WHITE PAPER

Utilizing Real-World Evidence (RWE) to Design a Precision Formulary

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ATROPOSHEALTH

UTILIZING RWE TO DESIGN A PRECISION FORMULARY

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01. INTRODUCTION

A Brief Overview

About Us

Atropos Health is the developer of GENEVA OS™ (Generative Evidence Acceleration Operating System), the operating system for rapid healthcare evidence across a robust network of real-world data (RWD). Healthcare and life science organizations work with Atropos Health to close evidence gaps from bench to bedside, improve individual patient outcomes with data-driven care, expedite research that advances the field of medicine, and more. We aim to transform healthcare with timely, relevant, real-world evidence.

Health System Pharmacy Spend

Healthcare expenditures account for nearly 1 in 5 dollars spent in the United States and show no signs of slowing down as health inflation outpaces general inflation[1]. An effort to reduce this level of spending almost always ends up with some focus on medication or pharmaceutical spend as it accounts for nearly 10% of overall healthcare spending[2].

Solutions targeting medication spend fall within two large domains. Pharmacy benefit managers can reduce the overall price paid for drugs through supply negotiations with manufactures including securing rebates. Formulary management[3] is an activity within payers/providers to offer an inventory of drugs matched to disease conditions that are the most cost effective option for care. More costly drug options for a condition may be offered only when the primary options show poor disease response or are in a higher tier where patients are responsible for more of the cost.

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02.

Tools Essential to Formulary Management

Pharmacy and therapeutics committees are responsible for maintaining a list of evidence supported medication options for treating a variety of common and uncommon conditions. This review focuses on data from clinical trials, FDA released information, and post-market publications on comparative effectiveness and safety of a particular drug to treat a specific condition. Key tools for making formulary decisions include evidence reviews, budget impact models (typically with a 1-year horizon), and cost-effectiveness models (often extending 3 or more years). Formulary management work continues through continued monitoring of utilization patterns and evolving external and internal evidence.

There are important ethical considerations such that decisions for clinical effectiveness are often separated from the cost consideration of a particular drug versus other options in that disease process.

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03.

What is Missing for Formulary Decisions?

A significant portion of clinical evidence for a drug in a disease process comes from randomized controlled trials required for drug registration and indication changes. While these are required for making federal market access decisions and can be helpful in making care decisions, they fall short of how medicine choices are made in the real-world.

1. Clinical trials have lengthy inclusion and exclusion criteria that create a more skewed population from the heterogeneous mix of patients with multiple comorbidites and adjacent medication usage.

2. The frequency of monitoring laboratory, imaging, and clinical assessments performed in a trial to observe impact and side effects are not representative of typical actual patient care processes.

3. Study results are often for the impact of a single drug in a disease or comparison to an existing drug rather than mimicking the practice of combination drug therapy and dosage escalations and delays that occur in real practice.

In addition to these constraints in extrapolating trial data, the elephant in the room remains that cost is an important, sometimes the ultimate, deciding factor in a patient's decision to initiate therapy. Drug inflation has typically exceeded inflation in other economic sectors and patient sensitivity has increased with higher copays and high deductible health plans. If a new drug leads to a marginal impact for a patient, let's say 5% reduction in monthly migraine days, is it worth paying an extra $600 out of pocket for it monthly? How should an employer think about associated costs?

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04.

Benefits of Real-World Evidence (RWE) in Formulary Decision Making

Actual clinical and utilization data from millions of patients in RWE offers a robust augmentation to making pharmaceutical decisions based on trials or small published studies. It allows modeling of one therapy versus another (or combinations, different doses, and delays) in the clinical outcomes of a disease as well as looking at overall healthcare utilization. Changes in acute healthcare use, such as inpatient admission days or emergency room visits, can have a significant impact on total annual cost of annual care for a patient relative to drug cost.

The heterogeneity of patients in RWE becomes a strength rather than a weakness as it allows for the assessment of differential clinical impact based on factors such as underlying comorbidities, markers of disease severity such as BMI or A1c, past utilization, or past or concomitant treatment. Individual patient differences can be balanced or leveraged through statistical and machine learning techniques to enable fair comparisons between different treatment options and/or highlight heterogenous effects. Understanding treatment heterogeneity is especially important in determining optimal policy not just for whether but for where and when to prefer one treatment option over others.

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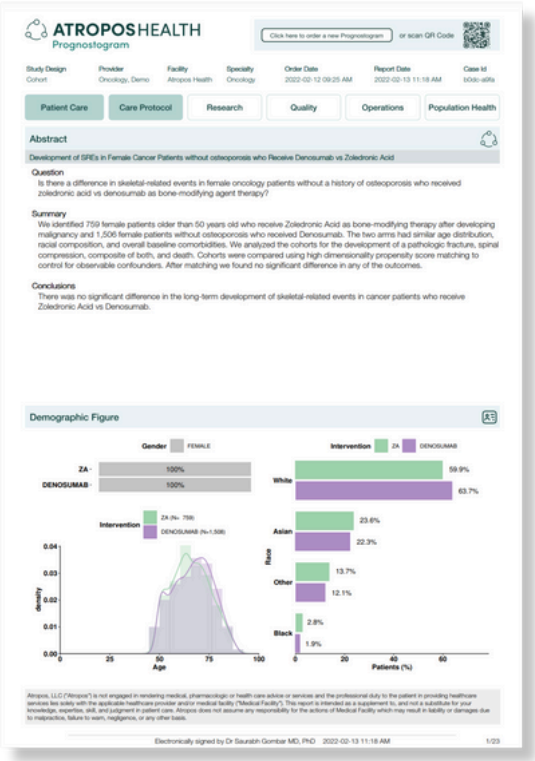
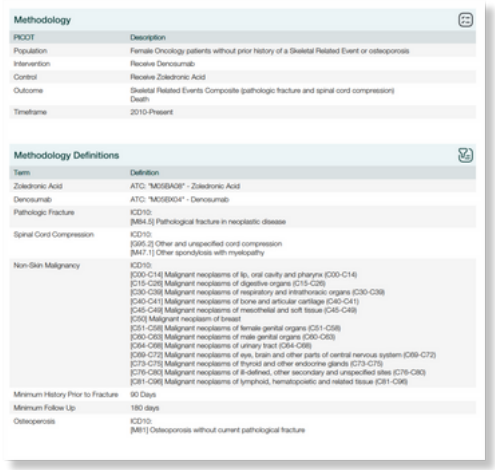
Example Prognostogram -
An Observational Grade Research Study

Is there a difference in skeletal-related events in female oncology patients without a history of osteoporosis who received zoledronic acid vs. denosumab as bone-modifying agent therapy?

Question from a clinician at an AMC





REQUEST YOUR OWN

05. EXAMPLE 1

Biosimilar for Autoimmune Conditions (TNF-alpha Inhibitors)

Medications targeting autoimmune conditions such as rheumatoid arthritis, Crohn's disease, and ulcerative colitis account for a disproportionately high percentage of spend of all outpatient drugs. Drugs such as adalimumab, ustekinumab, and infliximab take up several of the top spots in the Vizient Winter 2025 Spend Management Outlook[4] and may account for almost 20%[5] of all pharmacy benefit drug spend.

The per patient per year costs for TNF-alpha inhibitors in Crohn's disease alone add up to $20,000-$40,000[6]. Switching to an equally effective biosimilar could cut this annual cost in more than half as evidenced by Kaiser Permanente's switch from AbbVie Humira to Amgen Amjevita[7]. **This represents a potential $10,000 to $20,000 annual savings opportunity per patient on TNF-alpha therapy with IBD.**

The below RWE analysis for infliximab shows that disease specific health outcomes as well as healthcare utilization were no different in the originator drugs versus a biosimilar. Markers of inflammation such as C-reactive protein as well as hospitalizations and office visits related to IBD/autoimmune causes were similar. Propensity score matching helps ensure relevant comparisons.

Propensity Score Matched (crp. 1 yr)

Intervention	Number	Mean (SD)	MD (95% CI)	SMD (95% CI)	pvalue	E-value
REMICADE	61	5.4 (6.6)	NA	NA	NA	NA
BIOSIMILARS	61	6.4 (7.8)	1 (-1.6, 3.6)	0.14 (-0.22, 0.5)	0.44	NA

Propensity Score Matched (office.visit.ibd)

Intervention	Negative	Positive	OR (95% CI)	pvalue	E-value
REMICADE	343	348	1 (1, 1)	NA	NA
BIOSIMILARS	356	335	0.927 (0.751, 1.15)	0.48	NA

Propensity Score Matched (hospitalization.autoimmune)

Intervention	Negative	Positive	OR (95% CI)	pvalue	E-value
REMICADE	440	251	1 (1, 1)	NA	NA
BIOSIMILARS	433	258	1.04 (0.839, 1.3)	0.7	NA

Calculate Your Costs

Detailed approach

current drug-spend in select autoimmune biologics x .25 achievable savings via transition to biosimilars (25%) =

Simpler approach

total outpatient drug spend x .20 estimated autoimmune biologic cost (20%) x .25 achievable savings via transition to biosimilars (25%) =

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06. EXAMPLE 2

Peri/Post-procedural Care

Atropos Health contains a plethora of RWE analysis on procedural care decisions ranging from post-operative pain management to preventing complications such as post-operative ileus. Procedural care forms a significant portion of healthcare spend and small differences in price can lead to large total savings due to volume.

For the prevention of post-operative ileus, Atropos Health compared the use of alvimopan versus naloxegol and discovered that naloxegol performed better across a number of condition-specific outcomes such as inpatient length of stay, incidence of post-operative ileus, and 30 day re-admission. What is interesting is that the clinically better performing medication here (naloxegol) is orders of magnitude less expensive than alvimopan and could save a health system more than $2,000 per patient over the course of a typical 6-day hospital stay for radical cystectomy[8] by favoring naloxegol.

Propensity Score Matched (inpatient.los)

Intervention	Number	Mean (SD)	Diff in Means	IRR (95% CI)	pvalue	E-value
ALVIMOPAN	465	1.589 (4.629)	0.000	NA (NA, NA)	NA	NA
NALOXEGOL	465	0.406 (1.864)	-1.183	0.581 (-0.415, 0.814)	0.002	NA

Propensity Score Matched (post.surgical.ileus)

Intervention	Negative	Positive	OR (95% CI)	pvalue	E-value
ALVIMOPAN	362	103	1 (1, 1)	NA	NA
NALOXEGOL	439	26	0.208 (0.132, 0.327)	<0.001	5.6 (H)

Propensity Score Matched (30.day.readmission)

Intervention	Negative	Positive	OR (95% CI)	pvalue	E-value
ALVIMOPAN	381	84	1 (1, 1)	NA	NA
NALOXEGOL	428	37	0.392 (0.26, 1.591)	<0.001	2.8 (H)

Calculate Your Costs

Alvimopan annual spend x median number of days x $300 daily cost savings by switching to Naloxegol =

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07. EXAMPLE 3

Weight Management: Glucagon-like Peptide-1 (GLP-1), Bariatric Surgery, Behavior Change

GLP-1 medications have taken the healthcare industry and larger discussions in weight management and care of diabetics patients by storm in the last several years. They have shown a number of improvements in reduction of BMI and A1c as well as long term reductions in cardiovascular and renal risks. There is a material cost difference between GLP-1s and other drugs for diabetes such as metformin or for weight loss such as buproprion/naltrexone. Therefore, many health systems and payors ask pertinent questions as to what subpopulation of diabetic patients and/or weight management patients would benefit most from the higher cost of therapy. Additionally, can this higher cost of therapy be offset with measurable reductions in inpatient admissions due to cardiovascular disease or spending on knee osteoarthritis in the subsequent 1-3 years after therapy initiation?

Atropos Health often conducts its analysis in an entire population (such as diabetics or obese) but also in subpopulations that can be varied based on age, gender, race/ethnicity, comorbidities, disease severity, concurrent medications, and prior healthcare history. This allows finding subpopulations with the highest quantifiable impact in terms of improved health outcomes and balancing cost of therapy versus total cost of care.

As an example, Atropos Health found that using tirzepatide could lead to a reduction in mean length of stay of almost 5 days in a patient population with BMI over 27 with common comorbidities such as hypertension or dyslipidemia. The reduction in inpatient cost for these patients could be magnitudes larger than the cost of the drug over a year period. The impact size of health benefits of GLP-1s vary in patients based on gender, initial BMI, comorbidities, and prior healthcare interactions. Atropos Health is able to identify precisely the patient populations that benefit most alongside the potential cost increases (medication cost X ideal duration) versus savings in healthcare utilization.

Calculate Your Costs

Inpatient cost savings

( ) days of reduced inpatient length of stay x ( ) average cost of an inpatient stay, paid amount x ( ) total covered lives = ( )

ICU cost savings

( ) days of reduced inpatient length of stay x ( ) average cost of an inpatient stay, paid amount x ( ) total covered lives = ( )

Additional medication cost

$250 average cost of GLP1 therapy per patient per month x 12 ideal treatment duration (months) x ( ) total covered lives = ( )

Net savings

(( ) Inpatient cost savings (above) divided by total covered lives + ( ) ICU cost savings (above) divided by total covered lives) − ( ) Additional medication cost (above) divided by total covered lives = ( )

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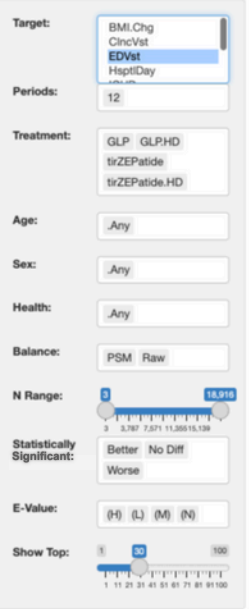
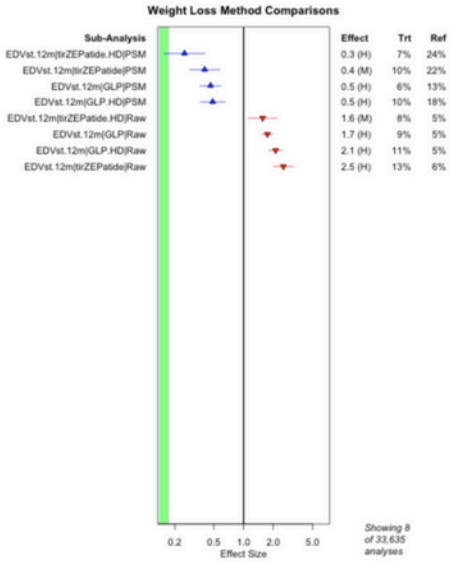
07. EXAMPLE 3

Weight Management: Glucagon-like Peptide-1 (GLP-1), Bariatric Surgery, Behavior Change

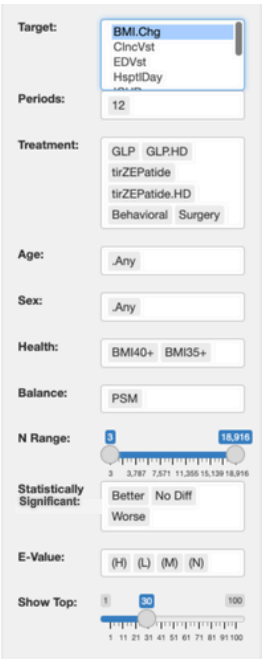
Exhibit 1: Analyze ED visits based on treatment types

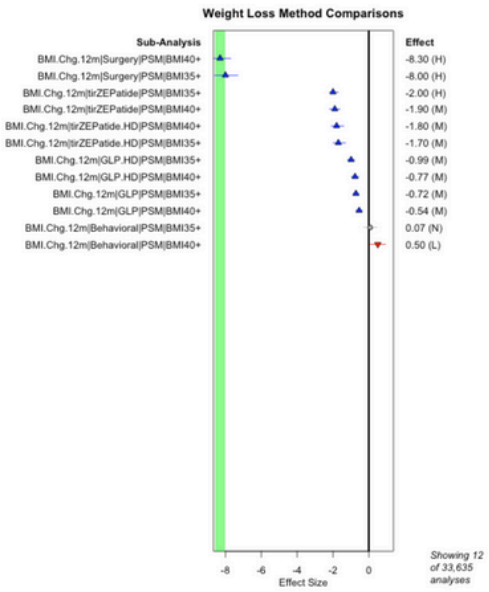




This is a specific example of where propensity score matching (PSM) is critical for proper analysis. Raw (unadjusted) comparisons show that the group treated with tirzepatide high dose actually has higher ED visits. Once you account for comorbidities, the PSM that selects equally sick individuals from the untreated group shows that tirzepatide in fact significantly reduces ED visits.

Exhibit 2: Analyze BMI changes based on treatment types





BMI 12 month change: comparing medications versus surgery and behavioral change

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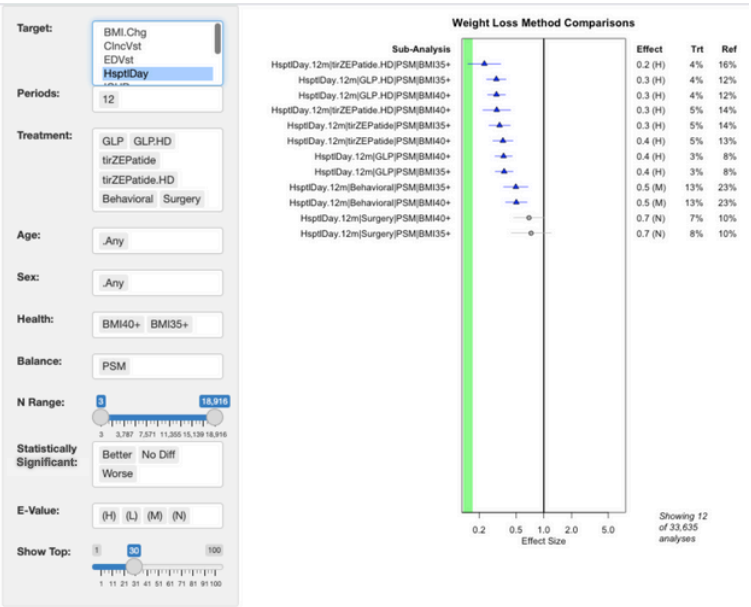
07. EXAMPLE 3

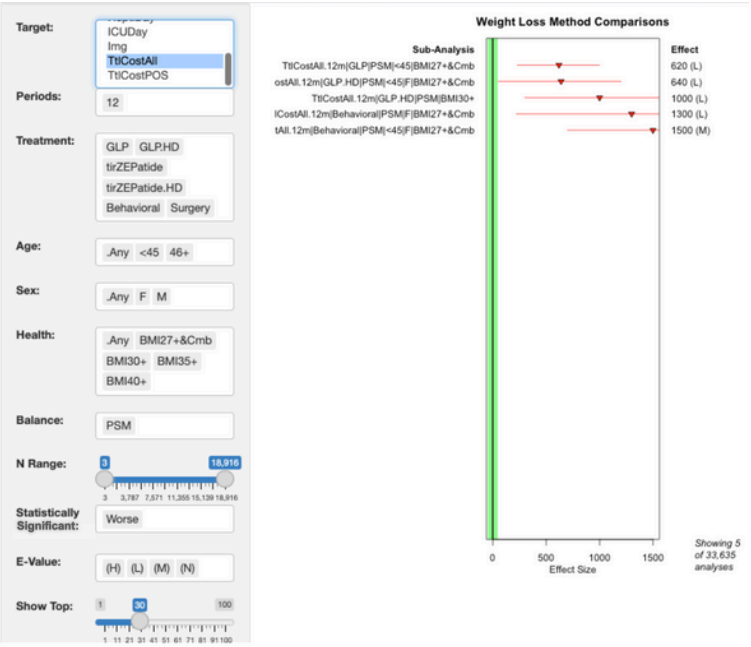
Weight Management: Glucagon-like Peptide-1 (GLP-1), Bariatric Surgery, Behavior Change

Exhibit 3: Analyze hospital length of stay based on treatment types



Inpatient length of stay 12-month: comparing medications versus surgery and behavioral change. Medications are more impactful than surgery compared to BMI change.

Exhibit 4: Analyze total cost of care based on treatment types



Any cost negatives – Where am I at risk for overspending in total costs?

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08.

Conclusions

The landscape of healthcare is defined by two constants: rising costs and the increasing complexity of patient needs. Traditional formulary management, while a crucial component of cost control, is often constrained by its reliance largely on evidence from randomized controlled trials, which does not reflect the heterogeneity of real-world patient populations or the true total cost of care. This evidence gap can lead to suboptimal decisions that impact both patient outcomes and an organization's bottom line.

By analyzing data from millions of diverse patients, real-world evidence (RWE) provides a more complete and nuanced understanding of a treatment's clinical and financial impact. This enables a shift from focusing purely on drug costs to assessing the total value of care, identifying opportunities to significantly improve outcomes and reduce overall healthcare spending.

Atropos Health addresses this critical need with AI-powered technology and an extensive, federated real-world data (RWD) network to generate high-quality RWE. Atropos Health's RWE solutions enable the identification of differential clinical impact across diverse patient characteristics, ultimately leading to significant cost savings and improved patient outcomes.

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Atropos Health is Built on More than a Decade of Research, Development, and Clinical Use

Clinician-led, peer-reviewed methodologies and outputs pave the road to real-world evidence for every clinical decision

The NEW ENGLAND JOURNAL of MEDICINE

Evidence-Based Medicine in the EMR Era: Dr. Frankovich uses rapid assessment of EHR to inform a decision about anticoagulation in a patient with systemic lupus erythematosus.

JAMIA
A SCHOLARLY JOURNAL OF INFORMATICS IN HEALTH AND BIOMEDICINE

ACE: the Advanced Cohort Engine for searching longitudinal patient records: Dr. Shah's Lab + Stanford clinicians collaborate to create ACE and TQL .

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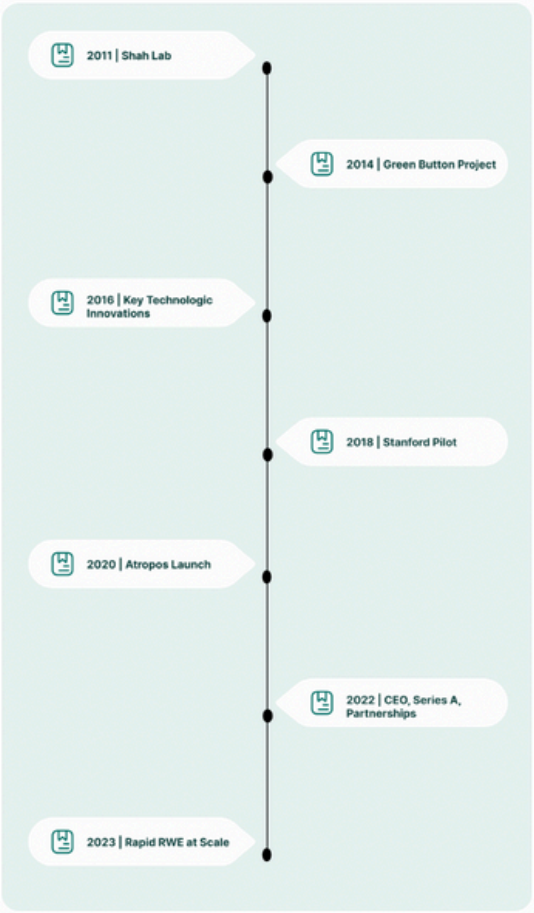
Atropos Health Launches: To scale clinical informatics consults and make RWE accessible where and when it's most needed in medicine.



HealthAffairs

A 'Green Button' For Using Aggregate Patient Data At The Point Of Care: Clinicians and biomedical informaticists work to bring evidence to the bedside.

npj | digital medicine

It is time to learn from patients like mine: Stanford Physicians lead world's first informatics consult pilot at Stanford

BECKER'S HOSPITAL REVIEW

Mayo Clinic Platform partners with Atropos Health: to unlock insights that will accelerate better care, via Mayo Clinic data & Atropos' clinical informatics technology.

09.

Sources

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