these pairwise comparisons, lower risk of kidney failure in patients with blinding diseases who are exposed to ranibizumab

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Implications of Study: Risk of Kidney Failure

- If there is a difference between medications
  - Retina specialist can offer personalized treatment
  - Reduce risk of morbidity/mortality from kidney failure
  - Reduce cost for society
- If there is no difference between medications
  - Important negative study
  - OHDSI network: most robust way of directly evaluating this question

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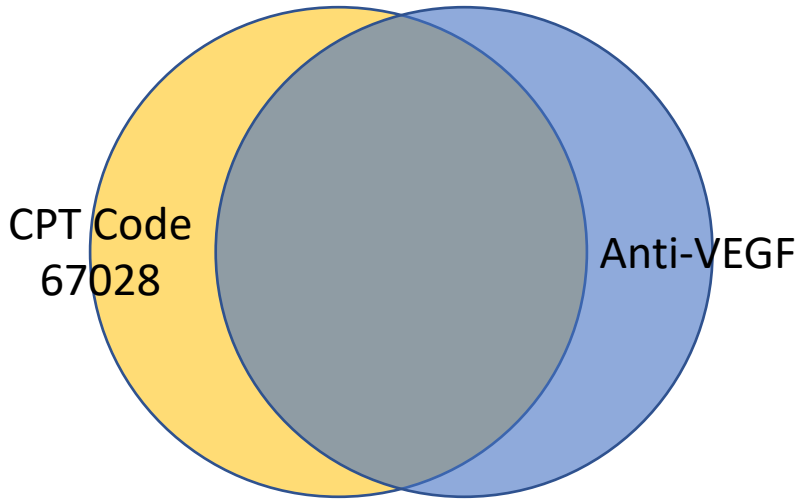
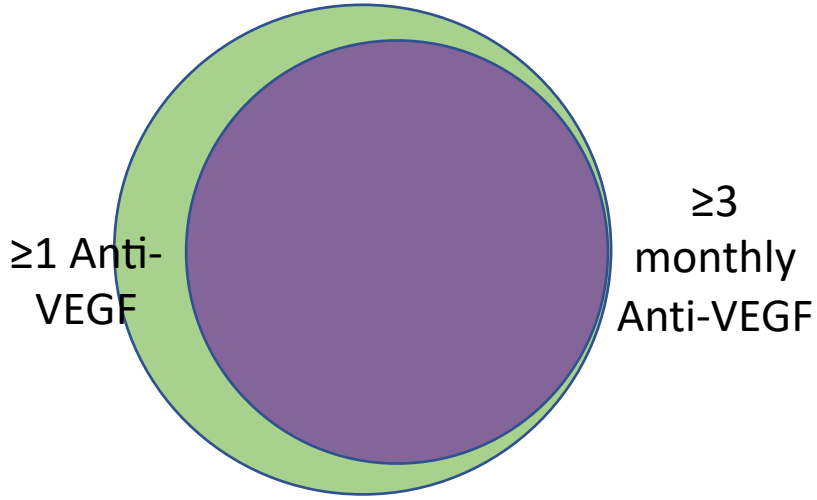
You Can Contribute

- Verification and validation of concept sets





- Data partners
  - No special data elements are required: ICD codes, CPT codes, medications
  - Administrative or EHR data (with ophthalmology department)

Kahn, M. G. *et al.* A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data. *Egems Generating Évid Methods Improv Patient Outcomes* **4**, 1244 (2016).

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Thank You!

Vote for this project:
Intravitreal Anti-VEGF and Kidney Failure

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