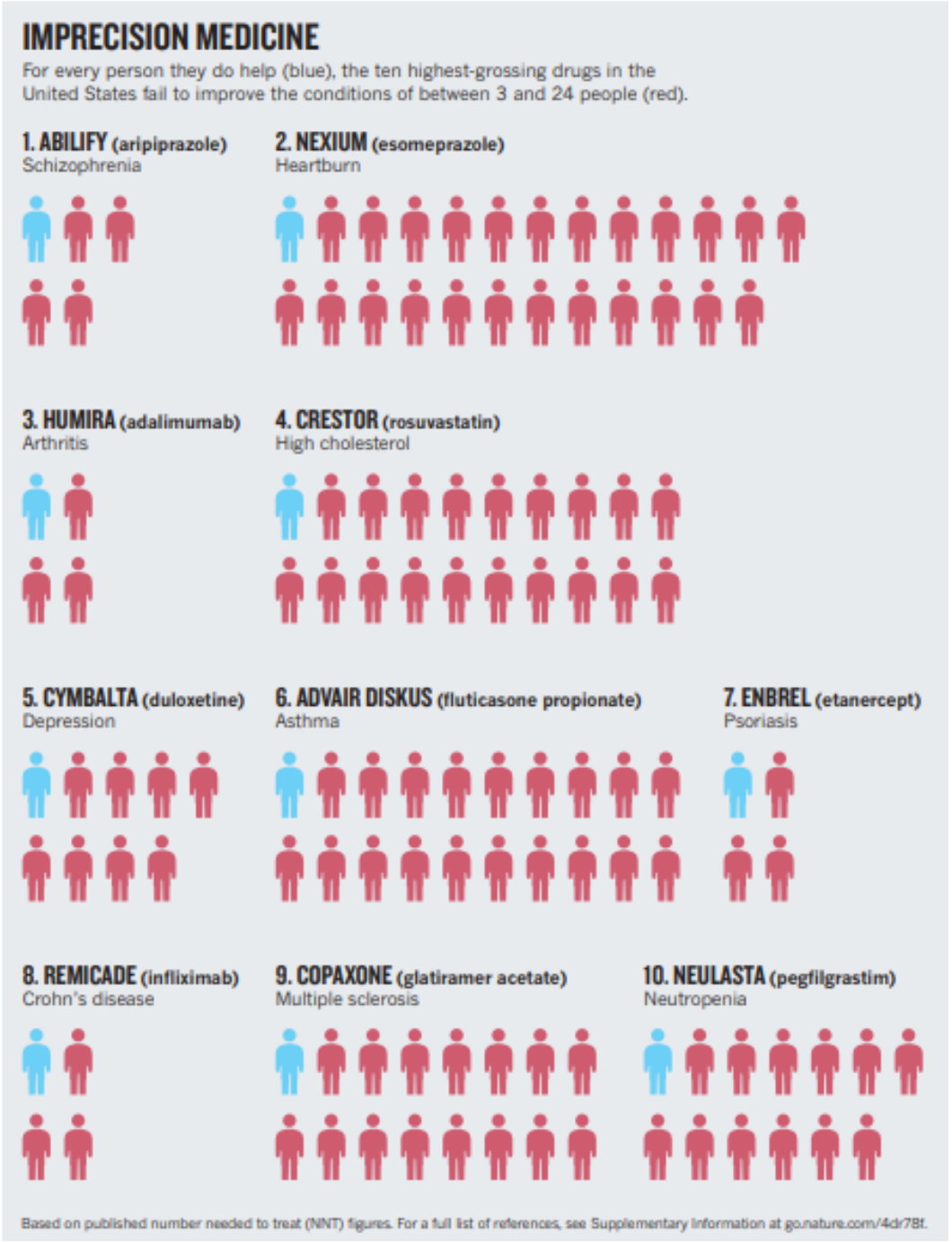
Pharmacogenomics Ventures

Luke Tso PharmD, BCPS

The Problem with Trial and Error Prescribing

- Less than 1 in 4 people benefit from some of the most common prescription medication[1]
- 1.3 million people in the US experience a drug related ER visit
  4th leading cause of death in the US[2]
- Annual cost of associated morbidity and mortality due to non-optimized prescription medications estimated at $528B in 2016 US dollars[3]



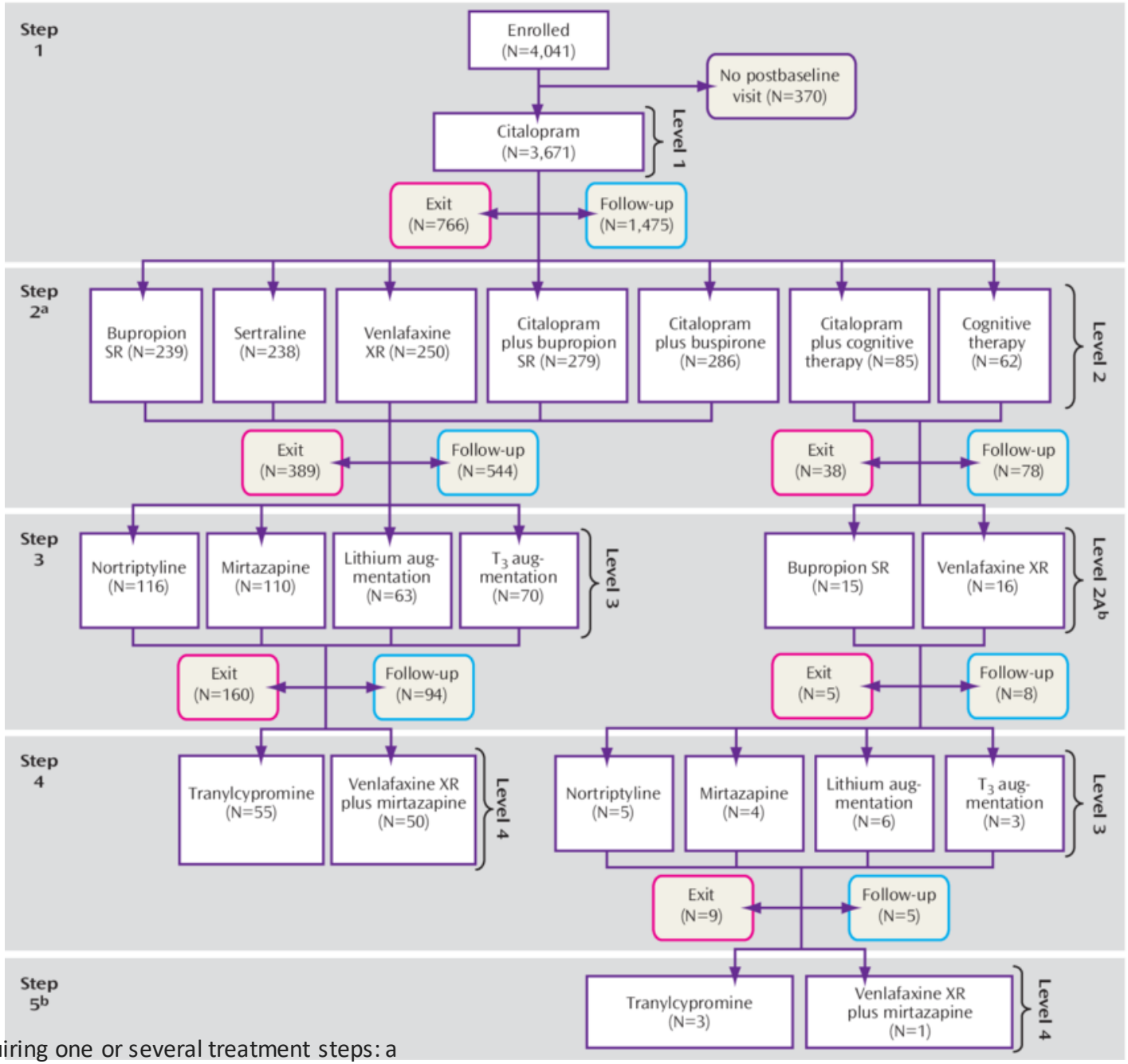
1. Schork NJ. Personalized medicine: Time for one-person trials. Nature. 2015 Apr 30;520(7549):609-11. doi: 10.1038/520609a. PMID: 25925459.
2. https://fourthcause.org/
3. Watanabe JH, McInnis T, Hirsch JD. Cost of Prescription Drug-Related Morbidity and Mortality. Ann Pharmacother. 2018 Sep;52(9):829-837. doi: 10.1177/1060028018765159. Epub 2018 Mar 26. PMID: 29577766.

Standard of Care for Treating Depression

Sequenced Treatment Alternative to Relieve Depression Trial (STAR*D)

- Less than 68% achieve remission after up to 4 trials, each trial lasting 4-6 weeks
- Risk of ADE increases with each step

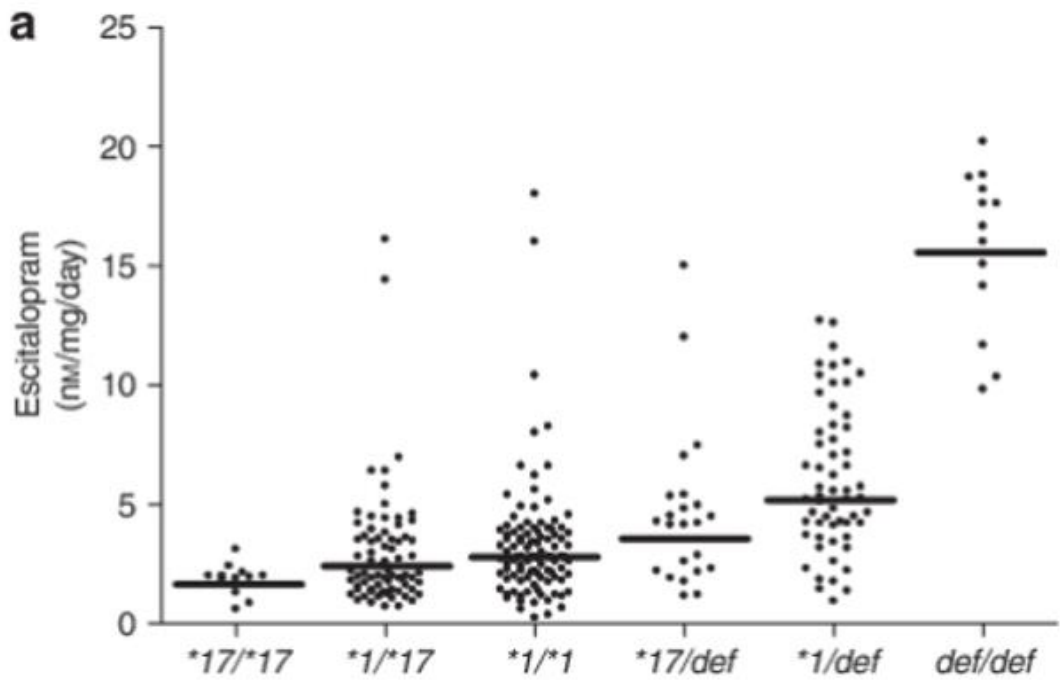
	Remission	Intolerance
Drug 1	37%	16%
Drug 2	31%	20%
Drug 3	14%	26%
Drug 4	13%	34%



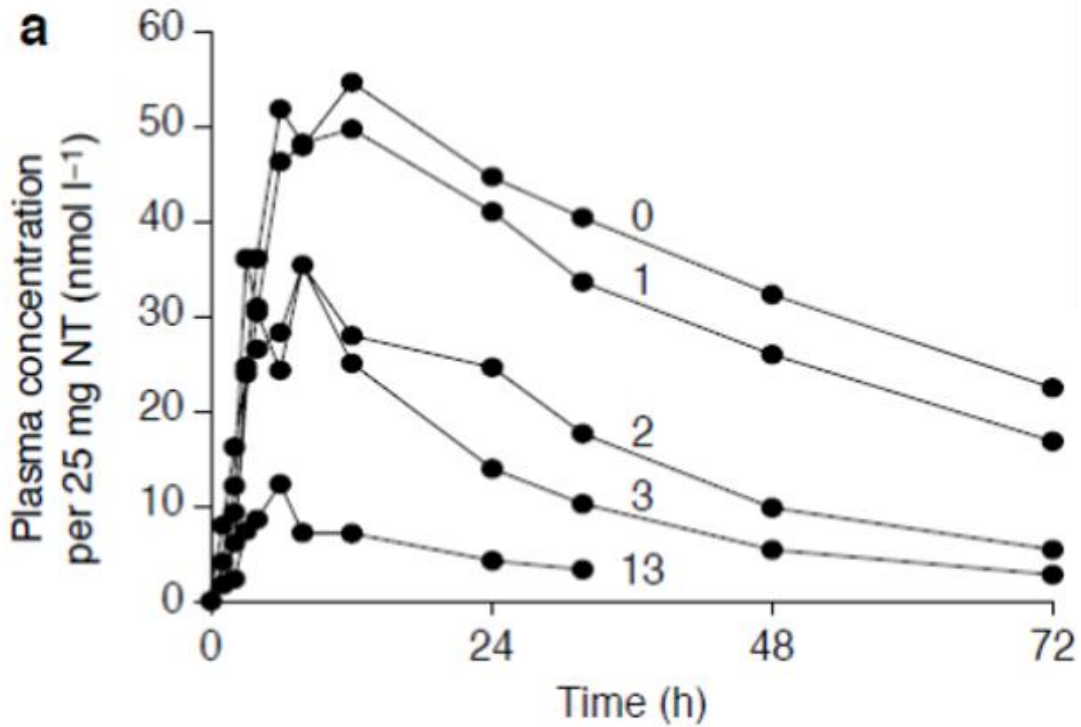
Rush AJ, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006 Nov;163(11):1905-17. doi: 10.1176/ajp.2006.163.11.1905. PMID: 17074942.

Single Gene Polymorphisms Result in Variable Drug Exposure

Escitalopram serum concentrations by CYP2C19 genotype.



Nortriptyline plasma concentration by CYP2D6 copy number



Rudberg I et al. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther. 2008 Feb;83(2):322-7
Ingelman-Sundberg M, et al. Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. Trends Pharmacol Sci. 1999 Aug;20(8):342-9

TABLE 1. Antidepressant Drug-by-Gene Associations With Moderate to High Levels of Evidence or Included in One of the Combinatorial Pharmacogenetic Tests Evaluated Here[a]

	Pharmacodynamic										Pharmacokinetic				
Agent	ADRA2A	BDNF	COMT	CRHR1	FKBP5	GRIK4	HTR1A	HTR2A	SLC6A2	SLC6A4	ABCB1	CYP1A2	CYP2B6	CYP2C19	CYP2D6
Amitriptyline[b]											3				1A
Bupropion															
Citalopram[b]		3			2B			2B		2A	3			1A	3
Desipramine[b]		3													1A
Doxepin[b]															1A
Duloxetine[b]					3			3		2A		1A			1A
Escitalopram[b]		3		3	2B		3			3		3			3
Fluoxetine[b]		3	3				3	3			3			1A	3
Fluvoxamine[b]											3				1A
Imipramine[b]														2A	1A
Maprotiline															3
Mirtazapine					2B					3			3		
Nefazodone[b]					3						3				
Nortriptyline[b]		3									3				1A
Paroxetine[b]		3	3		2B		3			3	3	3			1A
Sertraline							3			3	3			1A	
Trimipramine[b]															1A
Venlafaxine[b]			3		2B				3		3				2A
Antidepressants, unspecified		3		3	2B	2B	3	2B			3				1A
SSRIs, unspecified	3		2B		2B		3	2B			3				
Number of variants per gene	1	6	2	2	4	2	3	5	1	3	15	9	5	8	14
Interaction type[c]	E	E,T	E	E	E,T	E	E	E,T	E	E,T	E,T	E,T	E,O	E,M,T	E,D,M,T

[a] This is not a comprehensive representation of antidepressant drug-by-gene associations; it is limited to the PharmGKB search terms "depressive disorder, major; depressive disorder; depression; [antidepressant name]"; it excludes drug-gene interactions related to "bipolar disorder; anxiety disorder"; it excludes antipsychotic and some antidepressant drugs; and it excludes many drug-gene associations for which low/preliminary (level 3/4) evidence exists, as defined by PharmGKB. The PharmGKB knowledge base, which was used to generate this table, is not the sole source of relevant pharmacogenetic information. BDNF=brain-derived neurotrophic factor; COMT=catechol *O*-methyltransferase; SSRI=selective serotonin reuptake inhibitor.

[b] These agents have U.S. Food and Drug Administration labeling with CYP450 pharmacogenetic information.

[c] Pharmacogenetic information relevant to drug efficacy (E), dosage (D), metabolism/pharmacokinetics (M), toxicity/adverse drug reactions (T), and other (O). Values correspond to a high (1A, 1B), moderate (2A, 2B), or low (3) level of evidence according to the PharmGKB rating scale.

Zeier Z, Carpenter LL, Kalin NH, Rodriguez CI, McDonald WM, Widge AS, Nemeroff CB. Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing. Am J Psychiatry. 2018 Sep 1;175(9):873-886. doi: 10.1176/appi.ajp.2018.17111282. Epub 2018 Apr 25. PMID: 29690793; PMCID: PMC6774046.

Rapid Decline of Pharmacogenomic Test Costs

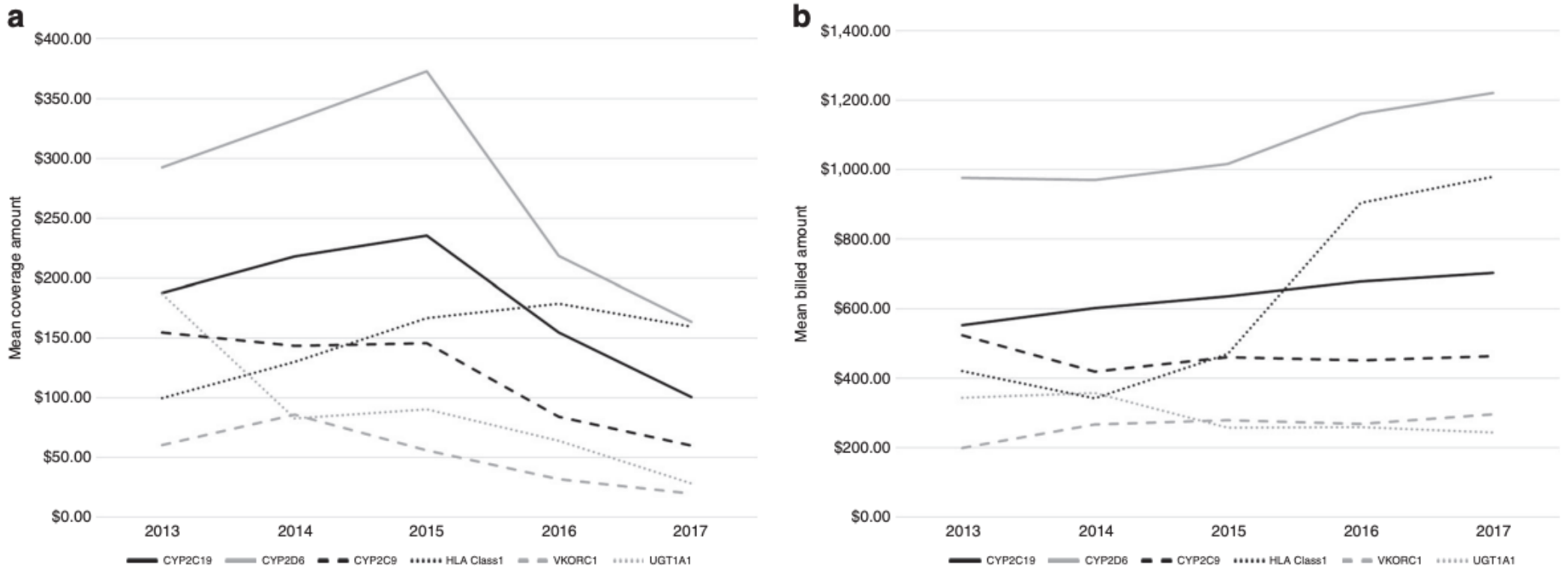
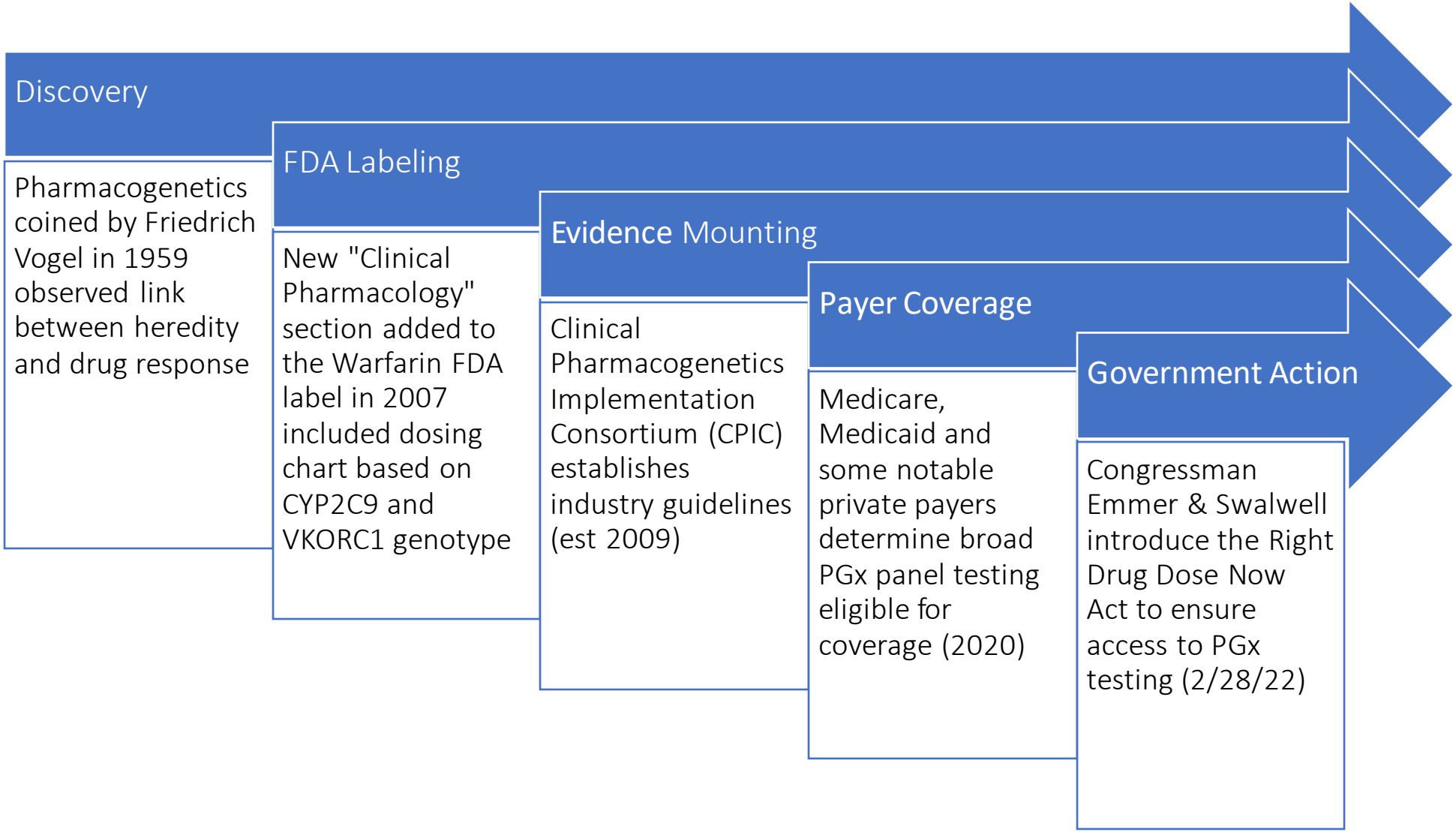


Fig. 2 Mean coverage amount (i.e., allowed cost) and billed amount for each single-gene pharmacogenetic test of interest from 2013 to 2017, for all tests (i.e., commercial insurance, managed Medicare/Medicaid, and other/unknown insurance). Note: 2017 only includes data through 30 September 2017. (**a**) Mean allowed cost from 2013 to 2017. Allowed cost is defined as the contracted or accepted reimbursable amount for covered medical services or supplies that the health plan agrees to pay to service providers. (**b**) Mean billed amount from 2013 to 2017. Billed amount is defined as the amount billed for services provided by the servicing provider or facility.

Anderson, H.D., Crooks, K.R., Kao, D.P. *et al.* The landscape of pharmacogenetic testing in a US managed care population. *Genet Med* **22,** 1247–1253 (2020). https://doi.org/10.1038/s41436-020-0788-3

Scaled and Standard Medical Practice Yet?



INVENTION

VERSUS

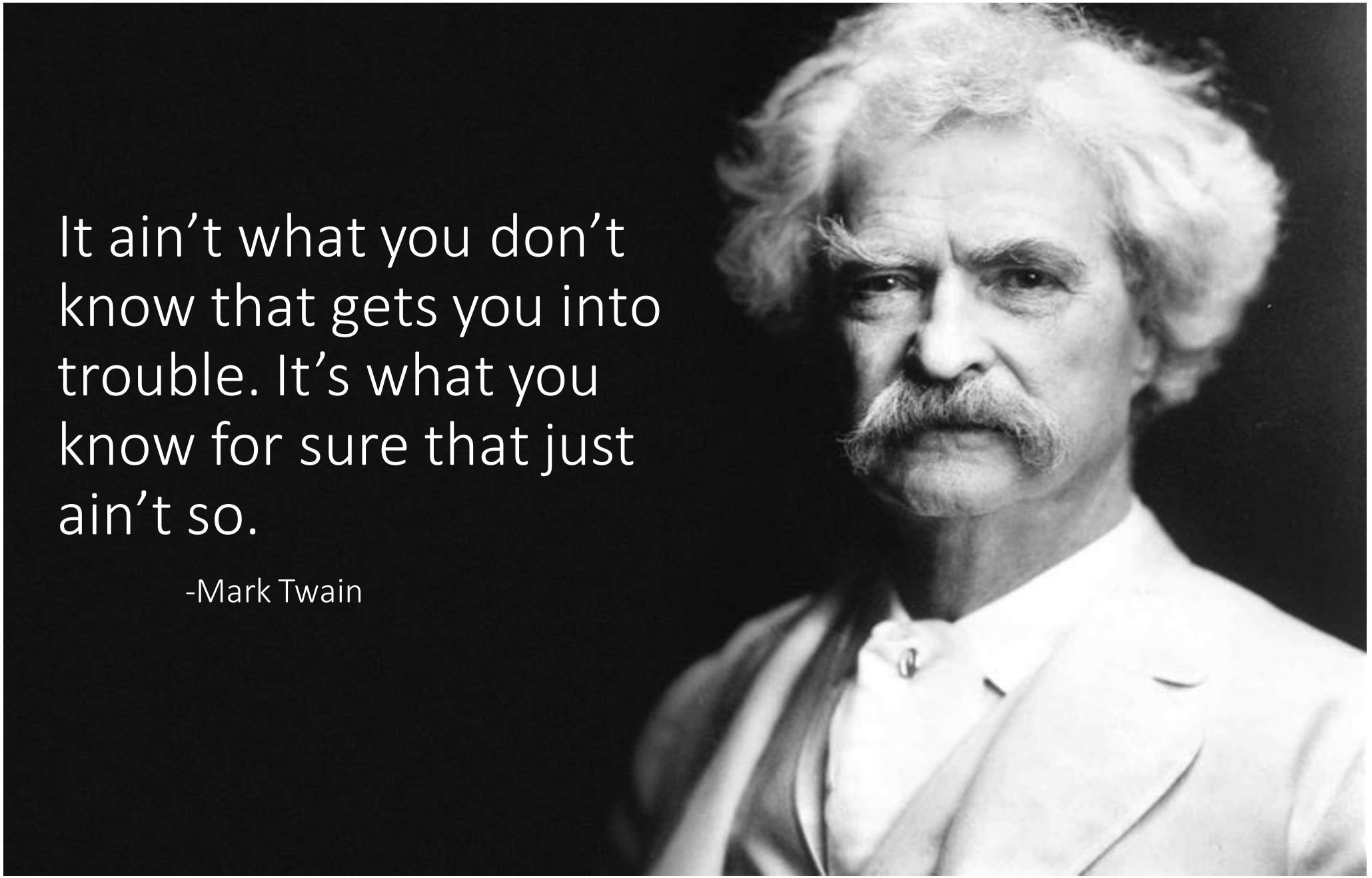
INNOVATION

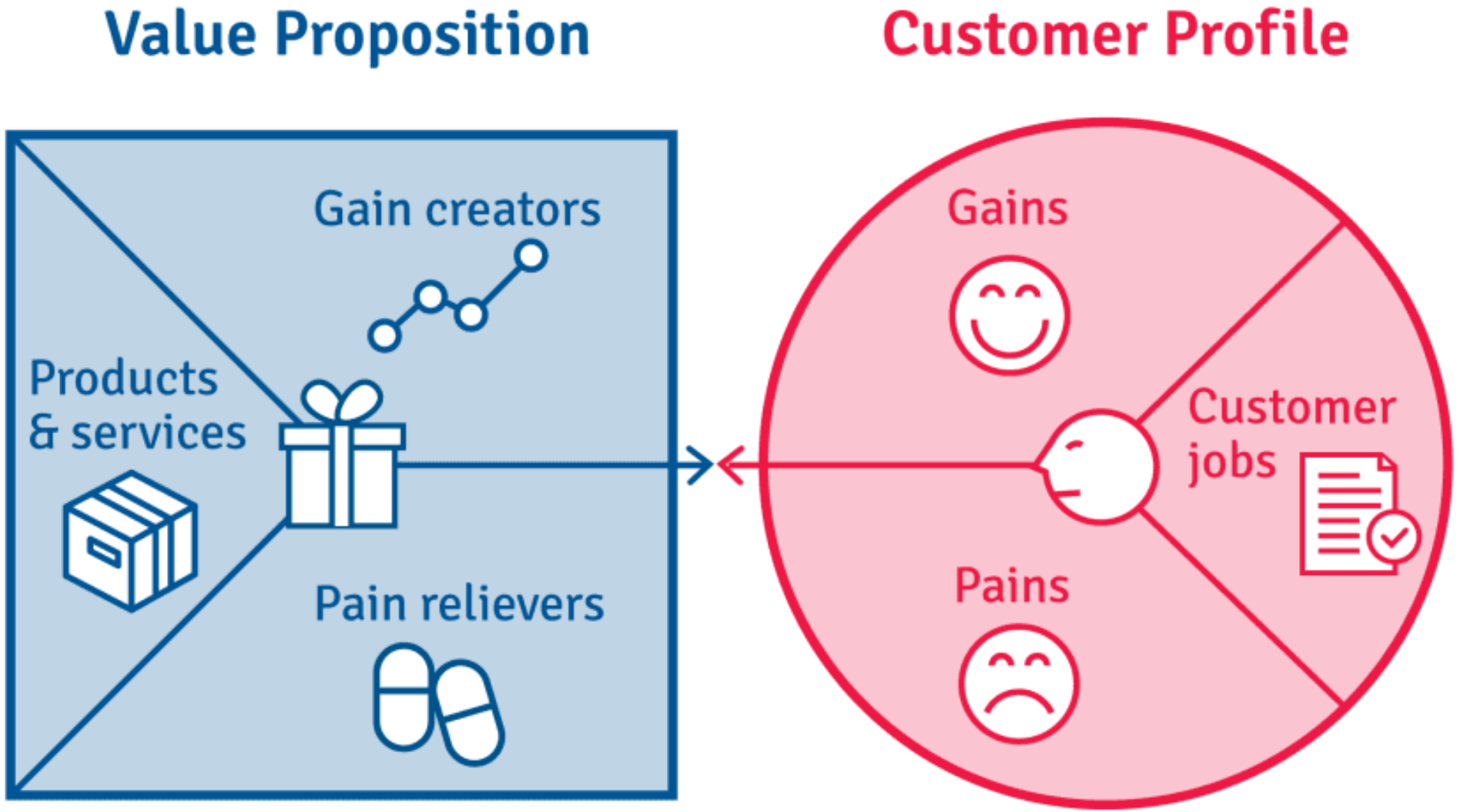
Invention:
The creation of something new

Innovation:
The creation of something new **+ its implementation and thereby the creation of value**

Many inventions don't become innovations because they are not implemented and **never create any value**

Inventions that are turned into innovations improve people's lives and often help us to do **solve a need better than existing solutions**


It ain’t what you don’t know that gets you into trouble. It’s what you know for sure that just ain’t so.
-Mark Twain


Value Proposition
Customer Profile
Gain creators
Products
& services
Pain relievers
Gains
Customer
jobs
Pains

The Washington Post

Magazine

Pearls Before Breakfast: Can one of the nation's great musicians cut through the fog of a D.C. rush hour? Let's find out.

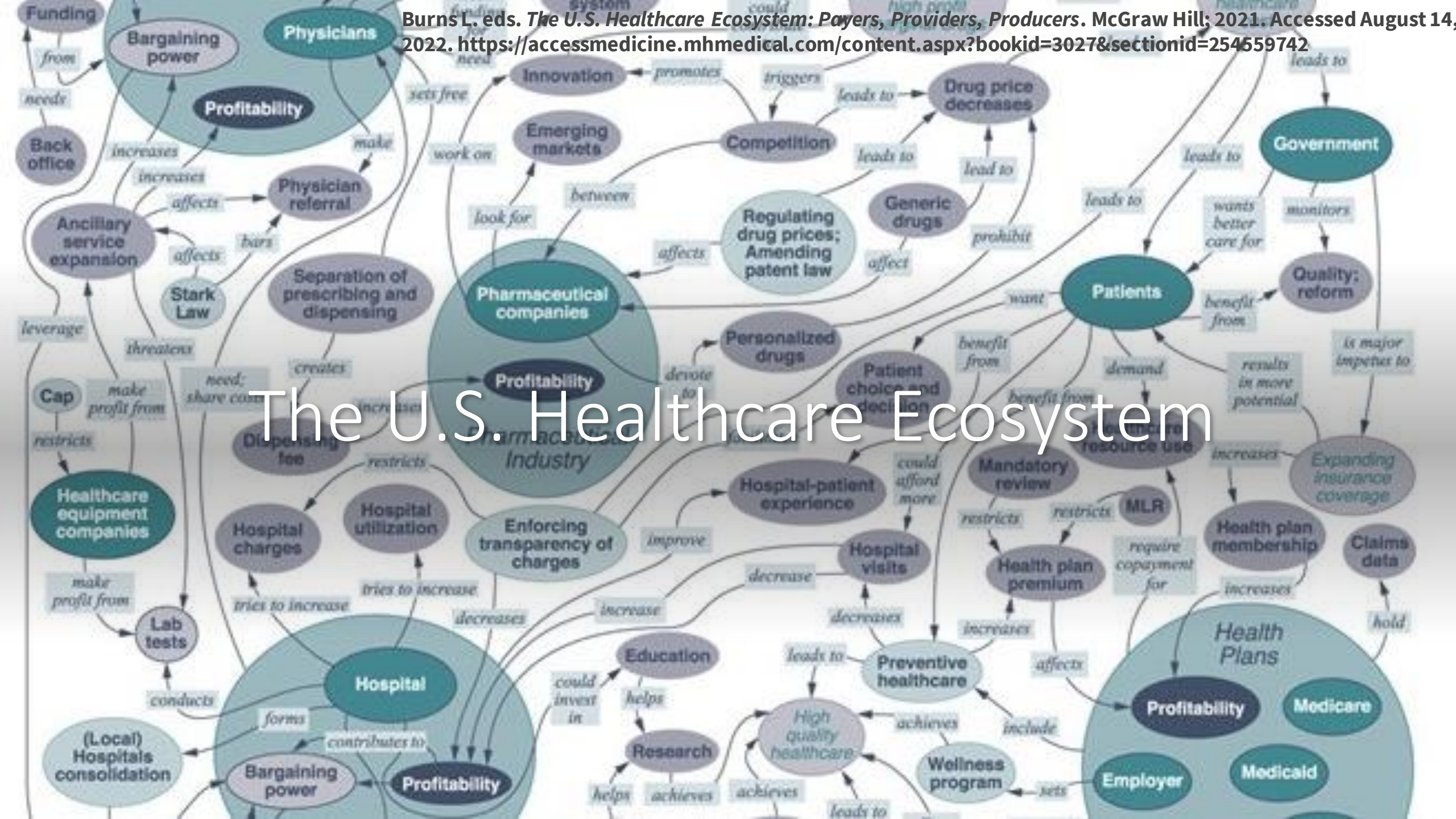
- Joshua Bell (child prodigy virtuoso) one of the greatest violinist of our time
- "Huberman" 1713 golden period Stradivarius violin worth over $14 Million
- Played the Bach "Chaconne" – considered the greatest violin solo piece ever written

In 42 minutes, made $32 in tips,
only 7 out of 1000+ people stopped

VS

2 nights prior at Boston's
Symphony Hall - sold out concert of
$100 per ticket

The U.S. Healthcare Ecosystem



Burns L. eds. *The U.S. Healthcare Ecosystem: Payers, Providers, Producers*. McGraw Hill; 2021. Accessed August 14, 2022. https://accessmedicine.mhmedical.com/content.aspx?bookid=3027&sectionid=254659742

Technology And Analytics

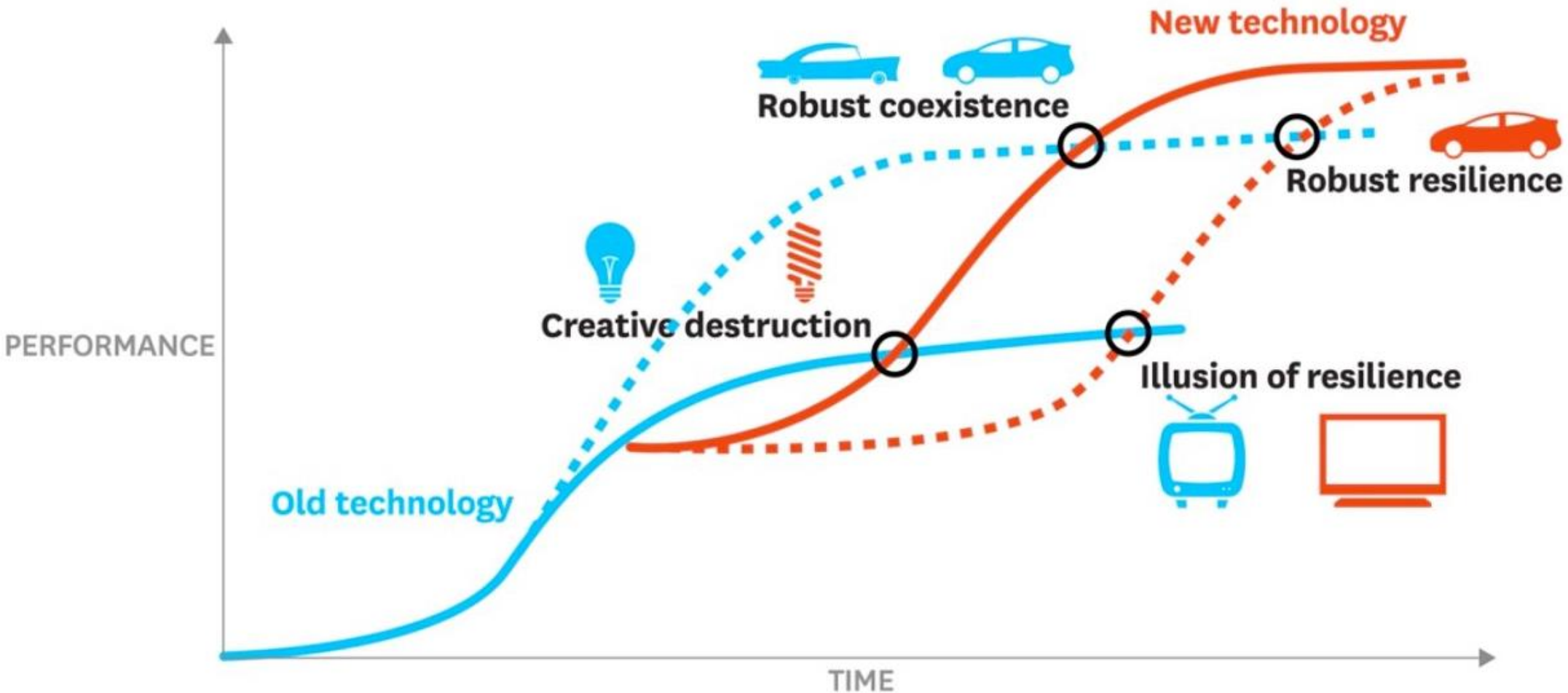
Right Tech, Wrong Time

How to make sure your ecosystem is ready for the newest technologies

by Ron Adner and Rahul Kapoor

From the Magazine (November 2016)

HOW FAST DOES NEW TECHNOLOGY REPLACE THE OLD?



https://hbr.org/video/5155033576001/why-better-technology-can-be-slower-to-take-off

Often Cited Barriers to Clinical Adoption

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Key Challenges to PGx Adoption

As identified by IGNITE Common Measures Working Group Analysis

- Lack of reimbursement for many genomic tests
- Few FDA approved or cleared PGx tests
- Lack of Provider knowledge and Education
- Lack of Patient understanding and Education
- EMR systems lacking PGx results entry or reporting
- CDS systems do not support PGx decision making and reporting
- Lack of clinical data supporting benefits of PGx
- Clinician concerns on liability associated with genomic Incidentalomes
- Concerns regarding FDA LDT enforcement

Orlando LA, Sperber NR, Voils C, Nichols M, Myers RA, Wu RR, Rakhra-Burris T, Levy KD, Levy M, Pollin TI, Guan Y, Horowitz CR, Ramos M, Kimmel SE, McDonough CW, Madden EB, Damschroder LJ. Developing a common framework for evaluating the implementation of genomic medicine interventions in clinical care: the IGNITE Network's Common Measures Working Group. Genet Med. 2018 Jun;20(6):655-663. doi: 10.1038/gim.2017.144. Epub 2017 Sep 14. Erratum in: Genet Med. 2020 Oct;22(10):1729. PMID: 28914267; PMCID: PMC5851794.

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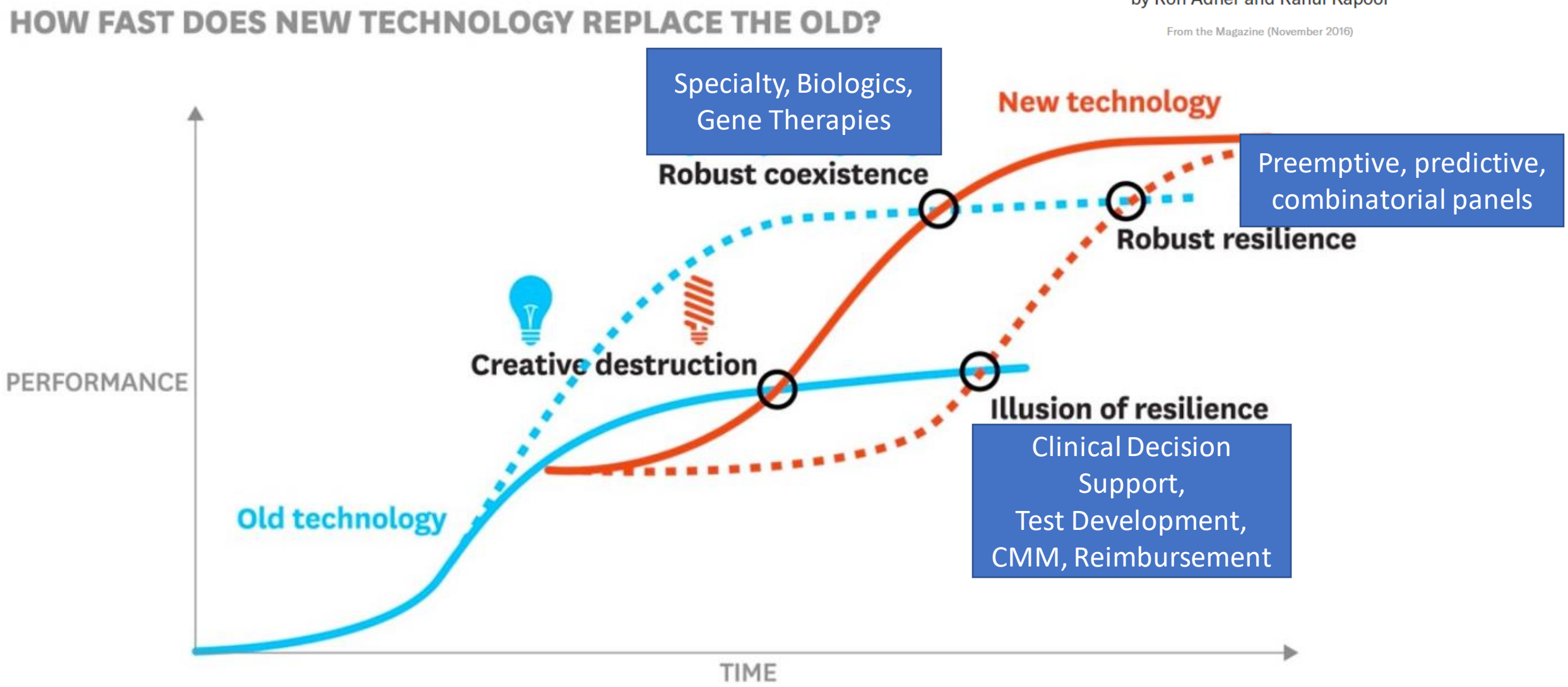


Which PGx test does the provider select?

FDA Oversight of Pharmacogenomics Tests

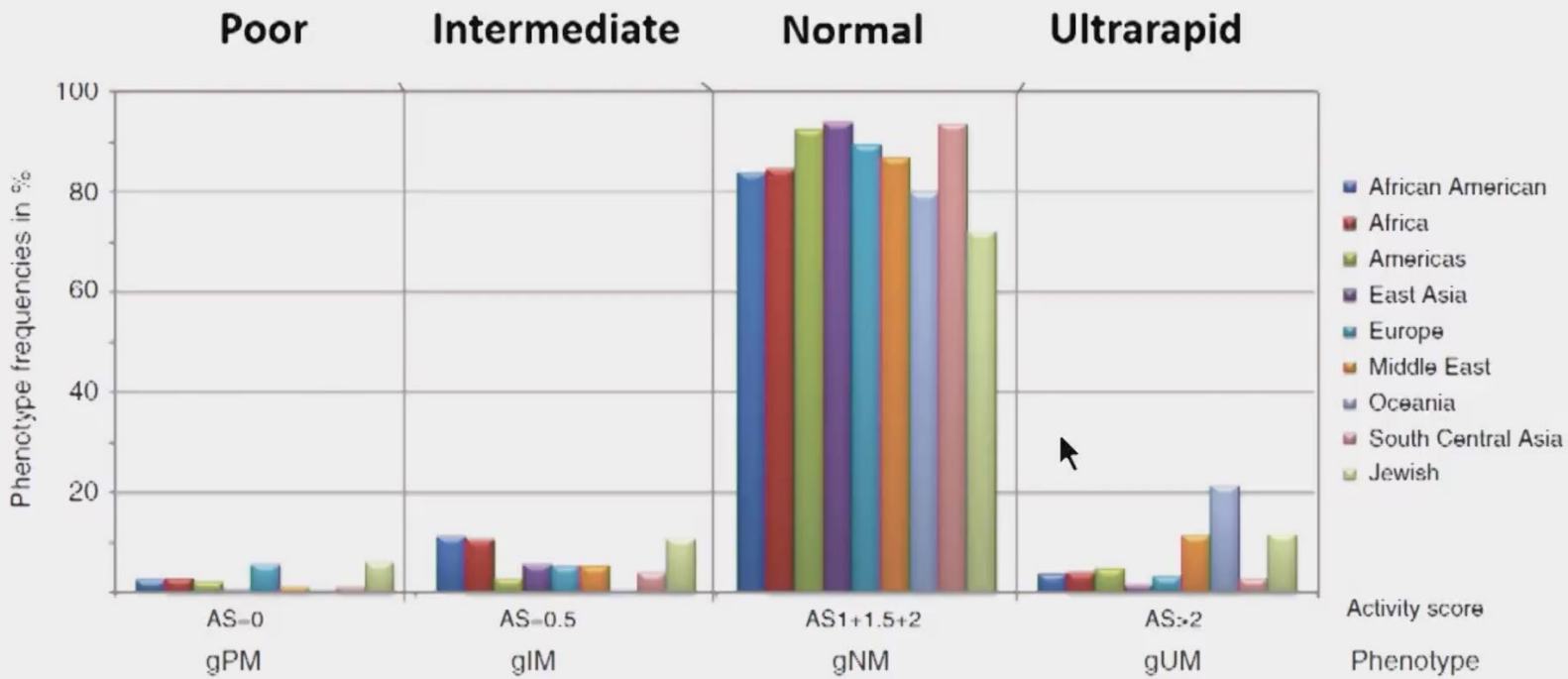
PGx are vitro diagnostic (IVD) tests, they include:

- Laboratory Developed Tests
  - IVD that is designed, manufactured and used within a single laboratory
  - Vast majority of Pgx tests fall in the general category
  - FDA only exercises discretionary oversight, CLIA certified, CAP accredited
- FDA approved companion diagnostic devices
  - Essential for the safe and effective use of a corresponding therapeutic product
  - Resource intensive to complete the approval process
  - Pharma manufacturers cite decreased access for patients
- FDA Approved tests via 510(K) premarket submission process
  - Very few, specific tests - only needed when IVD has potential for serious risk
  - Expensive, changes to test require updated submission
- Direct-to-Consumer Test with Marketing Authorization
  - Only one approved is the 23andMe Pharmacogenomics Report
  - *"This report is for over-the-counter use by adults over the age of 18 and provides genetic information to inform discussions with a healthcare provider about metabolism of therapeutics. This report describes if a person has variants associated with metabolism of some therapeutics, but does not describe if a person will or will not respond to a particular therapeutic, and does not describe the association between detected variants and any specific therapeutic. The PGS Pharmacogenetic Reports are not a substitute for visits to a healthcare provider. The information provided by this report should not be used to start, stop, or change any course of treatment."*

https://www.fda.gov/medical-devices/in-vitro-diagnostics/direct-consumer-tests#list

Global Distribution of ADME Variants

CYP2D6



Phenotype	Activity Score	Examples of CYP2D6 Diplotypes
Ultrarapid metabolizer (~1-2%)	> 2.0	*1/*1xN, *1/*2xN, *2/*2xN
Extensive metabolizer (~77-92%)	2.0-1.0	*1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41
Intermediate metabolizer (~2-11%)	0.5	*4/*10,*4/*41, *5/*9
Poor metabolizers (~5-10%)	0	*3/*4,*4/*4, *5/*5, *5/*6

Gaedigk, et al. Genet Med 2017; Table adapted from PharmGKB.org

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IRESSA® safely and effectively. See full prescribing information for IRESSA.

IRESSA (gefitinib) tablets for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Patient Selection (2.1) 08/2018

INDICATIONS AND USAGE

IRESSA is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. (1)
Limitation of Use: Safety and efficacy of IRESSA have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations. (1)

DOSAGE AND ADMINISTRATION

Recommended dose is 250 mg orally, once daily with or without food. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Interstitial lung disease (ILD): ILD occurred in patients taking IRESSA. Withhold IRESSA for worsening of respiratory symptoms. Discontinue IRESSA if ILD is confirmed. (2.4, 5.1)
- Hepatotoxicity: Obtain periodic liver function testing. Withhold IRESSA for Grade 2 or higher for ALT and/or AST elevations. Discontinue for severe hepatic impairment. (2.4, 5.2)
- Gastrointestinal perforation: Discontinue IRESSA for gastrointestinal perforation. (2.4, 5.3)
- Diarrhea: Withhold IRESSA for Grade 3 or higher diarrhea. (2.4, 5.4)
- Ocular Disorders including Keratitis: Withhold IRESSA for signs and symptoms of severe or worsening ocular disorders including keratitis. Discontinue for persistent ulcerative keratitis. (2.4, 5.5)
- Bullous and Exfoliative Skin Disorders: Withhold IRESSA for Grade 3 or higher skin reactions or exfoliative conditions. (2.4, 5.6)
- Embryo-fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

The most commonly reported adverse drug reactions (ADRs), reported in more than 20% of the patients and greater than placebo were skin reactions and diarrhea. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 Inducer: Increase IRESSA to 500 mg daily in patients receiving a strong CYP3A4 inducer. (2.4, 7.1)
- CYP3A4 Inhibitor: Monitor adverse reactions if concomitant use with IRESSA. (7.1)
- Drugs Affecting Gastric pH: Avoid concomitant use of IRESSA with proton pump inhibitors, if possible. (7.1)
- Hemorrhage in patients taking warfarin: Monitor changes in prothrombin time or INR. (7.2)

USE IN SPECIFIC POPULATIONS

Lactation: Discontinue breast-feeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MAYZENT safely and effectively. See full prescribing information for MAYZENT.

MAYZENT® (siponimod) tablets, for oral use
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------

MAYZENT is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Assessments are required prior to initiating MAYZENT (2.1)
- Titration is required for treatment initiation (2.2, 2.3)
- The recommended maintenance dosage is 2 mg (2.2)
- The recommended maintenance dosage in patients with a CYP2C9 *1/*3 or *2/*3 genotype is 1 mg (2.3)
- First-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 0.25 mg and 2 mg (3)

----------CONTRAINDICATIONS----------

- Patients with a CYP2C9*3/*3 genotype (4)
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure (4)
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker (4)

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to First Dose of MAYZENT

Before initiation of treatment with MAYZENT, assess the following:

CYP2C9 Genotype Determination

Test patients for CYP2C9 variants to determine CYP2C9 genotype *[see Dosage and Administration (2.2, 2.3), Contraindications (4), and Use in Specific Populations (8.6)]*. An FDA-cleared or -approved test for the detection of CYP2C9 variants to direct the use of siponimod is not currently available.

Other non-FDA approved LDTs

HCPL VIRAL RESPIRATORY PANEL

Health Care Providers Laboratory, Inc.

www.healthcareproviderslaboratory.us

Run Summary

Sample ID:	RYNAND0232	**Run Date:**	21 Jun 2013 7:34 PM
Detected:	Influenza A H1-2009 Respiratory Syncytial Virus	**Controls:**	Passed
Equivocal:	None		

Result Summary

Not Detected	Adenovirus
Not Detected	Coronavirus 229E
Not Detected	Coronavirus HKU1
Not Detected	Coronavirus NL63
Not Detected	Coronavirus OC43
Not Detected	**Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)**
Not Detected	Human Metapneumovirus
Not Detected	Human Rhinovirus/Enterovirus
✓ Detected	Influenza A H1-2009
Not Detected	Influenza B
Not Detected	Parainfluenza Virus 1
Not Detected	Parainfluenza Virus 2
Not Detected	Parainfluenza Virus 3
Not Detected	Parainfluenza Virus 4
✓ Detected	Respiratory Syncytial Virus
Not Detected	Bordetella pertussis
Not Detected	Chlamydophila pneumoniae
Not Detected	Mycoplasma pneumoniae

Run Details

Pouch:	Respiratory Panel v 1.7	**Protocol:**	NPS V2.0
Run Status:	Completed	**Operator:**	KMRAP
Serial No.:	00345787z	**Instrument:**	ITI FA "FA2004"
Lot No.:	114612		

Galleri™

Multi-cancer early detection test report

Galleri detects cancer 76% of the time in individuals with these 12 cancers

Cancer signal detection for various cancer classes in CCGA sub-study

Cancers Responsible for ⅔ of All Cancer Deaths in the US[5]

Cancer Classes[6]	Sensitivity[7] (95% CI)
Anus, Bladder, Colon/Rectum, Esophagus, Head and Neck, Liver/Bile-duct, Lung, Lymphoma, Ovary, Pancreas, Plasma Cell Neoplasm, Stomach	76.3% (74.0-78.5%)

Solid Tumors without Common Screening Options[2]

Cancer Classes[6]	Sensitivity[7] (95% CI)
Overall	65.6% (63.0-68.1%)
Anus	81.8% (61.5-92.7%)
Bladder	34.8% (18.8-55.1%)
Esophagus	85.0% (76.7-90.7%)
Gallbladder	70.6% (46.9-86.7%)
Head and Neck	85.7% (77.8-91.1%)
Kidney	18.2% (11.8-26.9%)
Liver/Bile-duct	93.5% (82.5-97.8%)
Lung	74.8% (70.3-78.7%)
Melanoma	46.2% (23.2-70.9%)
Ovary	83.1% (72.2-90.3%)
Pancreas	83.7% (76.6-89.0%)
Sarcoma	60.0% (42.3-75.4%)
Stomach	66.7% (48.8-80.8%)
Thyroid	0.0% (0.0-21.5%)
Urothelial Tract	80.0% (49.0-94.3%)
Uterus	28.0% (21.6-35.5%)
Other[8]	50.8% (38.4-63.2%)

Solid Tumors with Common Screening Options[2]

Cancer Classes[6]	Sensitivity[7] (95% CI)
Overall	33.7% (31.1-36.5%)
Breast	30.5% (26.7-34.6%)
Cervix	80.0% (60.9-91.1%)
Colon/Rectum	82.0% (76.2-86.7%)
Prostate	11.2% (8.5-14.6%)

Hematologic Malignancies[2]

Cancer Classes[6]	Sensitivity[7] (95% CI)
Overall	55.1% (49.3-60.8%)
Lymphoid Leukemia	41.2% (28.8-54.8%)
Lymphoma	56.3% (48.9-63.5%)
Myeloid Neoplasm	20.0% (5.7-51.0%)
Plasma Cell Neoplasm	72.3% (58.2-83.1%)

Galleri detects cancer 66% and 55% of the time in individuals with solid and hematologic cancers, respectively

[1] American Joint Committee on Cancer (AJCC) manual

[2] Solid tumors with common screening options include breast, cervix, colorectal, and prostate cancers. All other cancers found in this CCGA sub-study are grouped into "solid tumors without common screening options" or "hematologic malignancies" categories. Lung cancer is included in the category without common screening options because no broadly adopted guideline-recommended screening for the average risk population currently exists for lung cancer and only 10% of the 55-80 year old population meets current United States Preventive Services Task Force (USPSTF) high-risk criteria for lung cancer screening (Fedewa et al. State Variation in Low-Dose Computed Tomography Scanning for Lung Cancer Screening in the United States. *JNCI 2020*). It is estimated that about two-thirds of diagnosed lung cancers occur in patients who are not eligible for lung cancer screening (Pinsky et al. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? *J Medical Screening 2012*).

[3] 1248 of 1254 non-cancer participants had a "signal not detected" result.

[4] False Positive Rate is calculated as (1-Specificity).

[5] American Cancer Society. *Cancer Facts & Figures 2021*. Atlanta: American Cancer Society; 2021.

[6] Sensitivity is calculated for 24 cancer classes (and additional Other class) that are aggregated into 21 Cancer Signal Origins when reported by the Galleri test.

[7] Includes cancer participants with stage I-IV (96.9%), cancer participants with missing stage (0.7%), and cancer participants (2.4%) who had a cancer type which is not expected to have AJCC stage. To see sensitivity by clinical stage, please visit www.galleri.com/test-report.

[8] Other cancers include Adrenal (N = 1), Ampulla of Vater (N = 1), Brain (N = 6), Choriocarcinoma (N = 1), Mesothelioma (N = 7), Non-melanoma Non-basal Cell Cancer/Squamous Cell Carcinoma Skin Cancer (N = 2), Penis (N = 1), Small Intestine (N = 13), Testis (N = 6), Thymus (N = 2), Vagina (N = 2), Vulva (N = 7), and Other/Unspecified (N = 10).

Test Performance Characteristics continued on page 4

GRAIL

Laboratory Director: Rita Shaknovich, MD, PhD | CLIA #05D2154430 | CAP #8149563
1525 O'Brien Dr., Menlo Park, CA 94025 | 833-MY-GALLERI (833-694-2553) | FAX 650-999-9000 | customerservice@grail.com
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FDA NEWS RELEASE

FDA issues warning letter to genomics lab for illegally marketing genetic test that claims to predict patients' responses to specific medications

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For Immediate Release: April 04, 2019

Today, the U.S. Food and Drug Administration issued a warning letter to Inova Genomics Laboratory (Inova) of Falls Church, Virginia, for illegally marketing certain genetic tests that have not been reviewed by the FDA for safety and effectiveness. The tests claim to predict patients' responses to specific medications based on genetic variants. Selecting or changing drug treatment in response to the test results could lead to potentially serious health consequences for patients. The FDA is unaware of any data establishing that Inova's tests can help patients or health care providers make appropriate treatment decisions for the listed drugs. The action today reflects the agency's commitment to monitor the pharmacogenetic test landscape and take action when appropriate to address a significant

GUIDANCE DOCUMENT

Clinical Decision Support Software

Draft Guidance for Industry and Food and Drug Administration Staff

SEPTEMBER 2019

Download the Draft Guidance Document | Read the Federal Register Notice

Draft

Not for implementation. Contains non-binding recommendations.

Share | Tweet | Linkedin | Email | Print

Docket Number: FDA-2017-D-6569

Issued by: Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research

The Food and Drug Administration (FDA) has long regulated software that meets the definition of a device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including software that is intended to provide decision support for the diagnosis, treatment, prevention, cure, or mitigation of diseases or other conditions (often referred to

Is this a lab test, or a startup?

	Evidence	Projects	Financial	Guidelines	Facilities	Stakeholders	Committee
Stage 1: Pre-Implementation	• Literature Review • Hospital records checked of drug use and diseases	• Review other institutions programs • Suggestions including setbacks	• Funding projects • Reimburse plans • Cost analysis • Feasibility of PGx test	• FDA/EMA • CPIC/PharmGKB • Drug labels • Key clinical areas	• Laboratory equipment • IT infrastructure • Communication platform between departments	• Engagement • Plan for raising awareness	• Appointment with suitable members • Development of protocols • Consider ELSI barriers

	Laboratory	Information technology	Model development
Stage 2: Developmental	• Gene drug pair selection linked to evidence • Population Frequencies • Guidelines check • Compile diplotypes-phenotypes translation tables for interpretation of data • CLIA lab and standard protocols • Internal/external location • Array testing systems • Incidental findings/consent protocol	• CDS development-alerts/consult reports • EHR selection(Cerner/Epic) • Portal development (EHR/PHR) • Language (LOINC/SNOWMED) • Reference links in CDS alert • Databases-information storage, data formats • Omic information consideration • Security measures • Alert fatigue • Assessment of usage/cost/reimbursement	• Point of care/preemptive model • Flow between departments • Movement of information • Professionals involved(patient/physician/pharmacist) • Consider barriers and solutions • Education programs delivery • Outcomes data monitoring

	Stakeholders	Patient	Physician	Program	Evaluation	Collaboration
Stage 3: Clinical Implementation	• Communication • Feedback • Education	• Selection • Consent • Knowledge/awareness	• Acceptance/awareness • Usability • Feedback or recommendations	• Further expansion and improvements • Solutions to barriers	• Further evidence required? • Model Modification • Impact of implementation • Cost effectiveness analysis	• Global projects • Sharing of information

Figure 3. Clinical implementation strategy. Stage 1: Pre-implementation: research and synthesis of data are gathered to prepare the institution for the initial implementation. Stage 2: Developmental phase, all information researched and compiled is used to develop a suitable workflow model for the institution as well as IT infrastructure developed and laboratory operations decided. Stage 3: Clinical implementation and use of the workflow model, where the model is used in the clinic and further solutions to any barriers recorded. PHR, personal health record.

THE STARTUPS DISRUPTING THE PHARMACY SECTOR IN 2020

Which companies are gaining traction and where?

Virtual Pharmacy

NowRx, alto pharmacy, GeniusRx, Truepill, CAPSULE, phil, Carepoint, valisure, scriptdrop, Insightful, MEDLY

Digital Therapeutics

sidekick, PEAR THERAPEUTICS, AKILI, Click Therapeutics, kaia health, NightWare, VOLUNTIS, TABI, MEDRhythms, orexo, welldoc

Chronic Disease Management

PACK HEALTH, TILAK, Kaiku HEALTH, CareSignal, ginger, BehaVR, vida, virta, Veta Health, Healthy Quit, Digital Health-Pharmacy, Catalia Health, CANARY HEALTH, AVENUE, omada, onduo, lyra, Kardia, Hello Heart, IKONA, glooko

Pharmacogenomics

TOPG, 2bPrecise, MyGenome Rx, youscript, GENETICURE, genome MEDICAL, admera health, OneOme, GenXys Health Care Systems

Home Lab Testing & Monitoring

TestCard, inui, elektra labs, Scanwell, myLAB, everlywell, LetsGet Checked, Healthy.io, 1DROP DIAGNOSTICS, biofourmis

Direct-to-Consumer Prescription Services

LEMONAID, Dear Brightly, Curology, NURX, cove, hims & hers, Apostrophe, PILL CLUB, alpha, wisp, RORY, BLINK HEALTH, ro

Expand Pharmacist Services & Workflow

VUCAHEALTH, RXVIP Concierge, AZOVA, InpharmD, VigiLanz, arine, orbitalRX, PHOX HEALTH, Amplicare, Insight RX, AdhereHealth ADHERENCE RESOLVED, PHARMASALON, prescryptive, PHARMAPOINT, illuminate.health, aspen RxHealth, Troy MEDICARE, DIGITAL PHARMACIST, DocStation, AudibleRx, STACK, CONSANA, KITCHECK, cureatr comprehensive medication management, CHC Health, with me HEALTH, VAXITAXI.com

2020 EXITS & ACQUISITIONS

Who went public or got bought?

- **GoodRx** (IPO) — Went public launching their IPO in November 2020.
- **MedAvail** — Acquired MYOS RENS Technology and became listed in November 2020 .
- **divvyDOSE** — UnitedHealth acquired divvyDose in September 2020 for around $300M.
- **Livongo** — Teladoc acquired Livongo for $18.5B in October 2020.
- **zipdrug** — Anthems' new PBM (IngenioRx) acquires ZipDrug for an unknown amount in July 2020.

2021 PREDICTIONS

What happens post-COVID19?

MORE DELIVERIES
Post-pandemic will see patients more inclined to stop going into the pharmacy and see more mail order, meaning also pivoting other pharmacy products (eg. OTC).

FOCUS ON VACCINATIONS
With a likely need to use pharmacists to boost the vaccination needs of the public, there will be a focus on companies expanding their platforms to leverage or champion these services which may be a short term service.

REMOTE CARE
Pharmacy businesses will see a push for using remote care via RPM or DTx to add further clinical services - medication management and mental health are large areas.

IN PHARMACY SERVICES
Brick and mortar pharmacies will seek to expand services to draw customers back in, such as testing or a push for expanded clinical services only face-to-face can accomplish.

MOBILE ENGAGEMENT
No matter what, post-covid will see consumers of health expect mobile first then in-person if not feasible. Companies will stregthen mobile platforms and clinical services.

TheDigitalApothecary.com

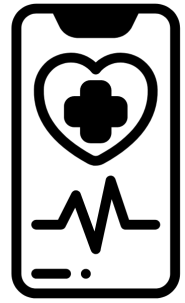
Ver. 3.2 | Last updated December 15, 2020

Created by
TIMOTHY AUNGST, PHARMD

Digital Health Startup Channels

Provider Referral

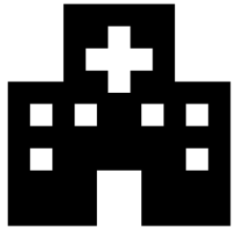
Payer Sponsored Program



Direct to Consumer

Patient

Provider Referred



Primary care in the community
- Fee for service vs value-based care
- Shortage of primary care physicians
- Prescriber education and training
- The role of community pharmacist

Vertically integrated academic health system – acute care
- Reimbursement based on DRG fee structure
  - Demonstrate cost savings
- Episodic care
- The role of Hospital Pharmacists – basement vs floor?

Barriers to prescriber buy in:
- Resistant to adapting workflow, solution must save time, make things easier
- Desire to treat patients consistently and systematically
- Reimbursement for ongoing services vs just the lab test

Opportunities in specialty practice settings
- Oncology (mainly diagnostic and FDA approved companion diagnostics)
- Transplant
- Pain/Anesthesia
- Mental behavioral health

Pharmacogenetic Testing

Policy Number: 2022T0587J
Effective Date: January 1, 2022

Instructions for Use

Table of Contents Page

Related Commercial Policies
- Cardiovascular Disease Risk Tests

Community Plan Policy
- Pharmacogenetic Testing

Medicare Advantage Coverage Summaries
- Genetic Testing
- Laboratory Tests and Services

Coverage Rationale

The use of pharmacogenetic Multi-Gene Panels to guide therapy decisions is proven and medically necessary for antidepressant and antipsychotic medications when all the following criteria are met:
- The individual has a diagnosis of major depressive disorder or generalized anxiety disorder; and
- The individual has failed at least one prior medication to treat their condition; and
- The Multi-Gene Panel has no more than 15 relevant genes

The use of pharmacogenetic Multi-Gene Panels for genetic polymorphisms for any other indication, including but not limited to pain management, cardiovascular drugs, anthracyclines, or polypharmacy, is unproven and not medically necessary for evaluating drug-metabolizer status due to insufficient evidence of efficacy.
Examples of these Panels include, but are not limited to the following:
- GeneSight® Analgesic
- GeneSight® ADHD
- SureGene Test
- Pain Medication DNA Insights®
- PharmacoDx

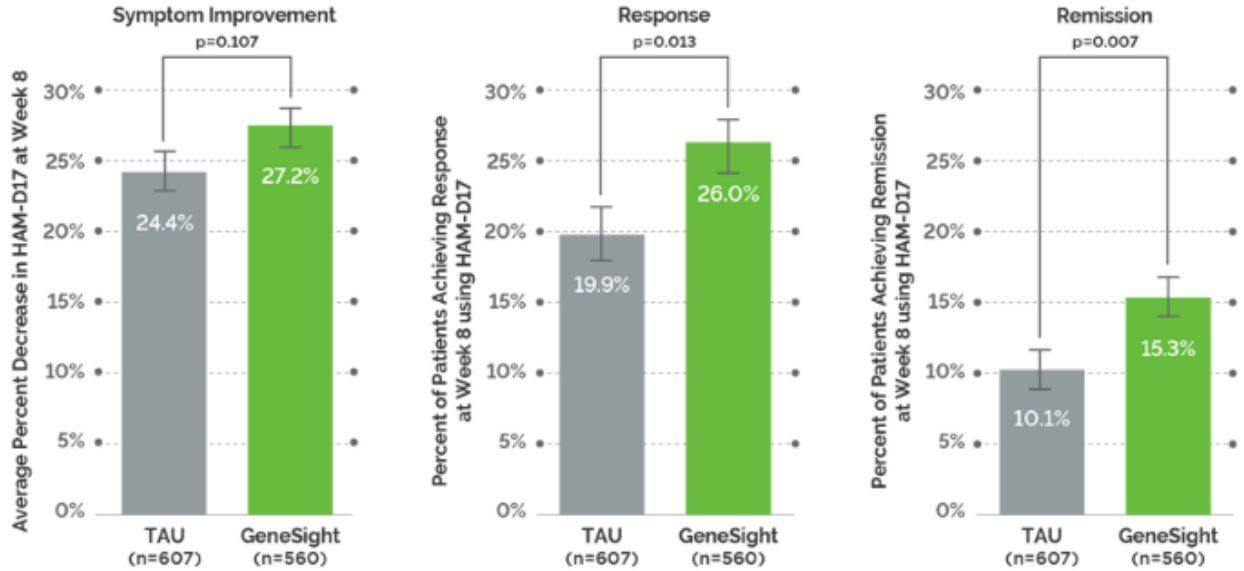
The use of the PrismRA® molecular signature test is unproven and not medically necessary for evaluating likelihood of inadequate response to anti-TNF therapies for rheumatoid arthritis due to insufficient evidence of efficacy.

GUIDED (Genomics Used to Improve DEpression Decisions) Clinical Study

Study Design: This was an 8 week, blinded, multi-center, randomized controlled trial of 1,167 subjects with major depressive disorder from 20 academic sites and 40 community sites. The trial was unblinded after the 8 week check-in, and the subjects were followed out to 24 weeks. The study assessed the impact of the GeneSight Psychotropic test on psychiatric treatment response compared to treatment as usual (TAU). The raters used the Hamilton Rating Scale for Depression (HAM-D17), and the subjects had to have a minimum score of 14 in order to be eligible for the study.

Study Endpoints: GUIDED compared two active treatment arms. The primary endpoint was symptom improvement with secondary endpoints of response and remission. Symptom improvement is defined as the change in HAM-D17 score, and this is based on the group average. Response is defined as a ≥50% reduction in HAM-D17 score, and remission is defined as a HAM-D17 score ≤7.

Study Limitations: The treating clinician was not blinded to study arm, the majority of the cohort was Caucasian, the primary results may not be generalizable for patients with mild depression, and the impact of polypharmacy on patient outcomes was not evaluated.



Key Findings

Directional improvement in symptoms: On the primary endpoint of symptom improvement, the data trended toward but did not achieve statistical significance between GeneSight and TAU arms at week 8.

Significant improvement in response and remission: There were statistically significant and clinically meaningful increases in response and remission rates in the GeneSight arm versus the TAU arm at week 8.

The GeneSight effect on all endpoints was durable over 6 months: Symptom improvement, response, and remission continued to improve after unblinding at week 8 and up to 6 months.

Switching to a medication with no or moderate gene drug interaction improved patient outcomes: Symptom improvement, response, and remission were significantly improved when patients on a medication with significant gene-drug interactions were switched to a medication with no or

		response	probability after treatment with clozapine	ICER: 47,705$/QALY	based on WTP
Rejon-Parrilla et al. [54]	SCZ	*CYP2D6*	ADE probabilities owing to risperidone treatment	ICER: 19,252$/QALY	Likely to be cost-effective based on WTP
Hornberger et al. [48]	MDD	*CYP2D6, CYP2C19, CYP2C9, CYP1A2, SLC6A4,* and *HTR2A*	Treatment response and mortality rates	3764$ total cost savings ICER: −11,911$/QALY	PGx dominates the treatment as usual, Cost-saving
Olgiati et al. [51]	MDD	*5-HTTLPR*	Probabilities of remission, lack of remission and dropout	Euro A: 1147$/QALW Euro B: 1185$/QALW Euro C: 1178$/QALW	Cost-effective in high-income countries
Sluiter et al. [56]	MDD	*CYP2D6*	ADE occurrence	ICER: 77,406$/QALY	Likely to be cost-effective based on WTP
Groessl et al. [46]	MDD	IDgenetix (IDGx) PGx test	Response and mortality rates	ICER: −25,980$/QALY (MDD) ICER: −34,176$/QALY (Severely Depressed)	Cost-saving, Cost-effective and dominant
Girardin et al. [45]	SCZ	*HLA-DBQ1/HLA-B*	Clozapine response	ICER: 3.93 million/QALY	Cost-effective
Perlis et al. [53]	MDD	(SNP) in the serotonin 2A receptor *(HTR2A)* gene	Mortality, relapse, and remission rate	ICER: 93,520$/QALY	Likely to be cost-effective based on WTP
Berm et al. [42]	MDD	*CYP2D6*	ADR occurrence and efficacy of treatment with nortriptyline or trancylpromine	ICER: 1.33 million/QALY	Not cost-effective
Serretti et al. [55]	MDD	*5-HTTLPR*	Remission rates and delay in antidepressant response	ICER: 2890$/QALY	Cost-effective
Najafzadeh et al. [50]	Dep. & Anx.	IDgenetix (IDGx) PGx test	Remission and response rates	ICER: 1394$/QALY (based on direct costs)	Cost-effective and cost-saving
Herbild et al. [47]	SCZ	*CYP2D6, CYP2C19*	–	Actual excess costs for the extreme metabolizers group: 67,064$, Decrease of excess costs after PGx testing: 46,532$	Cost-saving
Winner et al. [57]	Psy diseases	GeneSight panel: *CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4* and *CYP1A2; SLC6A4* and *HTR2A.*	Adherence compared to standard of care	Medication savings after PGx: 1035.60$. Improved adherence after PGX testing: 0.11; Pharmacy cost savings averaged: 2774.53$	Cost-saving
Brown et al. [43]	Psy diseases	GeneSight panel: *CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4* and *CYP1A2; SLC6A4* and *HTR2A*	–	Medication cost savings for payers and patients of 3988$ per member per year ($p < 0.001$)	Cost-saving
Maciel et al. [49]	Dep & Anx.	NeurolDgenetix genetic testing: *COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, HTR2A, MTHFR, SLC6A4*	Response or remission rates	Remission rate in the experimental group: 35%; response rate in the experimental group: 73%; Total annual saving after PGx testing per patient: 3962$	Cost-saving
Fagerness et al. [44]	Psy diseases	*CYP2D6, CYP2C19, SLC6A4, CACNA1C, DRD2, COMT, MTHFR*	Adherence to medication	Better medication adherence by using PGx. Cost-saving in outpatient costs over 4-month follow-up period 9.5% or 562$ in total savings	Improved adherence and cost-saving
Benitez et al. [41]	Psy diseases	*GeneSight panel: CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4* and *CYP1A2; SLC6A4* and *HTR2A.*	–	Post-index cost savings (US 5505$) drove a per-member-per-month savings of US 0.07$.	Cost-saving
Winner et al. [58]	Dep & Anx.	*GeneSight panel: CYP2D6, CYP2C19, CYP2C9,*	Health care visits	Poor metabolizers had 69% more total health care	Increased health care

Karamperis, Kariofyllis et al. "Economic Evaluation in Psychiatric Pharmacogenomics: a Systematic Review." The pharmacogenomics journal 21.4 (2021): 533–541. Web.

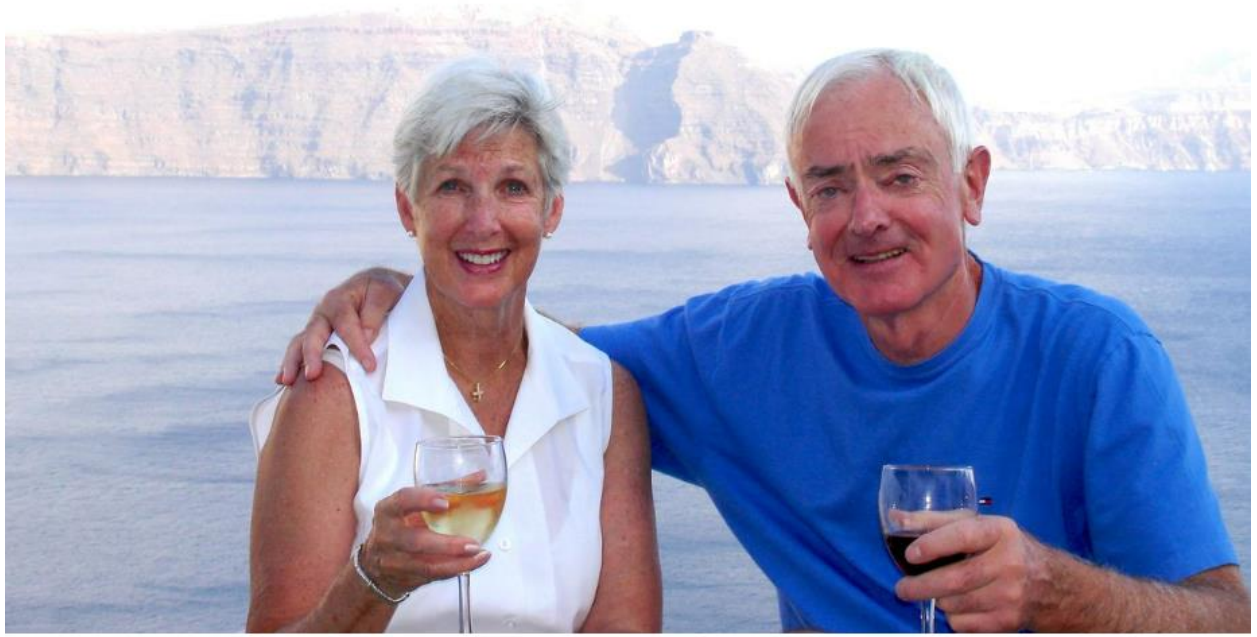
Nystrom & Associates, Ltd.
20 Januari 2020 ·

We are excited to announce Optum and Genoa Healthcare Pharmacies have partnered with us for a pharmacogenomics pilot to complete GeneSight tests for major depressive disorder in New Brighton. Schedule an appointment to talk with a psychiatric medication provider to learn more!
http://bit.ly/2OM51eT

Health

OHSU to pay $1 million, promises change to settle lawsuit from widow of cancer patient

Updated: May. 04, 2022, 11:05 a.m. | Published: May. 04, 2022, 7:00 a.m.



David McIntyre had a fatal reaction to OHSU's chemotherapy for his cancer, his wife, left, claims in a lawsuit filed against the university.

- Treatment of bile duct cancer with 5-fluorouracil
- DPYD genetic mutation associated with 5-FU toxicity in approximately 3-5% of the population
- *OHSU denied fault in the case, saying in an email it "has followed, and continues to follow, national cancer and evidence-based medicine set forth by national expert consensus in the field."*
- *Although OHSU said testing for the genetic condition isn't standard practice, the university is nonetheless going to include education on the condition in its Oncology Fellowship program. It is also going to create a guide that describes the condition and how to identify symptoms of a toxic reaction to the chemotherapy drug.*
- McIntyre's suit originally asked for $6.4 million.

Payer Sponsored

Challenges

- Engagement, conversion, retention are common barriers
- Program tends to go around the primary care physician
- Need to build extensive enabling services (i.e. virtual provider, EMR like systems, etc.)

Opportunities

- Clinical programs like Medication Therapy Management are required of Medicare Part D plans

Medco's Clinical Department late 2000's

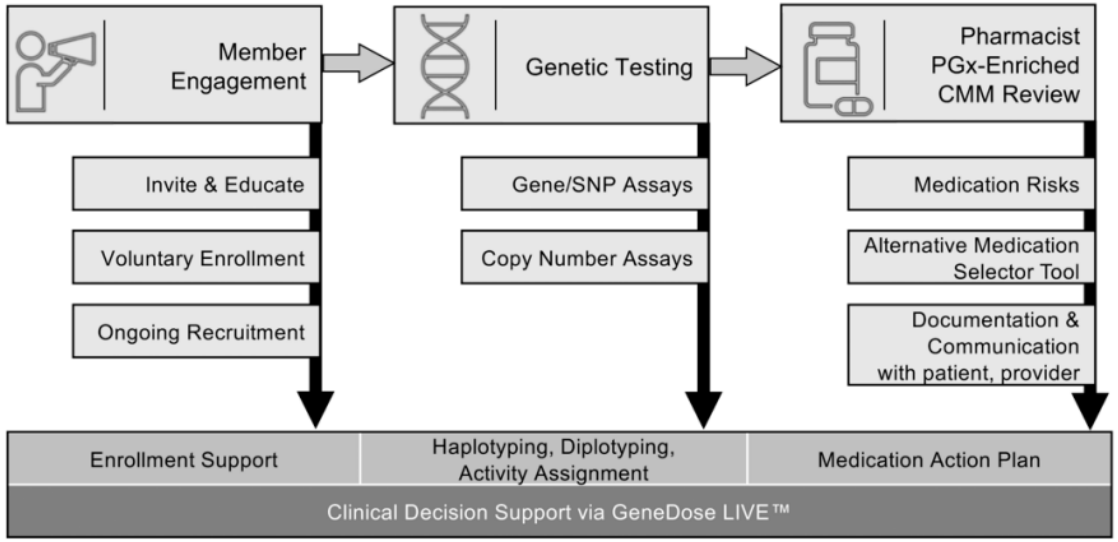
- Corresponding rise in PGx testing in clinical practice
- Design and implementation of rational benefit coverage polices
  - Capture cost efficiencies
  - Improve medication safety and effectiveness
- Establishing a Laboratory and Therapeutics Committee
  - Laboratory experts, geneticists to determine clinical validity and utility of LDT's
- Utilizing prior authorization guidelines that require Pgx testing
- Health economic studies that demonstrate the value of tests and companion clinical programming
- Acquired by Express Scripts

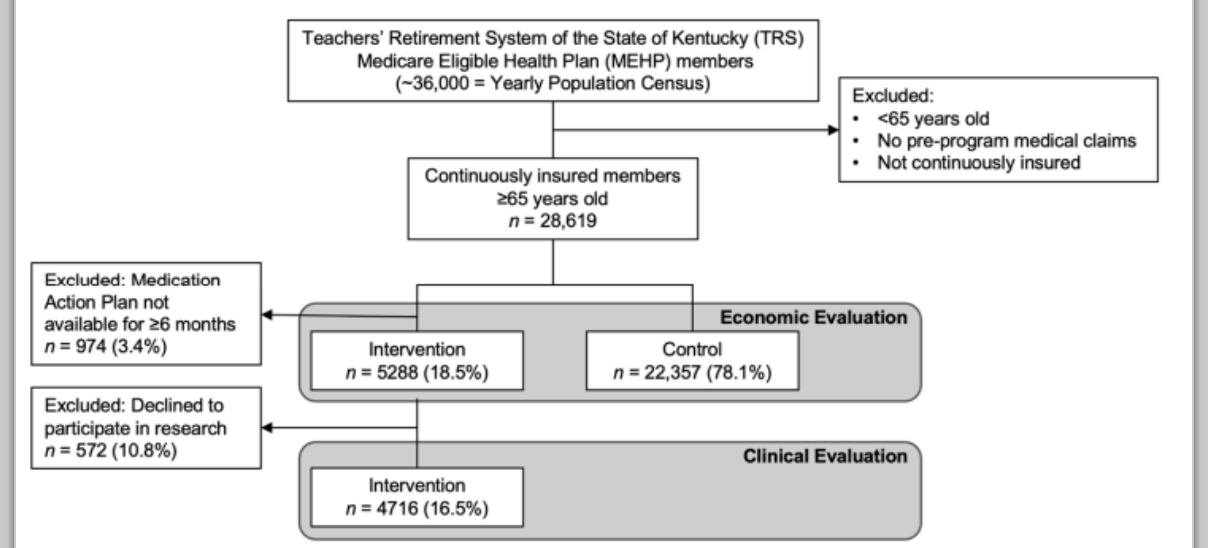
On Pharmacogenomics in Pharmacy Benefit Management

J. Russell Teagarden, M.A., D.M.H., and Eric J. Stanek, Pharm.D.

Recently, the separate trajectories of pharmacy benefit management and pharmacogenomics converged. Pharmacogenomic tests have become more widely available for clinical use and at costs within the range of typical health care services. Pharmacy benefit payers continue to seek the precision they can apply to their coverage policies and clinical programs that pharmacogenomics offers. We describe how pharmacogenomics can now make sense as part of a pharmacy benefit and also how pharmacogenomics can be applied in a benefit coverage policy and clinical programs. Detail is provided on clinical program development and implementation processes featuring pharmacogenomics. We also discuss the research needed to support ongoing program development involving pharmacogenomics and describe the current roles of benefit payers and administrators in these research efforts. The legal and ethical dimensions of applying pharmacogenomics in pharmacy benefits are covered and in particular how benefit payers and administrators need to navigate between genetic exceptionalism and applicable laws and regulations. Finally, some thoughts are provided on future opportunities and challenges for pharmacogenomics in pharmacy benefit management and pharmacy in general.
Key Words: pharmacy practice, pharmacogenomics, managed care.
(Pharmacotherapy 2012;32(2):103–111)

Real-World Impact of a Pharmacogenomics-Enriched Comprehensive Medication Management Program[1]





1) Jarvis JP, Peter AP, Keogh M, Baldasare V, Beanland GM, Wilkerson ZT, Kradel S, Shaman JA. Real-World Impact of a Pharmacogenomics-Enriched Comprehensive Medication Management Program. J Pers Med. 2022 Mar 8;12(3):421. doi: 10.3390/jpm12030421. PMID: 35330421; PMCID: PMC8949247.

Medical Cost Savings Studies

Program	Year	Population	Savings	Citation
Coriell Life Science PGx Panel, Clinical Decision Support System + Comprehensive Medication Management	2022	5288 Kentucky School District Teachers Retirees	Estimated ~$7000 per patient in direct medical charges saved	Jarvis JP, Peter AP, Keogh M, Baldasare V, Beanland GM, Wilkerson ZT, Kradel S, Shaman JA. Real-World Impact of a Pharmacogenomics-Enriched Comprehensive Medication Management Program. J Pers Med. 2022 Mar 8;12(3):421
Tabula Rasa PGx Panel test plus CDS system + Clinical Pharmacist Intervention	2020	200 randomly selected program of all-inclusive care for the elderly (PACE) participants	$1983 avoided outpatient drug costs per participant	Bain KT, Knowlton CH, Matos A. Cost avoidance related to a pharmacist-led pharmacogenomics service for the Program of All-inclusive Care for the Elderly. Pharmacogenomics. 2020 Jul;21(10):651-661. doi: 10.2217/pgs-2019-0197. Epub 2020 Jun 9. PMID: 32515286.
Genelex PGx Panel + Youscripts clinical decision support tool + pharmacist intervention	2015	205 commercial patients, >64 y/o at 3 clinical sites	$1132 in health resource utilization cost reduction	Brixner D, Biltaji E, Bress A, Unni S, Ye X, Mamiya T, Ashcraft K, Biskupiak J. The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. J Med Econ. 2016;19(3):213-28. doi: 10.3111/13696998.2015.1110160. Epub 2015 Nov 11. PMID: 26478982.

HEALTH PLANS HAVE STARTED TO OFFER DIGITAL ECOSYSTEMS TO THEIR MEMBERS

DIGITAL HEALTH PLATFORMS OF US HEALTH PLANS (EXAMPLE)

PLATFORMS (# solutions)	CVS Health. POINT SOLUTIONS MANAGEMENT (12)	EVERNORTH DIGITAL HEALTH FORMULARY (12)	Walgreens FIND CARE (8)
Diabetes Care		Livongo, omada, Lifescan	FreeStyle Libre
Cardiovascular Care	Hello Heart	Livongo, omada	
Pulmonary Care		Propeller, Quit Genius	
Behavioural Health Care	whil, Sleepio, wondr HEALTH, daylight	learntolive, SilverCloud	betterhelp, SANVELLO
Women's Health Care	progyny	WILDFLOWER	
Musculoskeletal Care	Hinge Health	Hinge Health, omada, recoveryone	Hinge Health, spinezone
Caregiver Care	torchlight	Prevail	myPRIVIA
Other	WW, vida, PrudentRx, kurbo by	buoy	lexie, cologuard

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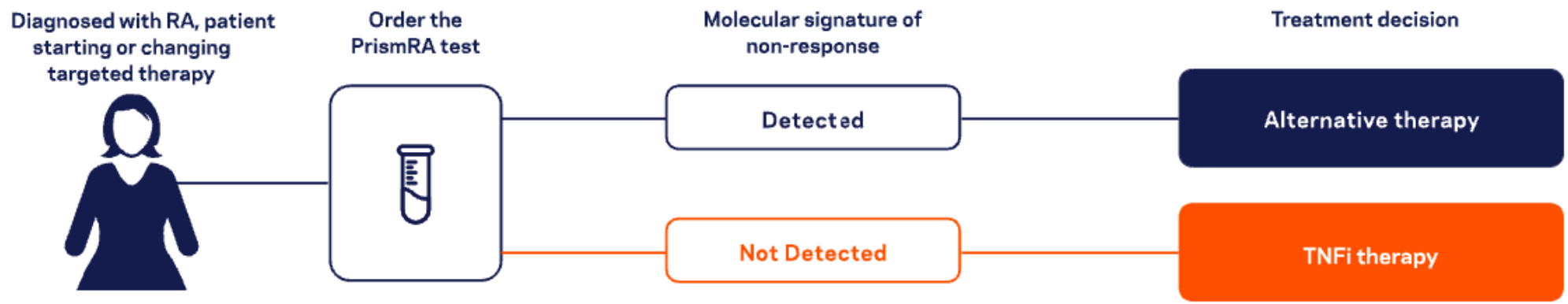
R2G Research 2 Guidance

Deciphering molecular signatures can predict how patients will respond to different therapies



Incorporating PrismRA into clinical management of patients with RA can improve patient quality of life and save time by enabling physicians to prescribe a more effective therapy sooner.[1,2]

Vertical Business Relationships Among Insurers, PBMs, Specialty Pharmacies, and Providers, 2021

1. Cigna partners with providers via its Cigna Collaborative Care program. However, Cigna does not directly own healthcare providers.
2. AllianceRx Walgreens Prime is jointly owned by Prime Therapeutics and Walgreens Boots Alliance.
3. Since 2020, Prime sources formulary rebates via Ascent Health Services. In 2021, Humana began sourcing formulary rebates via Ascent Health Services for its commercial plans.

Source: Drug Channels Institute research; Companies are listed alphabetically by insurer name.

This chart appears as Exhibit 210 in *The 2021 Economic Report on U.S. Pharmacies and Pharmacy Benefit Managers*. Available at http://drugch.nl/pharmacy

DRUG CHANNELS INSTITUTE

March 2021

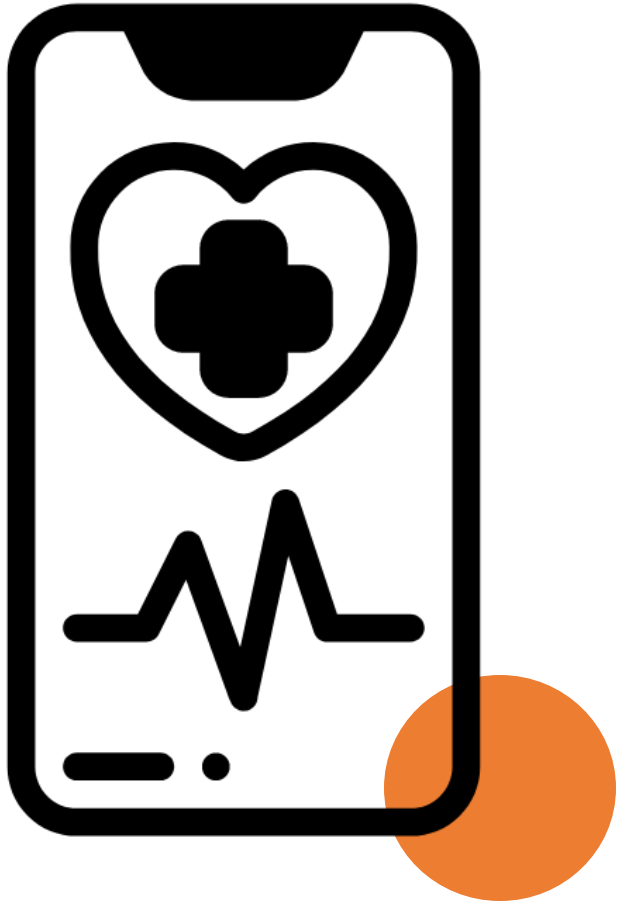
Direct to Consumer

Challenges:

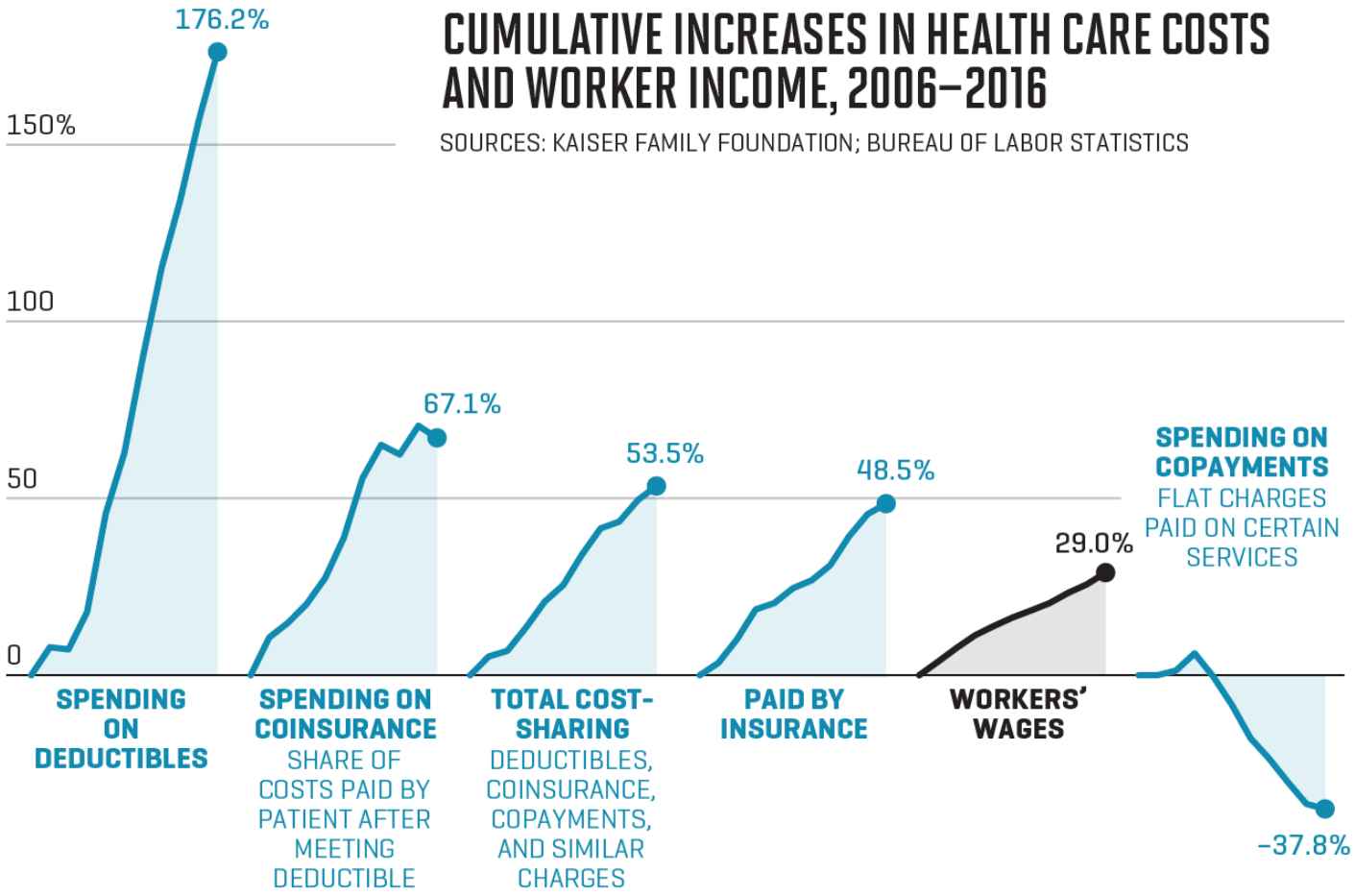
- Willingness to pay
- Ability to pay
- Cold start problem
- Program goes around the payer, and doctor
- Regulatory oversight

Opportunities:

- Possible to enroll many people quickly, effeciently
- Consumer experience is key



Healthcare Consumerism on the Rise



https://fortune.com/2019/03/25/health-care-costs-employees-medicare/

PHARMAZAM

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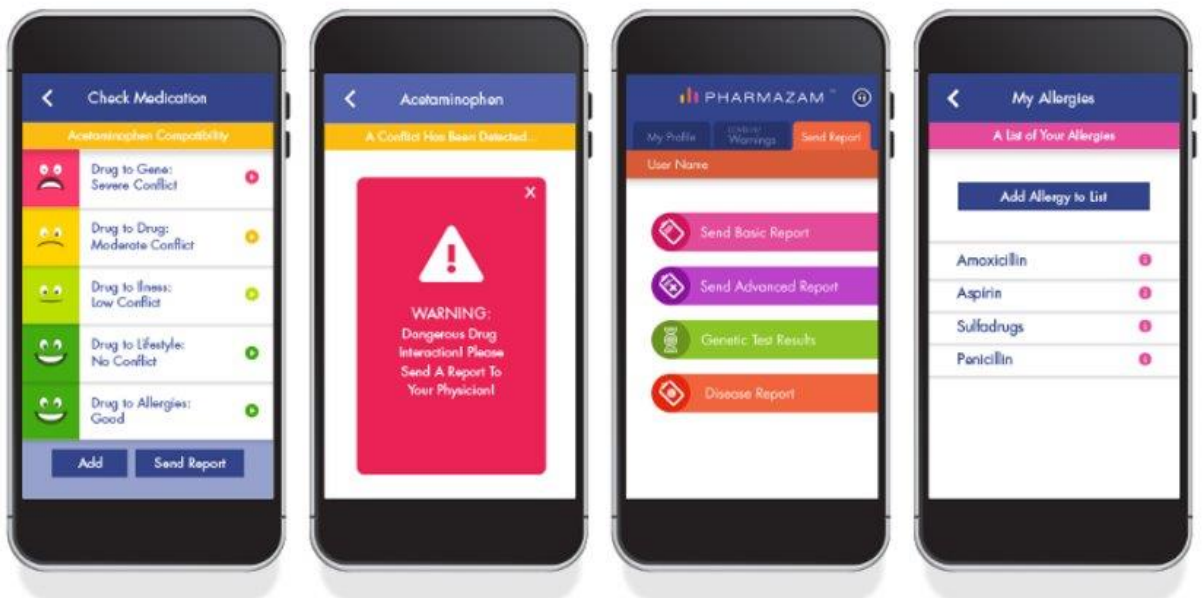
Home | How It Works | Get Tested | App | Pharmazam MD | FAQ | Solutions | Team | News | Contact

Pharmazam is a real-time personalized healthcare management system that can also deliver real-time emergency alerts such as information on pandemics or other healthcare issues

Pharmazam Also Helps Your Physician Determine Your Chances of getting over 4400 different diseases that have been tied to genetic anomalies and can be taken by anyone over 6 weeks old.

A baby cannot talk, but their genetics can!



Download the Pharmazam App | iPhone/iPad App | Android App

Growing consumer value over time

Prescriptions	Subscriptions	Pharmaceutical Manufacturer Solutions	Telehealth	Marketplace
				
Strong standalone unit economics	Upsell increases consumer savings and LTV	20% of GoodRx searches are for brand drugs[1]	20% of consumers don't have a prescription[2]	Expanding services and solutions

Increased consumer value

[1] data, 2019-2020.
[2] data, 2020.

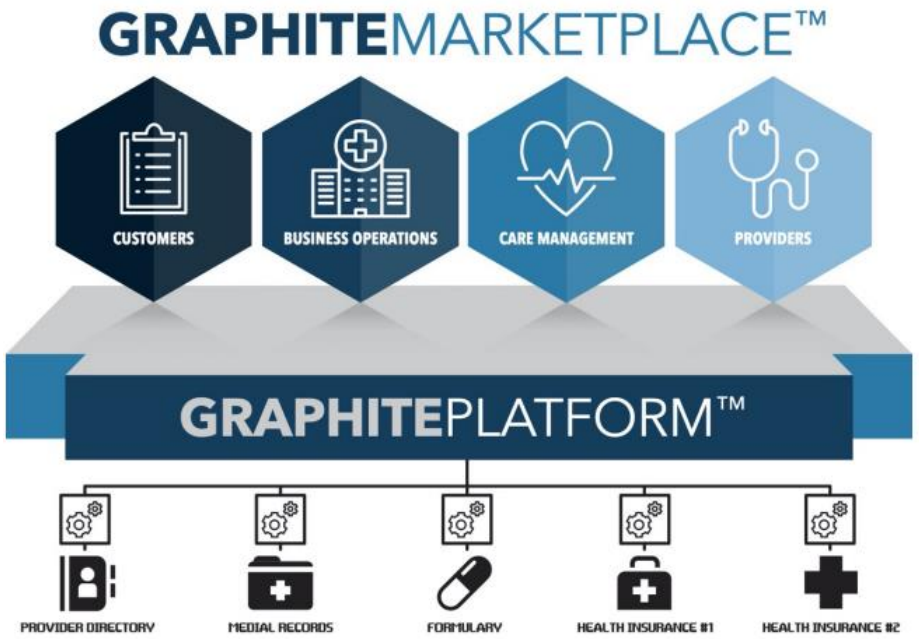
Governing Members

Presbyterian Healthcare Services

Intermountain Healthcare

SSM Health

Kaiser Permanente



The Graphite Marketplace will provide four different types of applications:

- **Consumer-facing apps.** This is where customers or patients can download applications that offer information relevant to them. Such applications may include tools that explain medication or laboratory tests.
- **Care coordination apps.** These are tools for monitoring and proactively treating patients. The health system monitors the resulting information. Applications could include IoT-related devices and data that help manage congestive heart failure, diabetes, and COPD.
- **Business efficiency apps.** Apps offered would focus on data management, efficiency, and utilization. The solutions could range from tools for creating care registries to analytic packages that transform the platform into a system of insights.
- **Provider satisfaction apps:** This represents apps that decrease documentation drudgery, improve efficiency, and enable healthcare providers to more efficiently access information.

Thank You

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