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OHDSI SOS Challenge: Intravitreal Anti-VEGF and Kidney Failure

Interpreting Results

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5/23/2023

Save Our Sisyphus Challenge

SOS Challenge Weekly Tutorial Schedule

Date	Times	Topic
Mar. 28	11 am / 7 pm ET	SOS Week 1 Tutorial: Initiating A Network Study
Apr. 4	11 am / 7 pm ET	SOS Week 2 Tutorial: Data Diagnostics
Apr. 11	11 am / 7 pm ET	SOS Week 3 Tutorial: Phenotype Development
Apr. 18	11 am / 7 pm ET	SOS Week 4 Tutorial: Phenotype Evaluation
Apr. 25	11 am / 7 pm ET	SOS Week 5 Tutorial: Creating Analysis Specifications
May 2	11 am / 7 pm ET	SOS Week 6 Tutorial: Network Execution
May 9	11 am / 7 pm ET	SOS Week 7 Tutorial: Study Diagnostics
May 16	11 am / 7 pm ET	SOS Week 8 Tutorial: Evidence Synthesis
May 23	11 am / 7 pm ET	SOS Week 9 Tutorial: Interpreting The Results

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Anti-VEGF and Kidney Failure Clinical Question

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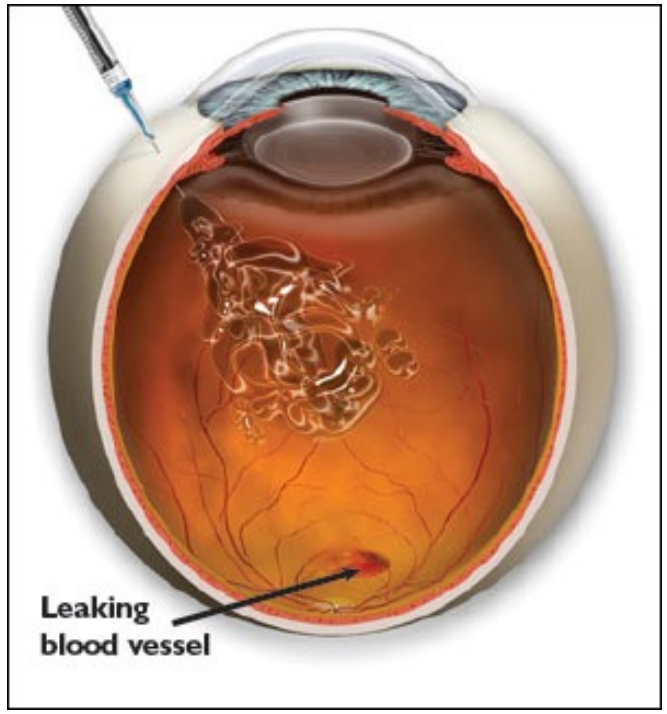
Background

- Anti-vascular endothelial growth factor (anti-VEGF) medications
- Systemic administration of anti-VEGF agents have known adverse kidney side effects
  - Acute kidney injury
  - Proteinuria
  - Hypertension
  - Vascular clotting events
  - Glomerular disease
  - Risk factors for: kidney failure (need for renal replacement therapy with dialysis or kidney transplant, aka end stage kidney disease or end stage renal disease)

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
Brandes, A. A., Bartolotti, M., Tosoni, A., Poggi, R. & Franceschi, E. Practical Management of Bevacizumab-Related Toxicities in Glioblastoma. *Oncol* **20**, 166–175 (2015).

Intravitreal Anti-VEGF and Systemic Absorption



Drug	Size	Systemic Elimination (half-life)
Ranibizumab	48 kDa	2 hours
Aflibercept	115 kDa	5-6 days
Bevacizumab	149 kDa	20 days

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

Bevacizumab > aflibercept >> 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
https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf

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 **ranibizumab** increase the risk of kidney failure, relative to **bevacizumab**?
  - Amongst people with blinding diseases, does exposure to **bevacizumab** increase the risk of kidney failure, relative to **aflibercept**?

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

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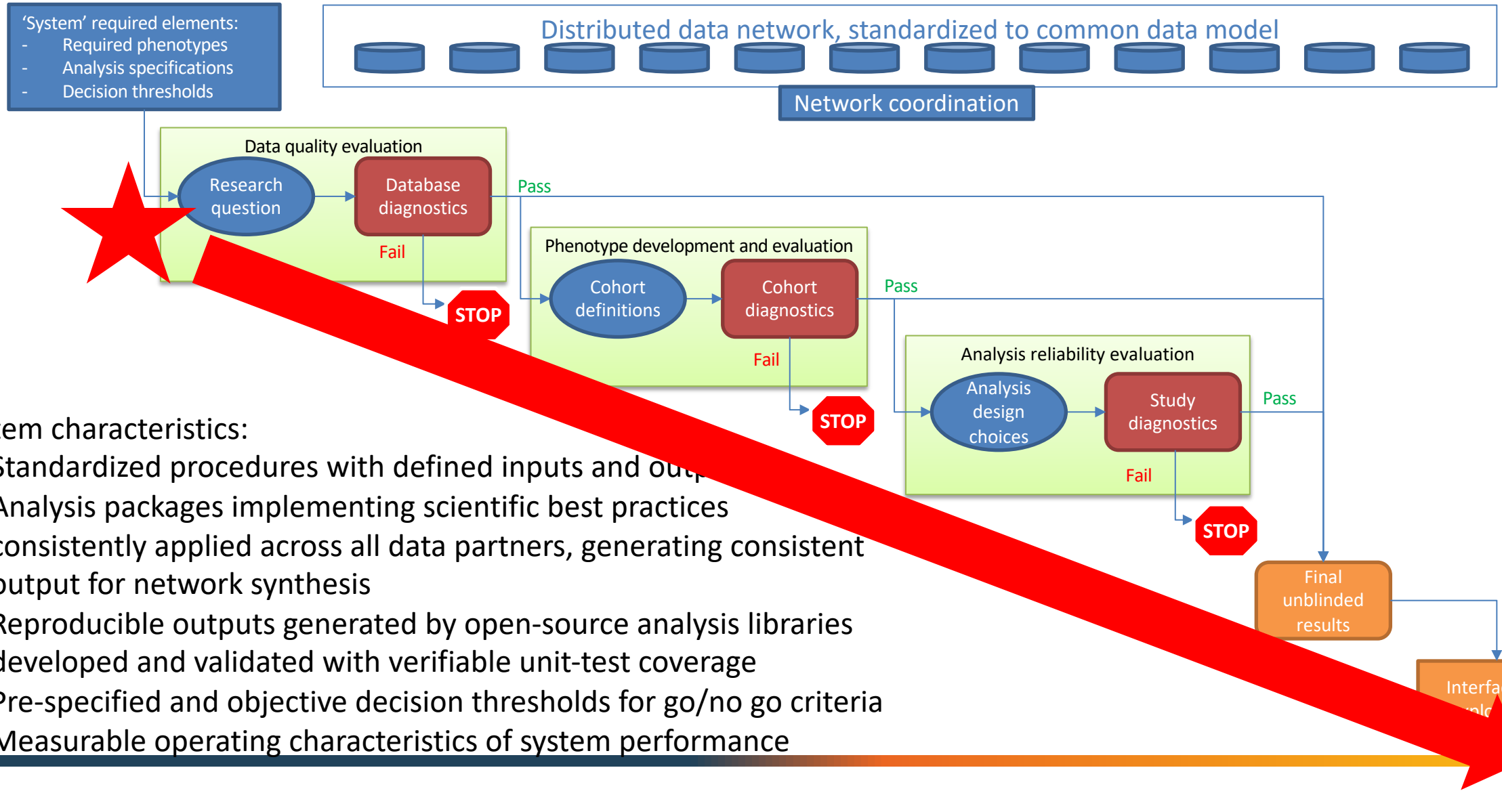
Process

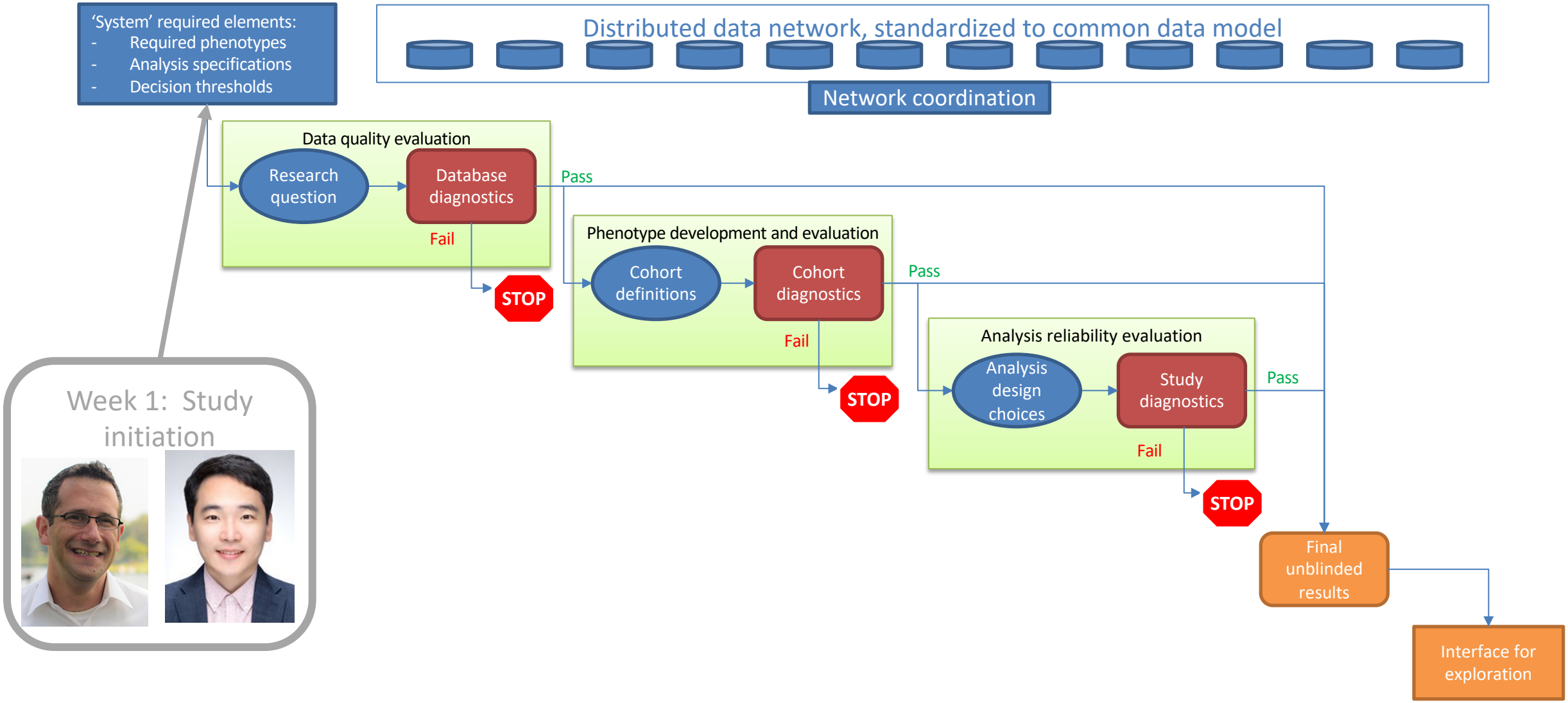
Engineering open science systems that build trust into the real-world evidence generation and dissemination process



System characteristics:

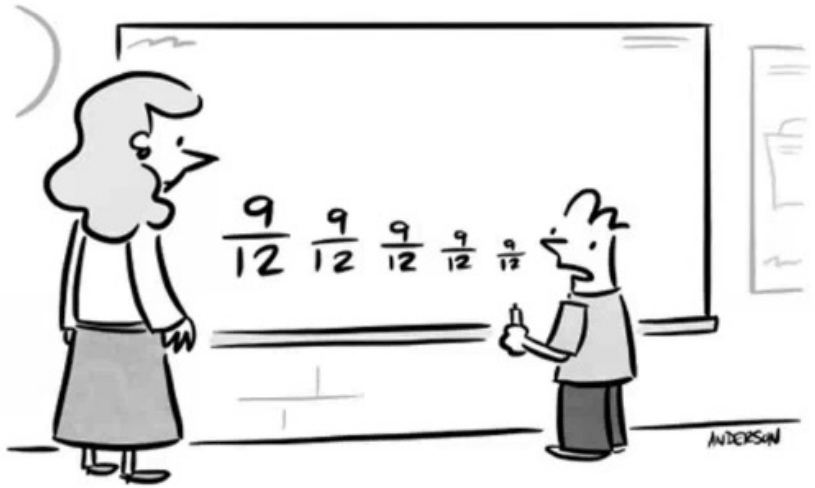
- Standardized procedures with defined inputs and outp
- Analysis packages implementing scientific best practices consistently applied across all data partners, generating consistent output for network synthesis
- Reproducible outputs generated by open-source analysis libraries developed and validated with verifiable unit-test coverage
- Pre-specified and objective decision thresholds for go/no go criteria
- Measurable operating characteristics of system performance

Engineering open science systems that build trust into the real-world evidence generation and dissemination process



Lesson plan for the day

- OHDSI R tool-stack / software
- Github: repos and pull-requests
- Draft a protocol and post it
- Set-up a manuscript document
- Teams environment

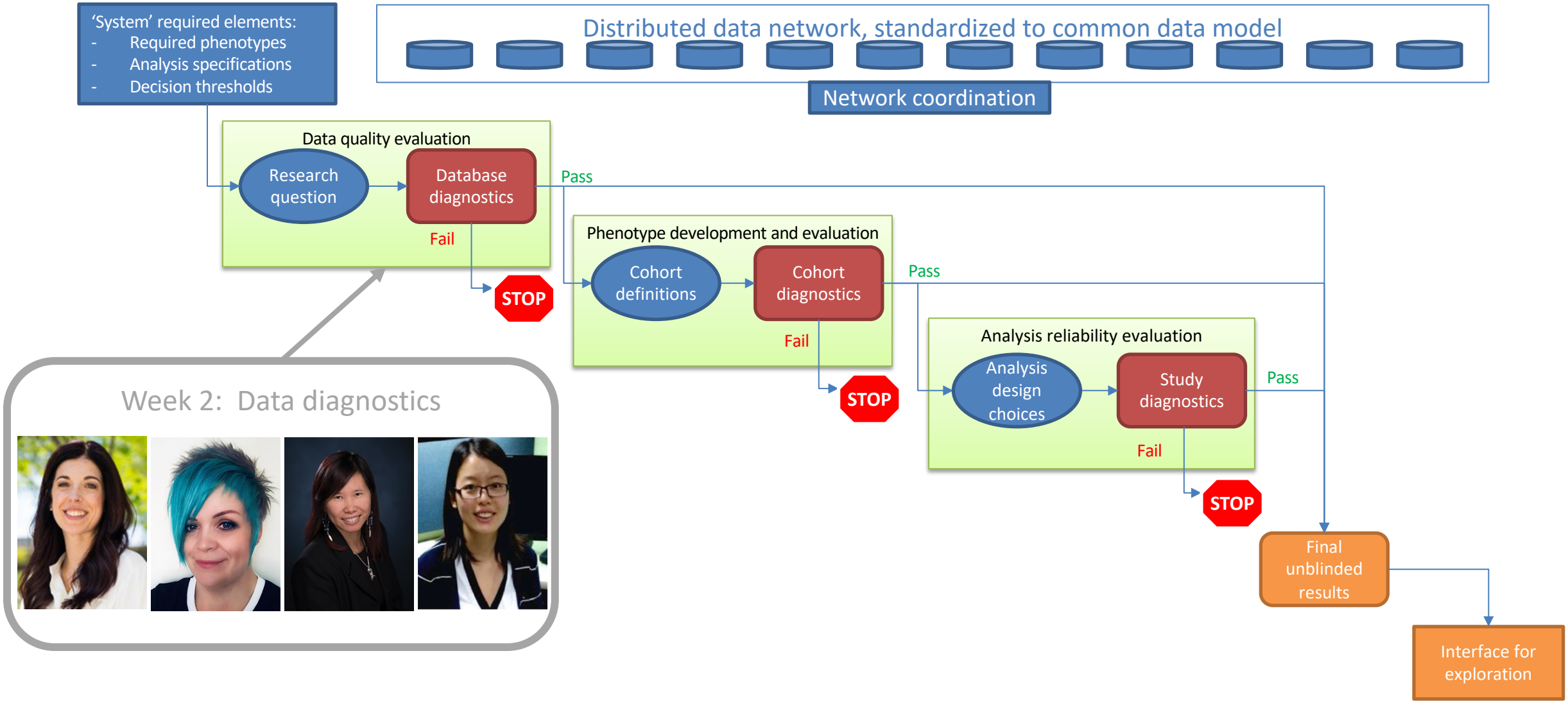


"If I reduce it anymore you won't be able to read it."

(Disclaimer: this is my **first** attempt at a virtual lecture using **multiple** windows … wish me luck)

Week 1: Study initiation

Engineering open science systems that build trust into the real-world evidence generation and dissemination process



Agenda

Overview of Data Diagnostics

- Explain what data diagnostics is and how it works

Build a Database Profile together

- Demo of the executeDbProfile function and the outputs to share

Data Diagnostic Study Question Inputs

- What elements of a study question you need to know to run data diagnostics
- Show the inputs for the 4 study questions

Go through the output

- Demo the shiny app and how to interpret data diagnostic r

Week 2: Data diagnostics

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'System' required elements:
- Required phenotypes
- Analysis specifications
- Decision thresholds

Distributed data network, standardized to common data model

Network coordination

Data quality evaluation

Research question → Database diagnostics

Database diagnostics: Pass → Phenotype development and evaluation

Database diagnostics: Fail → STOP

Phenotype development and evaluation

Cohort definitions → Cohort diagnostics

Cohort diagnostics: Pass → Analysis reliability evaluation

Cohort diagnostics: Fail → STOP

Analysis reliability evaluation

Analysis design choices → Study diagnostics

Study diagnostics: Pass → Final unblinded results

Study diagnostics: Fail → STOP

Final unblinded results → Interface for exploration

Week 3-4: Phenotype development and evaluation

ESRD: Simple

B.1.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[SOS] ESRD Ref'.
2. observations of '[SOS] ESRD Ref'.
3. procedure occurrences of '[SOS] ESRD Ref'.

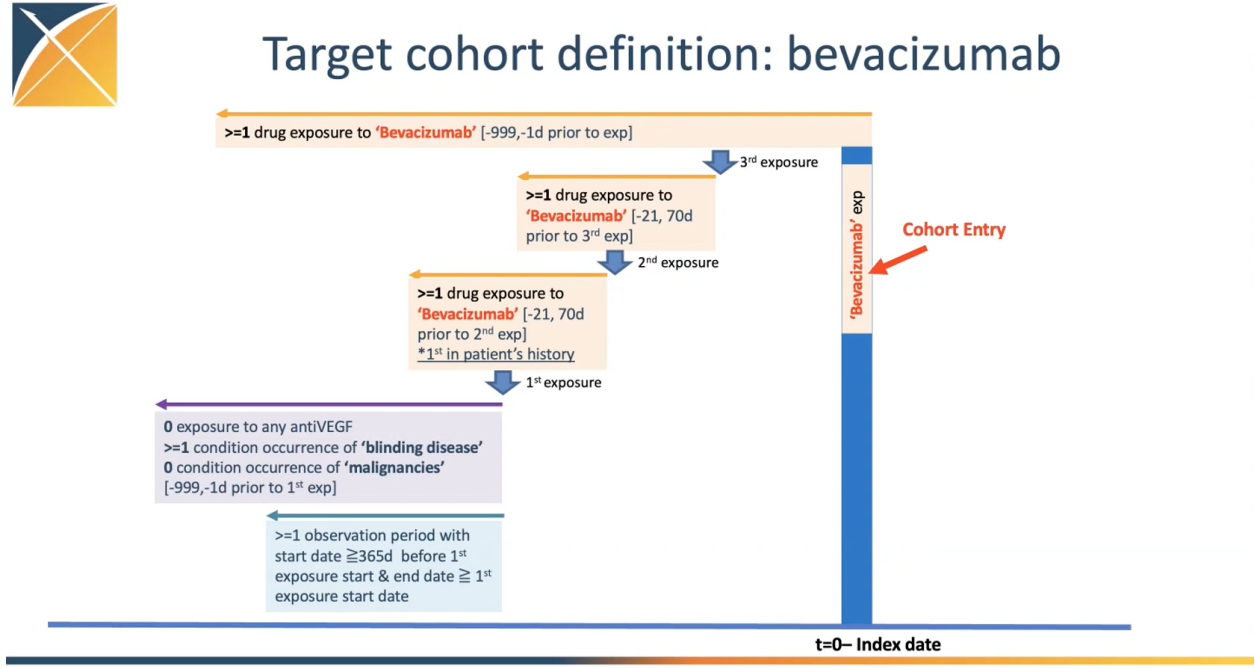
Limit cohort entry events to the earliest event per person.

ESRD: Complex

B.2.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[SOS] ESRD Ref'.
2. observations of '[SOS] ESRD Ref'.
3. procedure occurrences of '[SOS] ESRD Ref'.
4. condition occurrences of '[SOS] Renal transplant Ref'.
5. observations of '[SOS] Renal transplant Ref'.
6. procedure occurrences of '[SOS] Renal transplant Ref'.
7. measurements of '[SOS] eGFR Ref', numeric value between 1 and 15; unit: "milliliter per minute per 1.73 square meter" or "milliliter per minute per 1.73 square meter"; having at least 1 measurement of '[SOS] eGFR Ref', starting anytime up to 90 days before '[SOS] eGFR Ref' start date; numeric value between 1 and 15; unit: "milliliter per minute per 1.73 square meter" or "milliliter per minute per 1.73 square meter".
8. observations of '[SOS] Dialysis Ref'; with any of the following criteria:
9. having at least 1 procedure occurrence of '[SOS] Dialysis Ref', starting anytime up to 90 days before '[SOS] Dialysis Ref' start date.
10. having at least 1 observation of '[SOS] Dialysis Ref', starting anytime up to 90 days before '[SOS] Dialysis Ref' start date.
11. procedure occurrences of '[SOS] Dialysis Ref'; with any of the following criteria:
12. having at least 1 observation of '[SOS] Dialysis Ref', starting anytime up to 90 days before '[SOS] Dialysis Ref' start date.



Week 3-4: Phenotype development and evaluation

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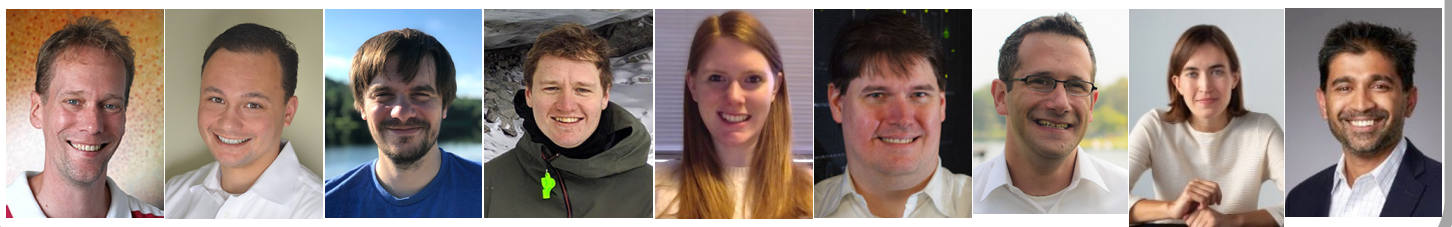
Only possible because of standardized analytics developed across our community



Week 5: Analysis design

Design choices for antiVEGF study

- **Target***:
  - T1: aflibercept exposures after new use with 3 exposures in 21-70d windows
  - T2: ranibizumab exposures after new use with 3 exposures in 21-70d windows
  - T3: bevacizumab exposures after new use with 3 exposures in 21-70d windows
- **Comparator(s)***:
  - T1 vs T2; T2 vs. T3; T1 vs. T3
- **Indication(s)***: Blinding diseases
- **Outcome(s)***: End stage renal disease
- **Time(s)-at-risk**: 'on treatment': cohort start + 1d → cohort end + 0d
- **Age/sex/calendar time restrictions:** age>=18
- **Negative controls:**
- **Excluded concepts**

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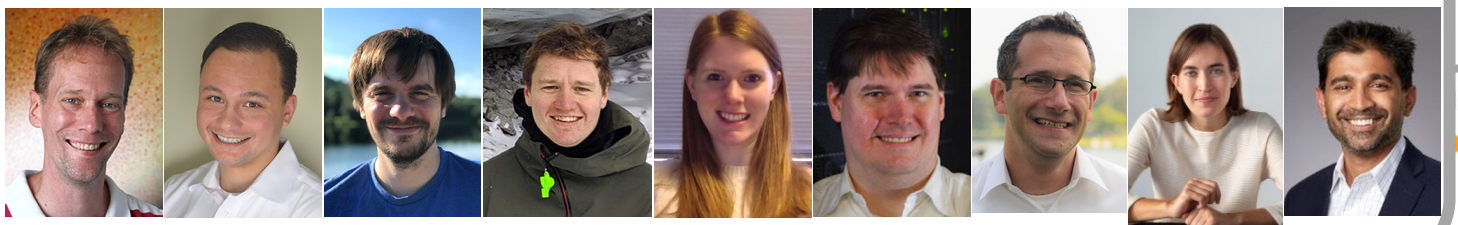

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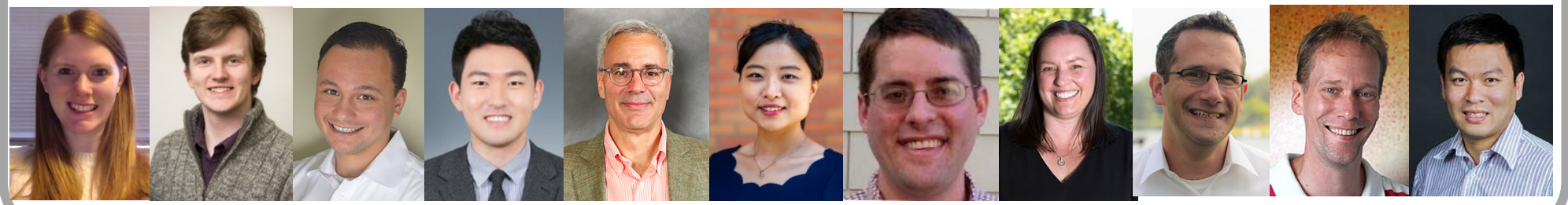
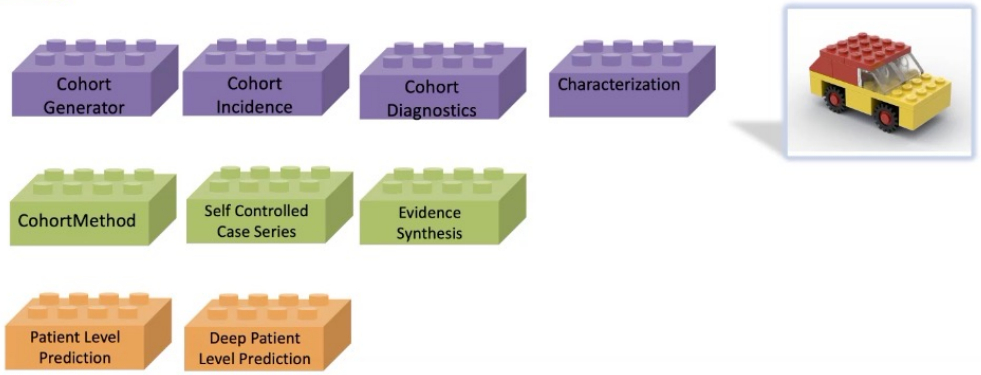
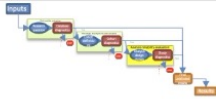
Week 6-8: Analysis execution, study diagnostics, evidence synthesis



Strategus Modules



Study diagnostics



- Characterization
  - Feature summary, incidence, cohort pathways
    - Temporal stability, subpopulation heterogeneity, heterogeneity across data sources
- Population-level Estimation
  - Comparative cohort
    - Statistical power, comparator similarity, between-person confounding, generalizability, residual bias
  - Self-controlled case series
    - Statistical power, time-varying confounding, protopathic bias, residual bias
  - Meta-analysis
    - Statistical power, heterogeneity across data sources
- Patient-level prediction
  - PROBAST criteria (https://doi.org/10.7326/M18-1376) : embedded in *PatientLevelPrediction* package

PROBAST= Prediction model Risk Of Bias ASsessment Tool

Derived from 2022 Symposium Plenary

Evidence Synthesis

The **EvidenceSynthesis** package implements

- Fixed-effects model
- Random-effects model using a Bayesian approach.
  - Uses the BEAST MCMC engine.

BEAST
Bayesian Evolutionary Analysis Sampling Trees

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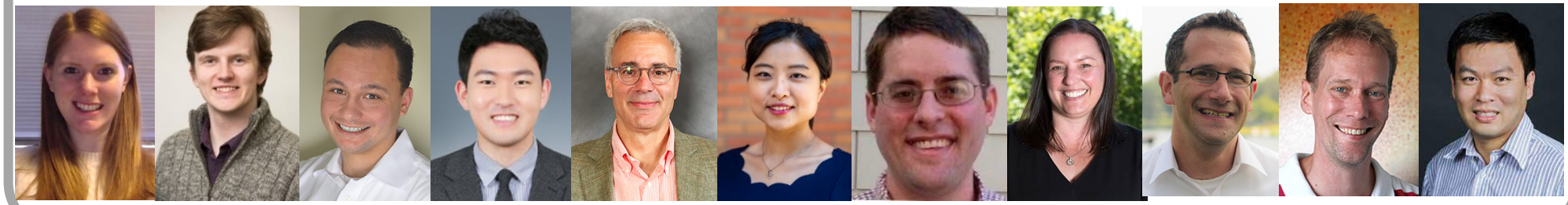
Week 6-8: Analysis execution, study diagnostics, evidence synthesis



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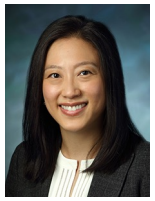
Week 9: Results interpretation

VEGF→ESRD

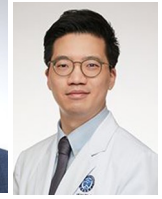
FQ→AA

MS biologics→PML

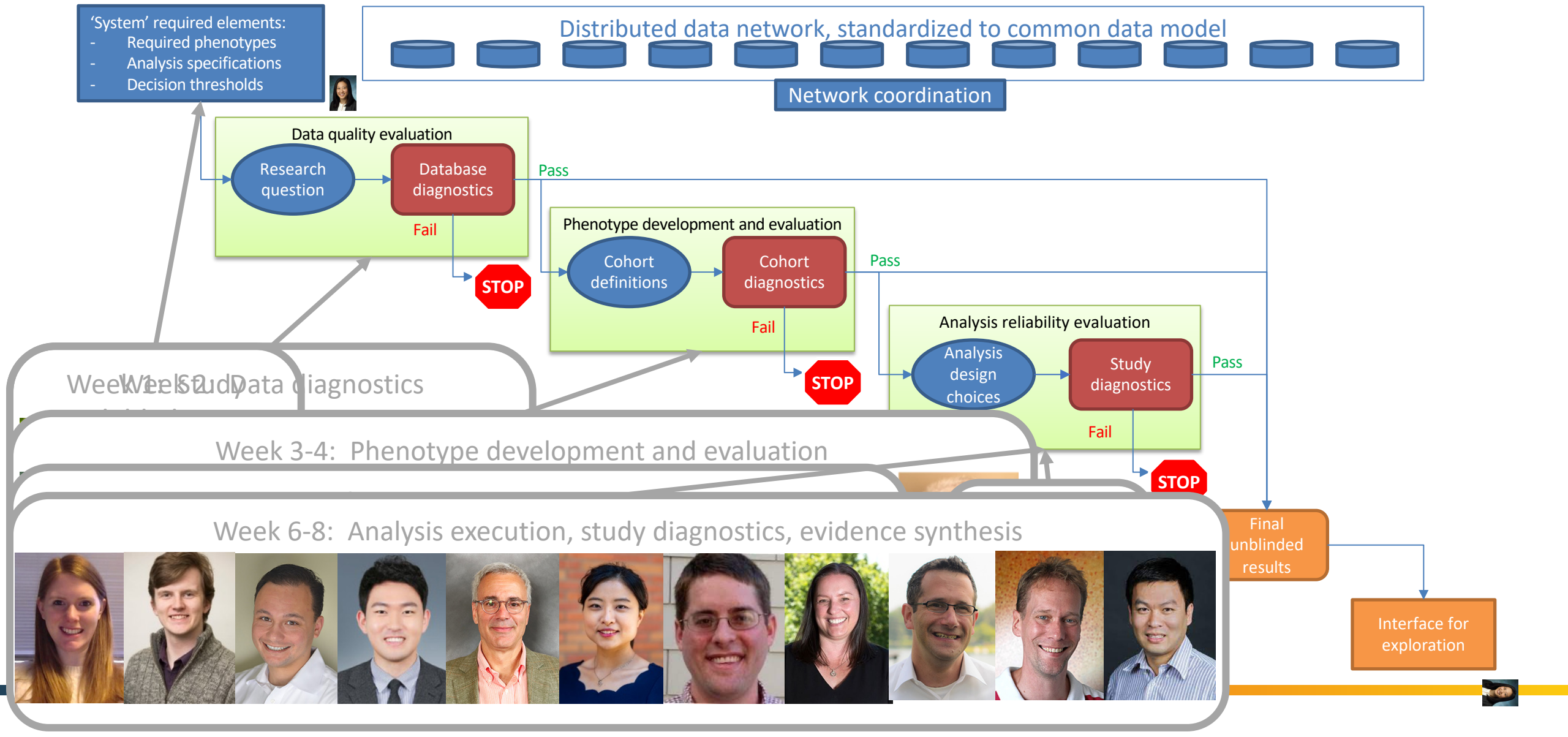
risankizumab→CVA







Engineering open science systems that build trust into the real-world evidence generation and dissemination process



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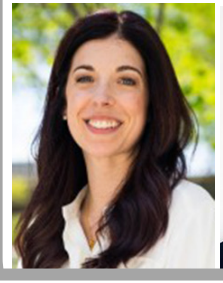
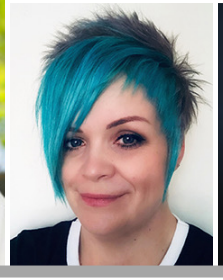
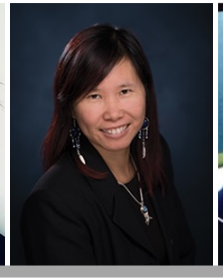
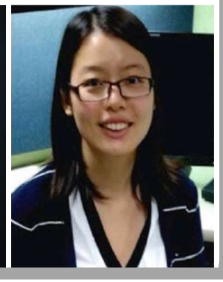
standardized to common data model

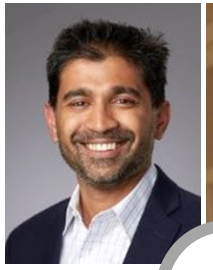
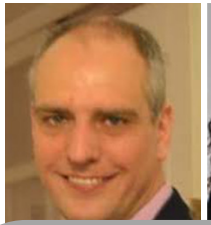
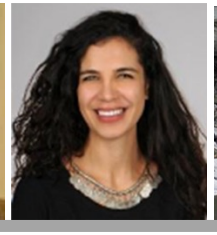
Week 1: Study initiation

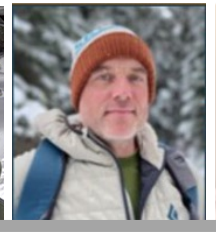
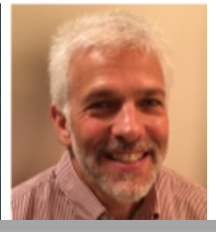

Week 2: Data diagnostics

Week 3-4: Phenotype development and evaluation



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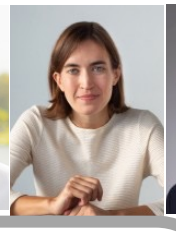
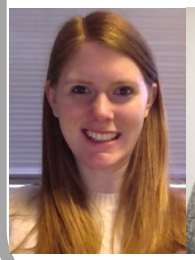



Week 5: Analysis design

al unblinded results

Interface for exploration

Week 6-8: Analysis execution, study diagnostics, evidence synthesis











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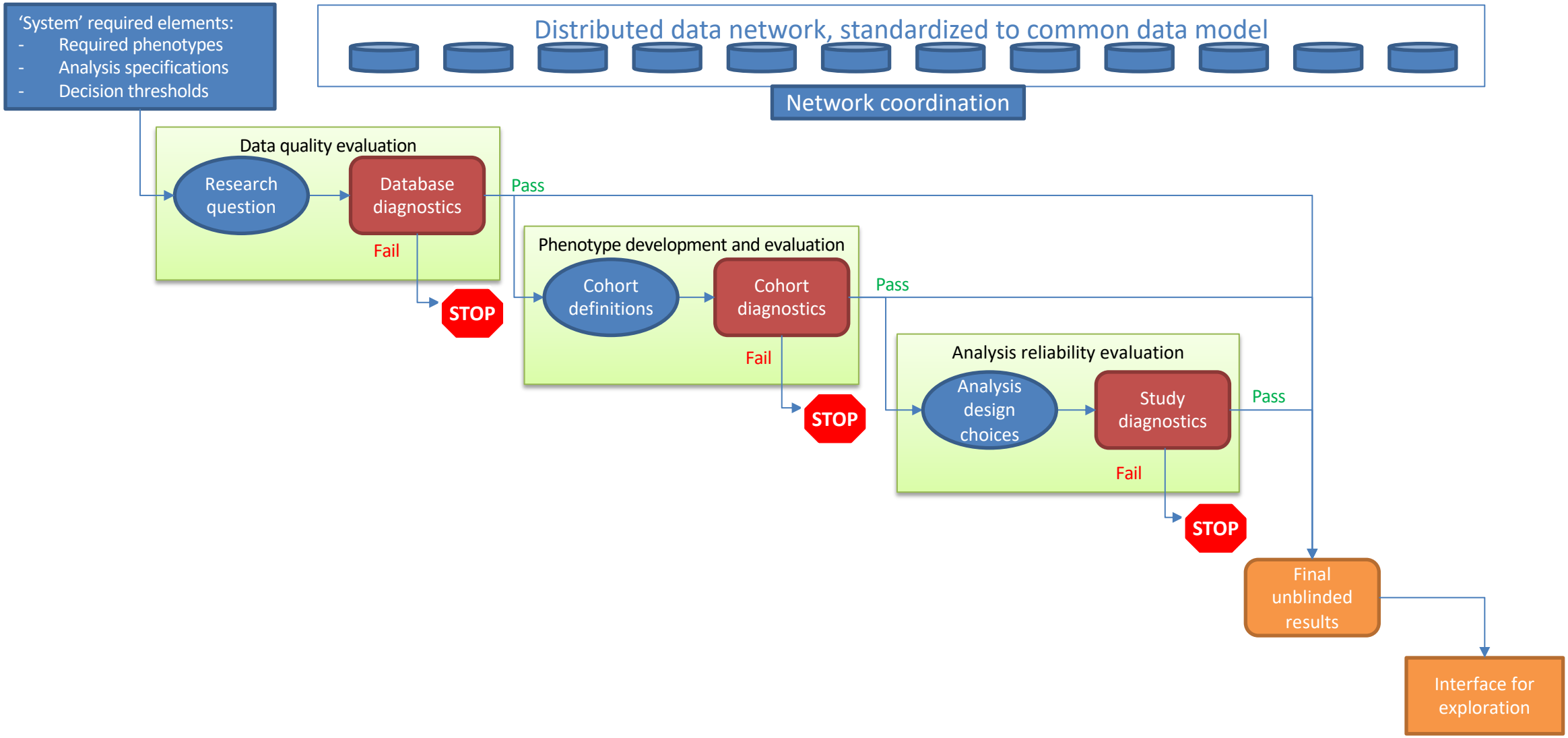
Preliminary Results

Discussion rather than Tutorial

Data Source	Population	Patients (millions)	History	Data Capture Process and Short Description	Included in Final Analysis? If not included, explanation?
IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database (**MDCR**)	USA, commercially insured, 65+ years	10	2000-2023	Adjudicated health insurance claims of retirees with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service or capitation health plans across the continuum of care (e.g., inpatient, outpatient, pharmacy)	
IBM Health MarketScan Commercial Claims and Encounters Database (**CCAE**)	USA, commercially insured, <65 years	166	2000-2022	Adjudicated health insurance claims across the continuum of care (e.g., inpatient, outpatient, pharmacy) from large employers and health plans who provide private healthcare coverage to employees, their spouses and dependents	
IBM Health MarketScan Multi-State Medicaid Database (**MDCD**)	USA, Medicaid enrollees, racially diverse	35	2006-2021	Adjudicated health insurance claims for Medicaid enrollees from multiple states covered under fee-for-service and managed care plans and includes claims across the continuum of care (e.g., inpatient, outpatient, pharmacy).	Failed study diagnostics
Optum(R) de-identified Electronic Health Record Dataset (**OptumEHR**)	USA, general	108	2007-2023	Combined claims and electronic health record data derived from >7000 hospitals and >7000 clinics. Clinical information includes vital signs, immunizations, allergies, medications, diagnoses, procedures and other data some of which are derived using natural language processing on provider notes.	Failed study diagnostics
Optum's Clinformatics Extended Data Mart - Socio-economic Status (**SES**)	USA, general	95	2000-2022	Adjudicated health insurance claims for large commercial and Medicare Advantage health plans and includes claims across the continuum of care (e.g. inpatient, outpatient, pharmacy)	
Japan Medical Data Center (**JMDC**)	Japan, general	15.2	2005-2022	Adjudicated health insurance data from 60 society-managed health insurance plans covering workers aged 18-65 and their dependents.	Failed study diagnostics
Johns Hopkins Medical Enterprise (**JHME**)	USA, general	2	2016-today	Non-profit academic medical center covering 6 hospitals and numerous outpatient facilities.	Failed study diagnostics
Department of Veterans Affairs (**VA**)	USA, veterans, older, racially diverse	12	2000-today	National VA healthcare system, the largest integrated provider of medical services in the USA, providing care at 170 VA medical centers and 1063 outpatients facilities	
PharMetrics Plus (**NEU**)	USA, commercially insured, <65 years	35	2017-2022	Adjudicated health insurance claims for >70 contributing health plans and self-insured employer groups across the continuum of care (e.g., inpatient, outpatient, pharmacy).	

9 Databases Evaluated: 478.2 million patients

Engineering open science systems that build trust into the real-world evidence generation and dissemination process

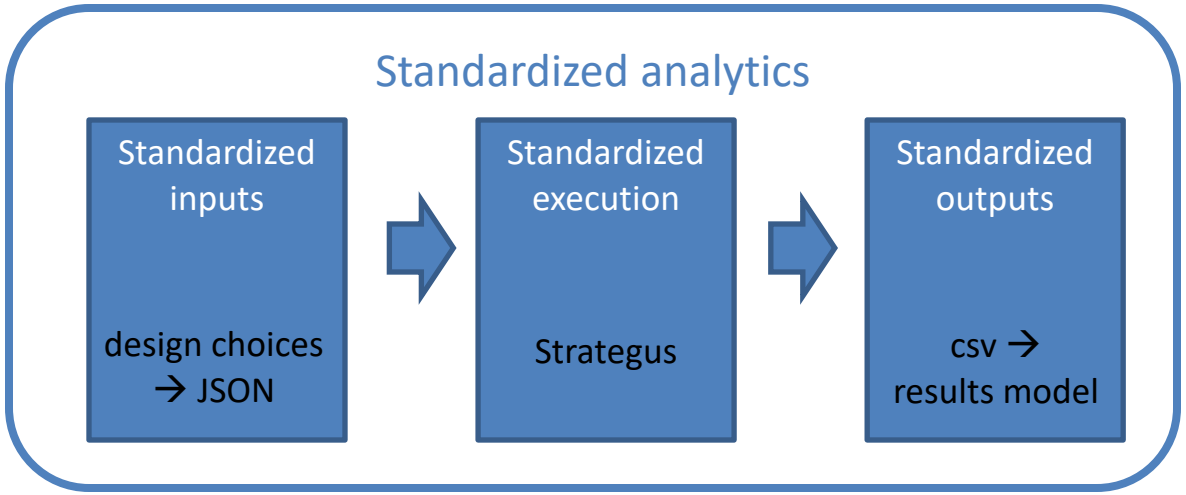


Data Source	Population	Patients (millions)	History	Data Capture Process and Short Description	Included in Final Analysis? If not included, explanation?
IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database (**MDCR**)	USA, commercially insured, 65+ years	10	2000-2023	Adjudicated health insurance claims of retirees with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service or capitation health plans across the continuum of care (e.g., inpatient, outpatient, pharmacy)	
IBM Health MarketScan Commercial Claims and Encounters Database (**CCAE**)	USA, commercially insured, <65 years	166	2000-2022	Adjudicated health insurance claims across the continuum of care (e.g., inpatient, outpatient, pharmacy) from large employers and health plans who provide private healthcare coverage to employees, their spouses and dependents	
IBM Health MarketScan Multi-State Medicaid Database (**MDCD**)	USA, Medicaid enrollees, racially diverse	35	2006-2021	Adjudicated health insurance claims for Medicaid enrollees from multiple states covered under fee-for-service and managed care plans and includes claims across the continuum of care (e.g., inpatient, outpatient, pharmacy).	Failed study diagnostics
Optum(R) de-identified Electronic Health Record Dataset (**OptumEHR**)	USA, general	108	2007-2023	Combined claims and electronic health record data derived from >7000 hospitals and >7000 clinics. Clinical information includes vital signs, immunizations, allergies, medications, diagnoses, procedures and other data some of which are derived using natural language processing on provider notes.	Failed study diagnostics
Optum's Clinformatics Extended Data Mart - Socio-economic Status (**SES**)	USA, general	95	2000-2022	Adjudicated health insurance claims for large commercial and Medicare Advantage health plans and includes claims across the continuum of care (e.g. inpatient, outpatient, pharmacy)	
Japan Medical Data Center (**JMDC**)	Japan, general	15.2	2005-2022	Adjudicated health insurance data from 60 society-managed health insurance plans covering workers aged 18-65 and their dependents.	Failed study diagnostics
Johns Hopkins Medical Enterprise (**JHME**)	USA, general	2	2016-today	Non-profit academic medical center covering 6 hospitals and numerous outpatient facilities.	Failed study diagnostics
Department of Veterans Affairs (**VA**)	USA, veterans, older, racially diverse	12	2000-today	National VA healthcare system, the largest integrated provider of medical services in the USA, providing care at 170 VA medical centers and 1063 outpatients facilities	
PharMetrics Plus (**NEU**)	USA, commercially insured, <65 years	35	2017-2022	Adjudicated health insurance claims for >70 contributing health plans and self-insured employer groups across the continuum of care (e.g., inpatient, outpatient, pharmacy).	

5 Databases Passed All Diagnostics

Standardized analyses currently available within Strategus pipeline

- Characterization
  - Cohort diagnostics
  - Cohort features
  - Incidence rates
  - Time-to-event
  - Dechallenge / rechallenge
- Patient-level prediction
- Population-level effect estimation
  - Comparative cohort
  - Self-controlled case-series (SCCS)



Characterization

Baseline characteristics of patients in each exposure cohort (ranbizumab, aflibercept, and bevacizumab) in the Optum's Clinformatics Extended Data Mart - Socio-economic Status (SES) database (before propensity score matching).

	Ranibizumab N=10051	**Aflibercept** N=9817	**Bevacizumab** N=71916
Age Group			
15-19	0 (0)	0 (0)	5 (0)
20-24	3 (0)	7 (0)	29 (0)
25-29	11 (0)	12 (0)	68 (0)
30-34	31 (0)	34 (0)	159 (0)
35-39	42 (0)	48 (0)	312 (0)
40-44	85 (1)	81 (1)	520 (1)
45-49	149 (1)	161 (2)	928 (1)
50-54	274 (3)	240 (2)	1691 (2)
55-59	428 (4)	444 (5)	2696 (4)
60-64	624 (6)	583 (6)	3841 (5)
65-69	1140 (11)	1267 (13)	8205 (11)
70-74	1624 (16)	1741 (18)	12120 (17)
75-79	1977 (20)	1736 (18)	14376 (20)
80-84	1970 (20)	1801 (18)	14352 (20)
85-89	1634 (16)	1609 (16)	12188 (17)
90-94	59 (1)	53 (1)	426 (1)

	Ranibizumab N=10051	**Aflibercept** N=9817	**Bevacizumab** N=71916
Sex			
Male	3878 (39)	4012 (41)	28282 (39)
Female	6173 (61)	5805 (59)	43634 (61)
Race			
White	7607 (76)	7109 (72)	52109 (72)
Black	1025 (10)	991 (10)	5956 (8)
Asian	254 (3)	308 (3)	1990 (3)
Unknown	1165 (12)	1409 (14)	11861 (16)
Ethnicity			
Hispanic	750 (7)	923 (9)	8326 (12)
Non-Hispanic	8886 (88)	8408 (86)	60055 (84)
Unknown	415 (4)	486 (5)	3535 (5)
Diabetes Comorbidity Severity Index (DCSI) score	3.8 (N=8504)	3.85 (N=8259)	3.99 (N=61182)
Charlson Index - Romano adaptation	3.29 (N=8319)	3.69 (N=8353)	3.65 (N=60952)

13 points, 7 organ systems
Mortality & hospitalization among patients with DM

19 categories
Death within 1 year of hospitalization

Comparing the DCSI and Charlson-Index in the Bevacizumab Exposure Cohort Across Various Databases

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	SES	MDCR	CCAE	NEU	MDCD	VA	OptumEHR	JMDC	JHME
DCSI	3.99	3.71	3.91	2.56	5.59		3.18	None	2.59
Charlson-Index	3.65	2.95	3.12	2.97	4.98		2.55	None	2.72

	Patients At Risk	On-Treatment Time (person-years)	Number of Outcomes	Incidence Rate of Kidney Failure (per 100 person-years)
Ranibizumab	Total = 26187			
SES	8256	10094	65	0.66
MDCR	7738	8547	48	0.57
CCAE	3924	3315	42	1.31
NEU	2121	2215	14	0.64
MDCD	1344	1190	17	1.52
OptumEHR	2576	2548	15	0.60
JMDC	209	139	0	0
JHME	19	13	0	0
Aflibercept	Total = 23363			
SES	8293	11300	72	0.65
MDCR	1865	1925	32	1.78
CCAE	3423	3527	58	1.71
NEU	3772	3780	17	0.46
MDCD	1865	1925	32	1.78
OptumEHR	3352	4774	24	0.51
JMDC	207	197	1	0.52
JHME	586	670	8	1.22
Bevacizumab	Total = 101072			
SES	54143	51981	317	0.63
MDCR	10811	9188	50	0.55
CCAE	10841	7011	104	1.54
NEU	8511	6404	25	0.40
MDCD	4191	2846	70	2.66
OptumEHR	12264	12901	69	0.55
JMDC	0	0	0	0
JHME	311	239	2	0.88

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Incidence Rate of Kidney Failure (Literature)

-Type 2 diabetes UK: 0.69 per 100 person-years

-Diabetes systematic review: 0.132 to 0.167 per 100 person-years

González-Pérez, A., Saez, M., Vizcaya, D., Lind, M. & Rodriguez, L. G. Incidence and risk factors for mortality and end-stage renal disease in people with type 2 diabetes and diabetic kidney disease: a population-based cohort study in the UK. *Bmj Open Diabetes Res Care* **9**, e002146 (2021).

Narres, M. *et al.* The Incidence of End-Stage Renal Disease in the Diabetic (Compared to the Non-Diabetic) Population: A Systematic Review. *Plos One* **11**, e0147329 (2016).

Population-Level Effect Estimation

Results from study diagnostics for population-level effect estimation (from databases that passed diagnostics).

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Database	Target (N)	Comparator (N)	Attrition Fraction Target (%)	Attrition Fraction Comparator (%)	MDRR	Preference Score (Equipoise)	EASE
	Aflibercept	Ranibizumab					
SES	4797	4797	51	38	1.81	0.78	0.03
MDCR	2826	2826	50	42	2.74	0.73	0.05
CCAE	1905	1905	54	52	2.05	0.61	0.05
NEU	1868	1868	58	25	3.22	0.90	0.08
VA	1215	1215	85	55	3.75	0.36	0.09
	Ranibizumab	Bevacizumab					
SES	7946	7946	21	89	1.65	0.67	0.04
MDCR	5505	5505	43	61	2.01	0.63	0.05
CCAE	3622	3622	25	76	1.90	0.83	0.05
NEU	2046	2046	18	82	3.30	0.83	0.12
VA	1811	1811	63	87	3.14	0.33	0.11
	Aflibercept	Bevacizumab					
SES	8016	8016	18	87	1.65	0.84	0.04
MDCR	3727	3727	34	60	2.61	0.77	0.04
CCAE	3144	3144	24	75	1.82	0.82	0.07
NEU	3533	3533	21	69	2.94	0.94	0.08
VA	2612	2612	67	79	2.54	0.36	0.08

Attrition fraction: who was excluded from the analysis

MDRR: minimum detectable relative risk (given the available data, what effect size would the analysis be able to detect)

- 1.65=65% increased risk
- 3.75=275% increased risk

EASE: expected absolute systematic error (pre-defined <0.25)

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Method for Population-Level Effect Estimation

- Large-scale propensity score method used to match target/comparison exposure cohort comparison using 1:1 propensity score matching
- Cox proportional hazards models used to estimate risk of kidney failure while on treatment

Hazard ratio estimates and their 95% confidence interval for the risk of kidney failure among new users of 3 monthly anti-VEGF medications comparing ranibizumab, aflibercept, and bevacizumab.

	Hazard Ratio (95% Confidence Interval)	P-value
Aflibercept versus Ranibizumab		
SES	0.84 (0.55, 1.27)	0.41
MDCR	0.92 (0.45, 1.87)	0.81
CCAE	1.23 (0.74, 2.09)	0.43
NEU	0.82 (0.36, 1.87)	0.64
VA	0.56 (0.21, 1.44)	0.24
Meta-Analysis	1.01 (0.70, 1.47)	0.45
Ranibizumab versus Bevacizumab		
SES	0.94 (0.66, 1.34)	0.74
MDCR	1.01 (0.62, 1.65)	0.98
CCAE	0.79 (0.50, 1.24)	0.30
NEU	1.50 (0.64, 3.76)	0.37
VA	0.82 (0.36, 1.83)	0.63
Meta-Analysis	0.95 (0.68, 1.32)	0.62
Aflibercept versus Bevacizumab		
SES	1.05 (0.74, 1.51)	0.78
MDCR	0.72 (0.37, 1.43)	0.35
CCAE	0.99 (0.64, 1.54)	0.95
NEU	0.27 (0.59, 2.89)	0.56
VA	1.09 (0.56, 2.20)	0.81
Meta-Analysis	0.95 (0.65, 1.39)	0.60

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Patient Level Prediction

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Model

- Machine learning model: regularized logistic regression
- Predict the risk of kidney failure 6 months to 2 years after the 3rd monthly anti-VEGF medication among new users of anti-VEGF with blinding diagnoses

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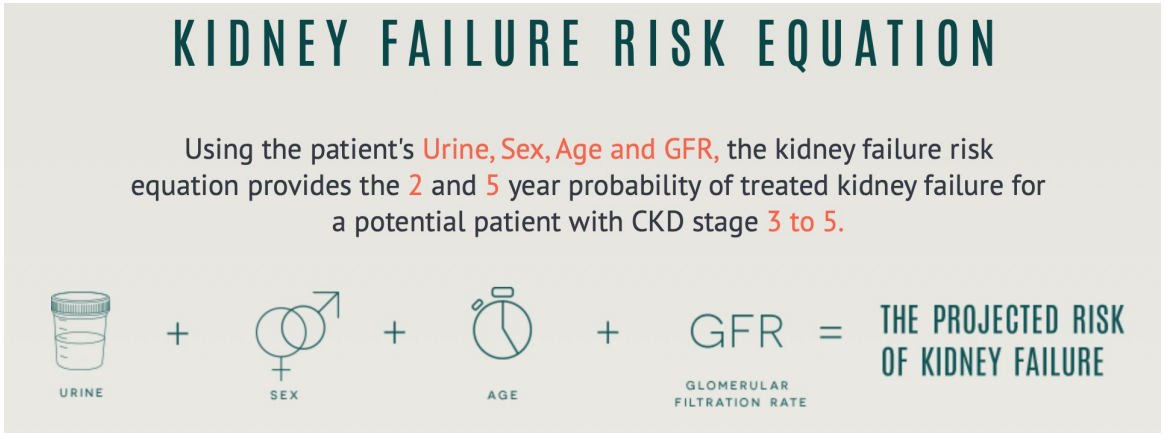
Exposure	Database	AUROC (95% Confidence Interval)	AUPRC
Ranibizumab	SES	0.89 (0.85, 0.93)	0.17
Aflibercept	SES	0.90 (0.85, 0.94)	0.23
Bevacizumab	SES	0.88 (0.86, 0.89)	0.16

AUROC: area under the receiver operating curve
AUPRC: area under the precision recall curve



https://kidneyfailurerisk.com

Tangri, N. *et al.* A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure. *Jama* **305**, 1553–1559 (2011).
Tangri, N. *et al.* Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. *Jama* **315**, 164–174 (2016).

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Interpreting Main Result: Clinical Context

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Discussion

- Clinicians were choosing ranibizumab
- Ranibizumab versus Aflibercept versus Bevacizumab
- 2015 Wholesale Prices
  - Ranibizumab: $1170
  - Aflibercept: $1850
  - Bevacizumab: $60
- 2013: Medicare Part B expenditures (ranibizumab + aflibercept): $2.5 billion

Ross, E. L. *et al.* Cost-effectiveness of Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema Treatment: Analysis From the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial. *Jama Ophthalmol* **134**, 888 (2016).

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Discussion

- Starting to compare in sample size in the IRIS Registry (national eye disease clinical registry)
- This study of patients with diabetic macular edema included ~150K patients
- Our study had 3 indications: DR/DME, AMD, VO

ARVO Annual Meeting Abstract | June 2022

Discontinuation, switching, and other long-term real-world treatment patterns among patients with diabetic macular edema initiating anti-VEGF: 6-year follow-up using the IRIS® Registry

Eunice Kim; Vince Garmo; David Tabano; Blanche Kuo; Theodore Leng; Meghan Hatfield; Andrew LaPrise; Rishi P Singh

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science June 2022, Vol.63, 2523 – F0249. doi:

Abstract

Purpose : This study aimed to characterize long-term treatment patterns among patients with diabetic macular edema (DME) from a large ophthalmology registry.

Methods : A retrospective analysis was performed among treatment-naïve DME patients (no prior anti-vascular endothelial growth factor (anti-VEGF) intravitreal therapy [IVT] in the past 12 months) initiating IVT from 1/1/2015-12/31/2019 using de-identified electronic medical records (IRIS® Registry). Anti-VEGF agent utilization patterns, including agent type, switches (defined as ≥3 consecutive injections of a different anti-VEGF agent from the original agent), and discontinuations (defined as no anti-VEGF IVT for ≥12 months). Results were stratified by baseline visual acuity (VA) and initial anti-VEGF agent including on-label (ranibizumab and aflibercept) and off-label agent (bevacizumab).

Results : Of 190,345 eyes (147,687 patients), 147,336 eyes (77%) received only 1 anti-VEGF agent over a mean follow-up of 2.3 years, with bevacizumab being the most commonly used agent (53% of eyes). Bevacizumab use decreased by a mean of 5.6% each year and on-label agent use increased by a mean of 6.9% each year (Figure 1). 15% of eyes switched anti-VEGF agents after a mean of 53 weeks, of which 74% switched from bevacizumab to an on-label agent. 52% of eyes discontinued anti-VEGF treatment after a mean of 24 weeks, of which 33% reinitiated after a mean of 91 weeks. Rates of discontinuation, switching, and reinitiation were mostly similar regardless of baseline VA, though discontinuation with no reinitiation of IVT during follow-up was highest in patients with VA ≤20/200 at baseline (Figure 2).

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Study Next Steps

- More Data Partners!
  - Deadline: July 14th, 2023
- Interpreting Results
  - https://data.ohdsi.org/AntiVegfKidneyFailure/
  - Patient-Level Prediction: message me in Teams
  - Further Discussion of Results:
  - Eye Care and Vision Research WG Meeting Monday June 12, 2023 @ 4PM EST
- Meetings
  - OHDSI Global Symposium: June 15th, 2023
- Target Journal
  - *JAMA Ophthalmology*, or *Ophthalmology*