Pharmacogenomics Overview

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National PHASER Pharmacy Program Manager

Learning Objectives

- Evaluate the clinical utility of pharmacogenomics
- Identify pharmacogenomics implementation challenges
- Describe strategies for stakeholder engagement in pharmacogenomics implementation

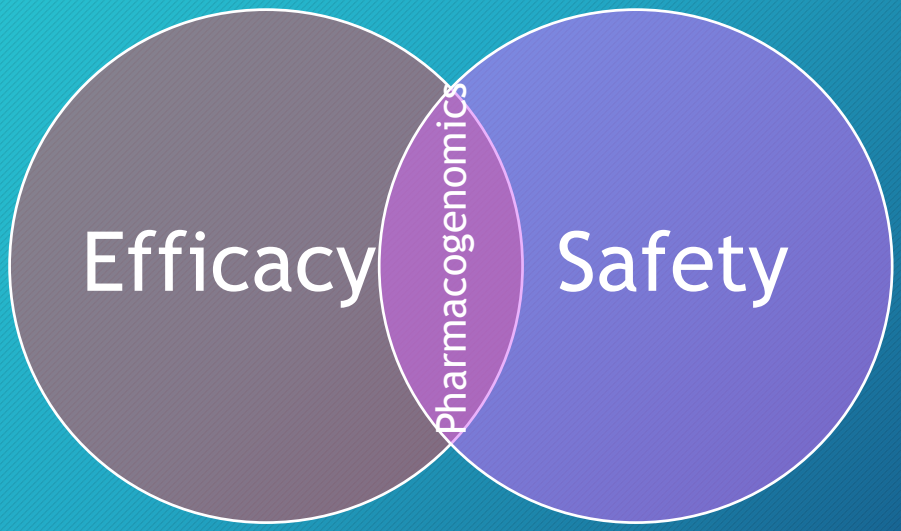
Quadruple Aim

- Better health
- Better patient experience
- Lower costs
- Improved clinician satisfaction

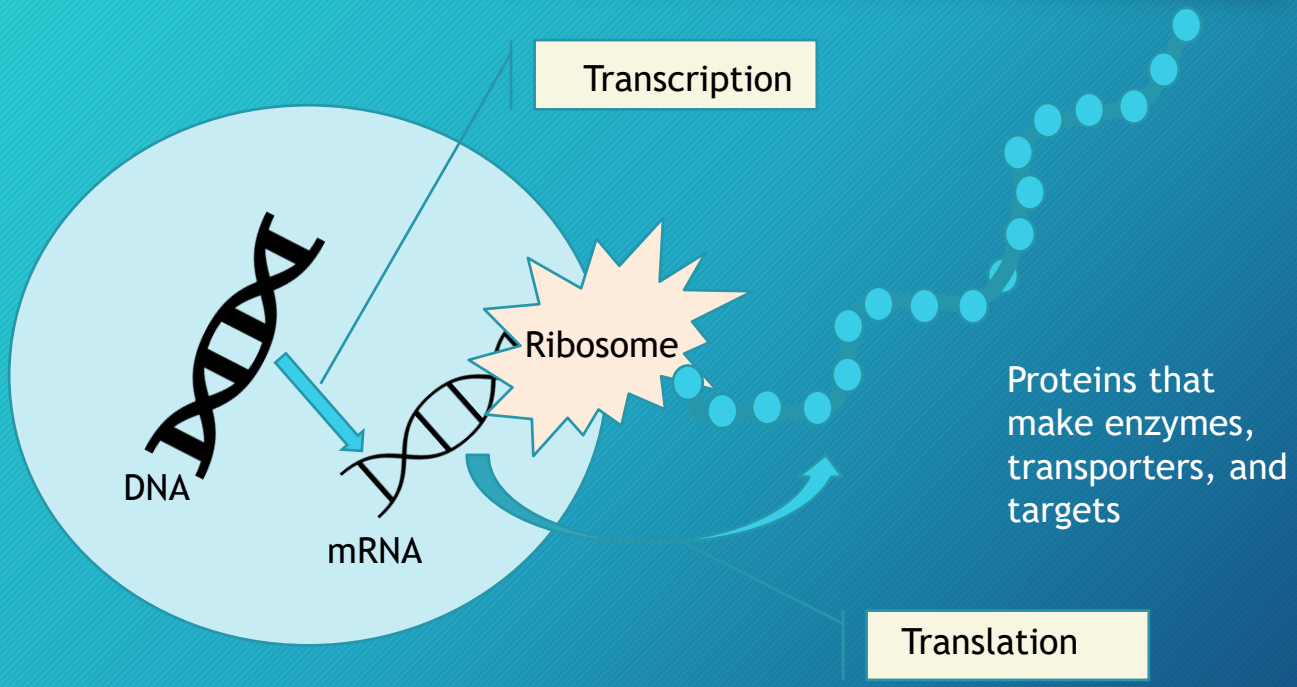
Brooks FA, et al. ASCO Ed book. 2017;833-40..

Pharmacogenomics (PGx)

- The study of how a person's genetic makeup can affect their response to a drug



Gene expression = Protein synthesis

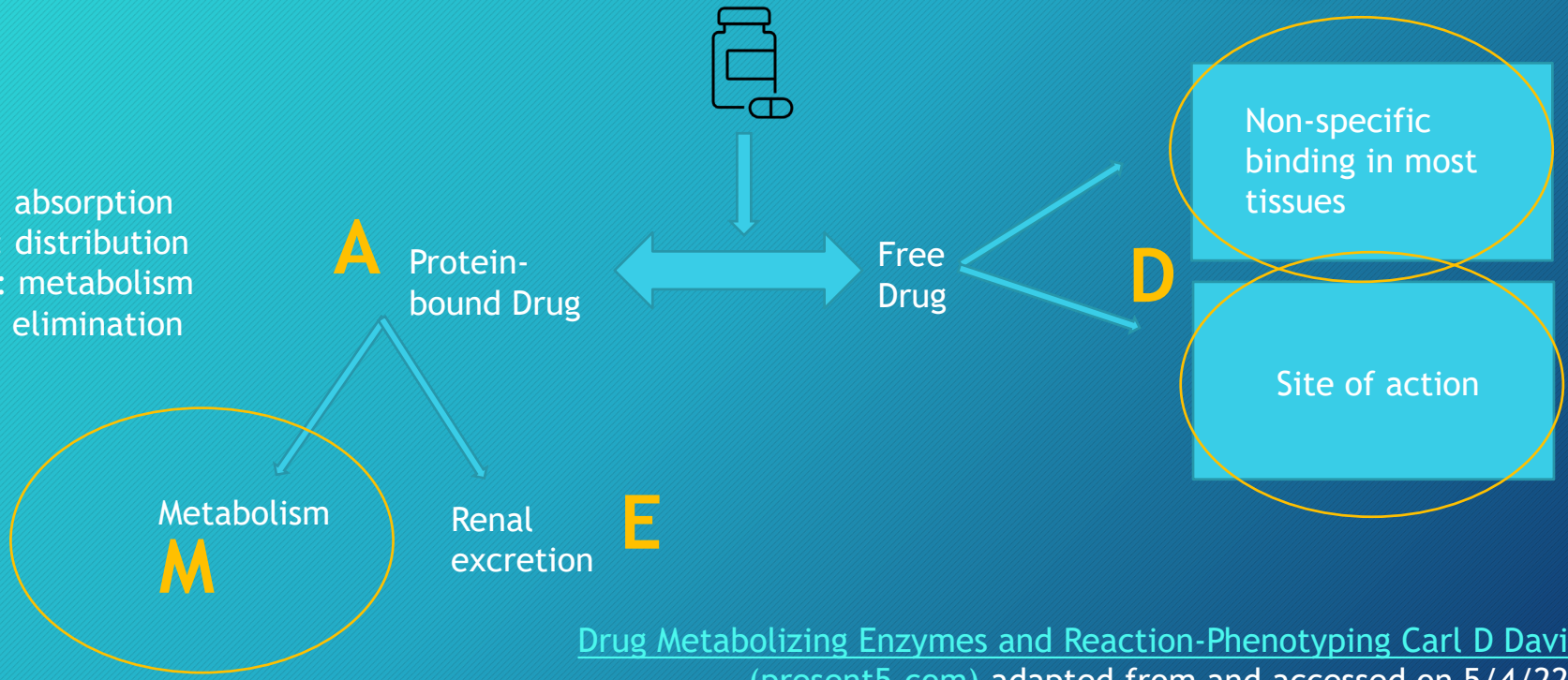


Drug-Gene Interaction

- A drug-gene interaction is said to occur when the disposition or effects of a drug are altered by a protein that is derived from variation in its gene
- Drug-gene interactions can involve proteins that function as drug metabolizing enzymes, transporters, or targets

PGx and ADME

A: absorption
D: distribution
M: metabolism
E: elimination



Drug Metabolizing Enzymes and Reaction-Phenotyping Carl D Davis (present5.com) adapted from and accessed on 5/4/22.

Approaches to PGx

Group #1: "Pre-emptive PGx"

- Any Veteran may benefit
- 1 in 2 Veterans will be prescribed an affected medication in the long-term.

Group #2: "Reactive PGx"

- Patients with high-risk diagnoses who are expected to (or have recently started) high-risk medications:
  - —Clopidogrel
  - —SSRIs
  - —Fluoropyrimidine
  - —Opioids
  - —Thiopurines

Group #3: "Diagnostic PGx"

- Patients with sub-optimal response to medicine on the PHASER panel:
  - —Lack of therapeutic response (e.g., depression symptoms)
  - —Treatment limiting side-effects (e.g., myalgias with statins)

What is Clinical Utility?

- The ability of a screening or diagnostic test to prevent or ameliorate adverse health outcomes
- Broad---includes ethical, legal, and social implications
- The clinical utility of a test depends on effective access to appropriate interventions

Grosse, S.D., Khoury, M.J. Gen Med. 2006;8:448-50.

PGx-Associated Clinical Outcomes

- Therapeutic choice: the use of test results in clinical management of an individual with a diagnosed disorder
- Outcomes: morbidity, mortality, quality of life, societal impacts, cost effectiveness

Grosse, S.D., Khoury, M.J. Gen Med. 2006;8:448-50.

Perspectives

- Hypothesis generating (e.g., genome wide association study) versus hypothesis testing (e.g., candidate gene association study)
- Single drug-gene pair versus Multi-gene panel
- Population heterogeneity

Bromley, C.M., et al. Pharmacogenomics J. 2009;9:14-22.

PGx Study Application Challenges

- Many PGx studies are frequently supplemental, often retrospective (i.e., prospective hypothesis tested in a retrospective cohort)
- Varying genotyping methodologies
- Heterogeneity of phenotypic endpoints
- Environmental impacts (gene by gene interactions, drug-drug-gene interactions, etc.)
- Population stratification

Bromley, C.M., et al. Pharmacogenomics J. 2009;9:14-22.

Economic Evaluation of Germline PGx

- Approximately 1 in 6 prescriptions involve high risk pharmacogenomics
- Only about 25% of currently available tests and 20% of tests with likely clinical utility have associated cost-utility data
- PGx cost-effectiveness by indication
  - Cancer
    - Annual patient savings with pharmacogenomics irinotecan dose reduction $272.34
    - Savings of $415 per patient receiving voriconazole for fungal infection
  - Psychiatry
  - Cardiology
  - Geriatric medicine
  - Pain

Snyder SR, et al. Public Health Cenomics. 2014;17:256-64.
Watanabe, et al. Ann Pharmacother. 2018;52:829-37.
Gold HT, et al. Cancer 2009;115:3858-67.
Mason NT, et al. J Antimicrob Chemother. 2015;70:3124-6.

Select Examples: “High Evidence” Drug-Gene Pairs

- Abacavir and HLA-B (BBW)
- Carbamazepine and HLA-B (BBW)
- Clopidogrel and CYP2C19 (BBW)
- Codeine, tramadol and CYP2D6 (BBW)
- Thiopurines and TPMT/NUDT15
- Fluoropyrimidines and DPYD

BBW= Black Box Warning

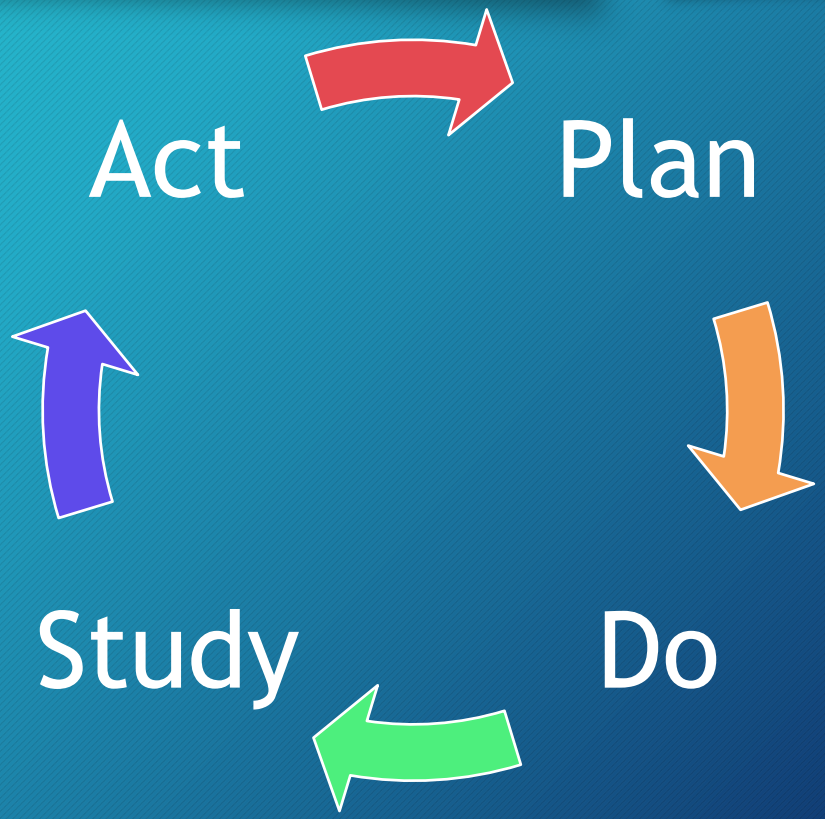
Implementation of PGx

- Growing need for germline PGx
  - > 150 individual drugs have FDA-approved pharmacogenomic information included in the drug label
  - On average, 3 actionable PGx variants per patient
- Key elements
  - Evidence
  - Personnel
  - Information technology
  - Reference laboratory
  - Education and Shared Decision-Making plan

Relling et al. Nature. 2015;526:343-350.
Arwood, et al. Clin Transl Sci. 2016;9:233-45.

Where is the starting line?

- Plan
  - Determine the approach i.e. reactive versus preemptive, germline versus somatic
  - Identify a drug/gene pair and patient population
  - Determine testing method
  - Create clinical decision support and education
- Do
  - Implement
- Study
  - Monitor clinical utility and implementation variables
- Act
  - Obtain feedback from end users, patients and incorporate into the next drug/gene pair implementation effort



PGx Clinical Implementation Challenges

- Economics
- PGx Technology
- Program sustainability
- Provider expertise

Arwood, et al. J Clin Med. 2020;9:doi: 10.3390/jcm9072274.
Arwood, et al. Clin Transl Sci. 2016;9:233-45.
Keeling, et al. Gen in Med. 2019;21:1224-32.

PGx Clinical Implementation Challenges

- Economics
  - Reimbursement for genetic testing
  - False reassurance with dropping cost of next generation sequencing (NGS)
- PGx Technology
  - Genotyping and result interpretation
  - Laboratory and workflow challenges
  - Interoperability
  - Electronically structured data and provision of clinical decision support
- Program sustainability
  - Attaining provider buy-in and acceptance
  - PGx is an interprofessional team sport
- Provider expertise
  - Varying levels of provider expertise
  - Lack of self-efficacy and confidence

Arwood, et al. J Clin Med. 2020;9:doi: 10.3390/jcm9072274.
Arwood, et al. Clin Transl Sci. 2016;9:233-45.
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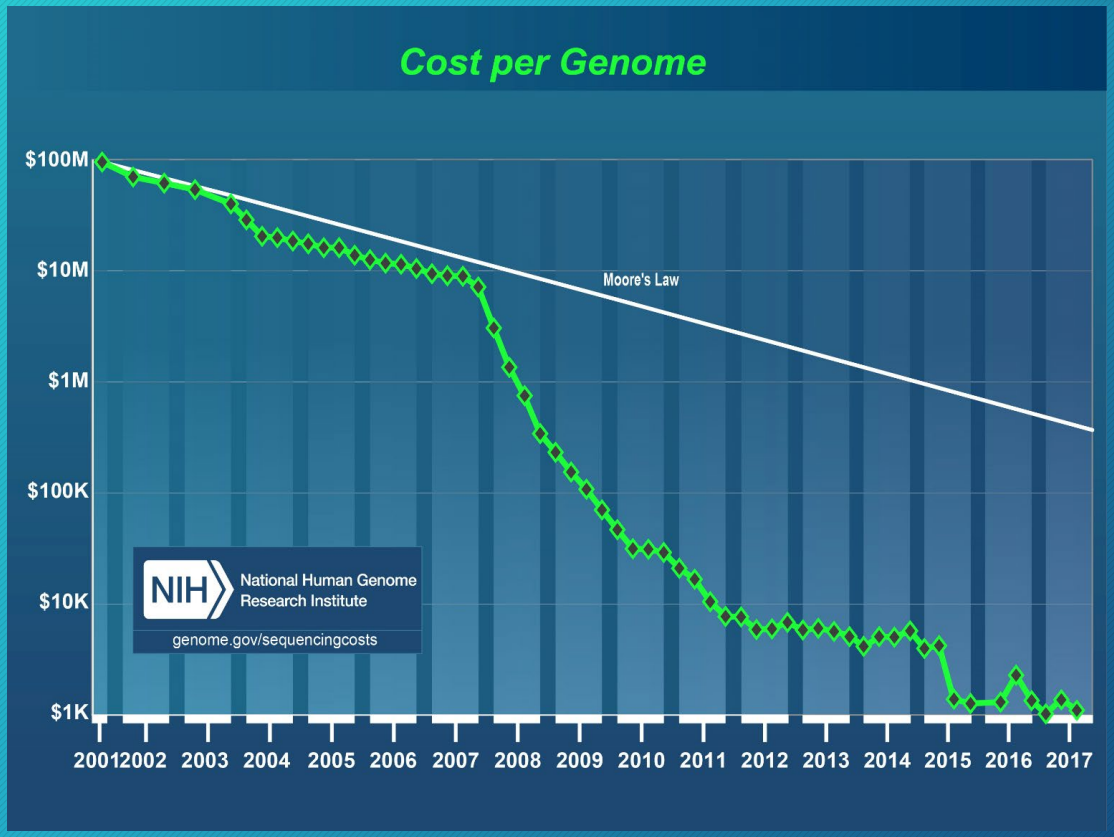
NGS Impact on Sequencing Cost



Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcostsdata. Accessed [date of access].

Economic Implementation Challenge

- False reassurance with dropping cost of next generation sequencing (NGS)
  - Sample processing and procurement
  - Informatics support and applications
  - Education materials and support
  - Laboratory services
  - Shipping materials and cost

Barriers Identified with PHASER 1.0

- Implementation science-based survey to evaluate pharmacogenomics intervention
- Survey (n= 153), overall response rate 30%
- Top 10 consolidated framework for implementation research (CFIR) Constructs Identified
  1. Evidence strength and quality
  2. Complexity
  3. Knowledge and benefits about the intervention
  4. Self-efficacy
  5. Individual stage of change
  6. Compatibility
  7. Relative priority
  8. Leadership engagement
  9. Available resources
  10. Access to knowledge and information

Olivia Dong, PhD
T32 Genomic Medicine Fellow

Ryanne Wu, MD
Duke Center for Applied Genomics & Precision Medicine

Educating the Workforce

- Qualitative evaluation of 25 physicians revealed that the prospect of receiving unsolicited genomic results raises important concerns
  - Actionability – especially with regard to lack of knowledge
  - Need for clinical decision support
  - Potential patient harm
  - Workflow issues i.e., unreimbursed time
  - Roles of providers responding to unsolicited genomic results
- A survey of pharmacists (n=737) demonstrated disparity in knowledge of general genetics according to years since graduating pharmacy school
  - Mean total positive attitude increased with self-reported level of knowledge of pharmacogenomic testing

Pet PB, et al. Genet Med. 2019;21:311-8.
Rpderer, et al. Personal Med. 2012;9:19-27.

PGx Pharmacy Landscape Survey

Survey deployed February 2021

- 674 responses
- Respondents:
  - 71% of respondents have not completed any training in PGx course work
  - 82% have a scope of practice

Practice Area	No. (%)
Internal medicine	49 (7.3)
Primary care	232 (34.4)
Cardiology	13 (1.9)
Infectious disease	6 (0.9)
Solid organ transplant	1 (0.1)
Mental health	128 (19.0)
Oncology	54 (8.0)
Administration	41 (6.1)
Other	142 (21.1)
No response	8 (1.2)

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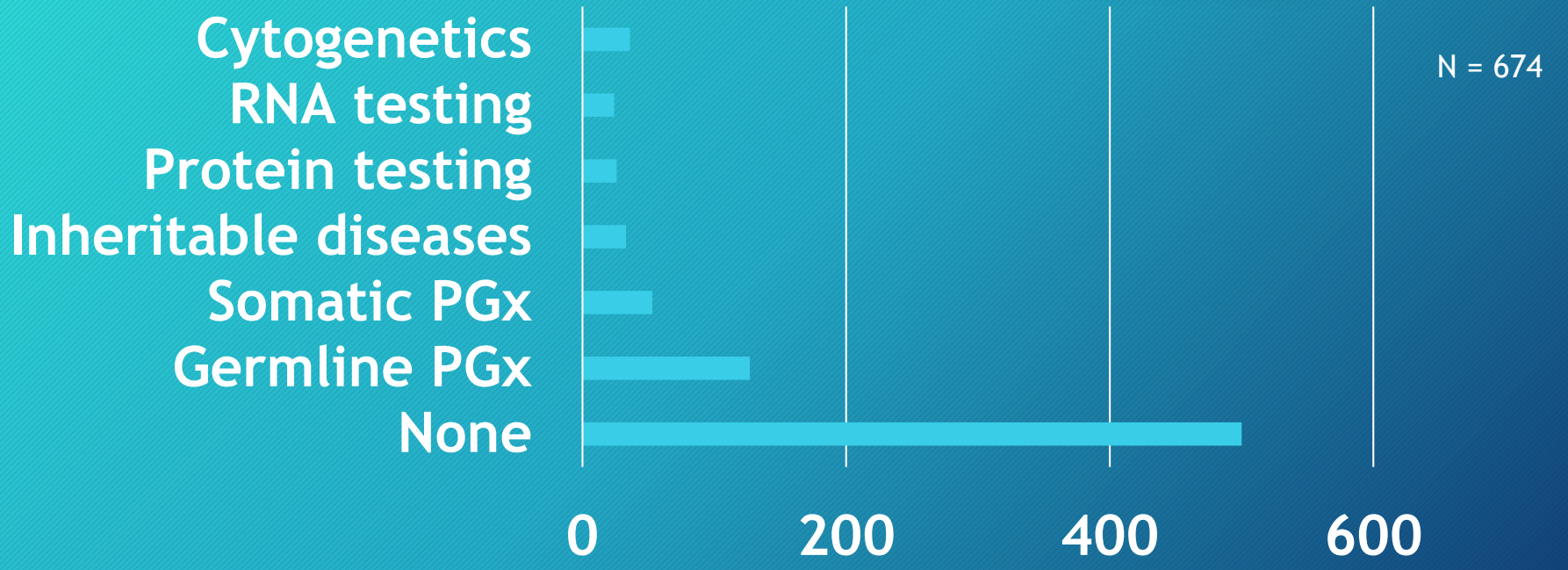
PHASER
Pharmacogenomic Testing for Veterans

Please identify any of the following pharmacogenomics tests that you have utilized as part of your practice?



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Pharmacogenomic Testing for Veterans

Have you ordered any of the following?

N = 674

Orders	Yes	No	N/A
Companion diagnostic matched to a drug prescribed	21 (3%)	517 (78%)	123 (19%)
Complementary diagnostic matched to a drug prescribed	37 (5%)	524 (80%)	98 (15%)
Changed medications or adjusted dosing based on germline PGx	75 (11%)	470 (72%)	112 (17%)

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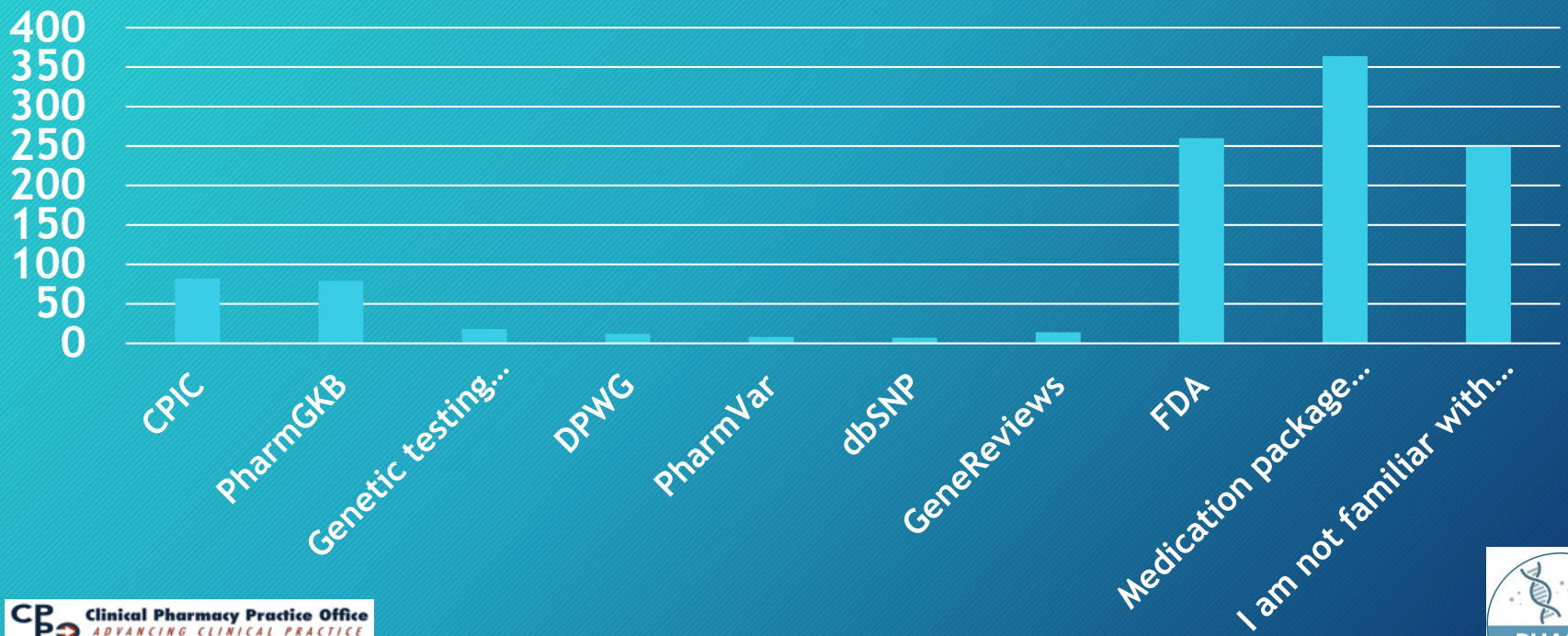
Pharmacogenomic Testing for Veterans

Which of the following pharmacogenomics resources have you used in practice or are familiar with and could use in practice where applicable?

N = 674



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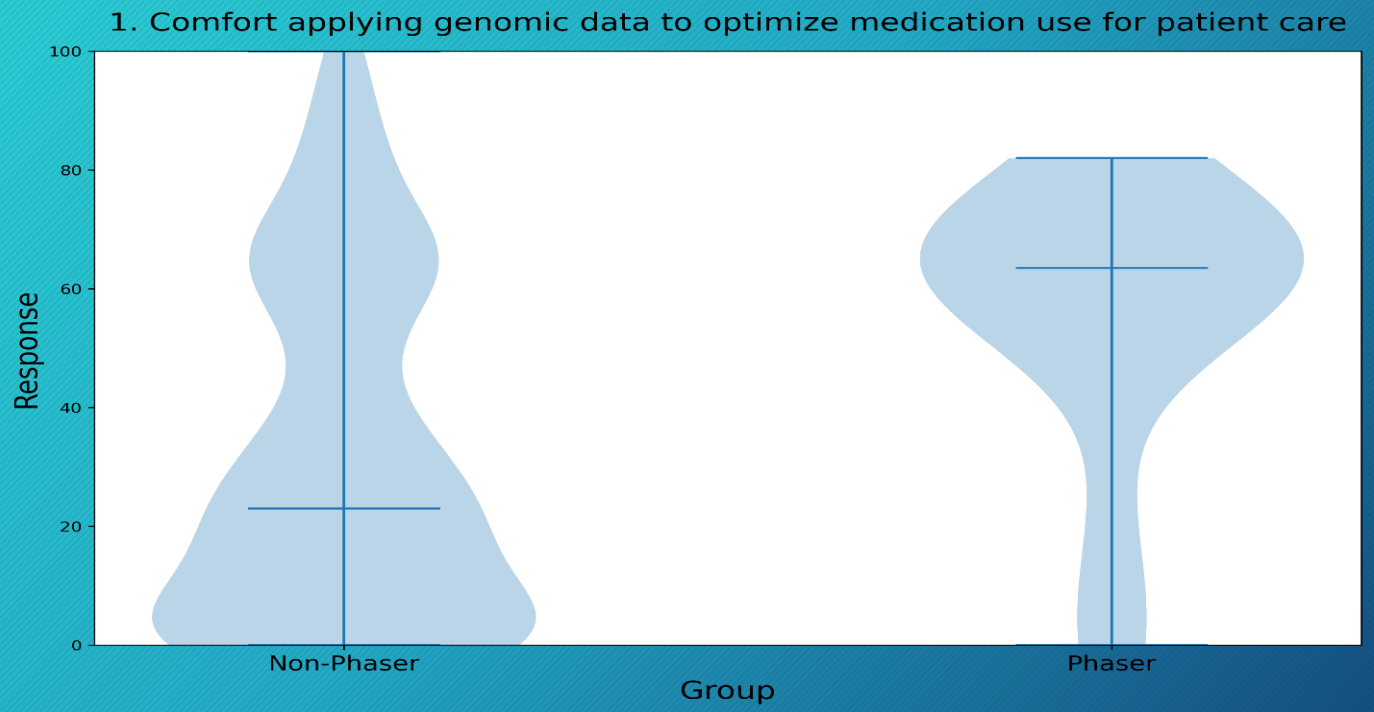
How comfortable are you in performing the following patient care services?

Very Uncomfortable - 0 → Uncomfortable - 25 → Neutral - 50 → Comfortable - 75 → Very Comfortable - 100

Service	Average Score
Applying genomic data to optimize medication use for patient care	32
Educating patients about family history, genomic risk, and PGx test results as they relate to health behaviors	30
Recommend strategies regarding the potential use of handling incidental findings with PGx test results	26
Recommend genomic screening for early detection and diagnosis	24
Apply PGx drug dosing guidelines in practice and guide healthcare providers on their appropriate use and interpretation	33
Educate patients and healthcare providers about privacy and other potential concerns with PGx data	29

Stratified Results by PHASER and Non-PHASER Respondents



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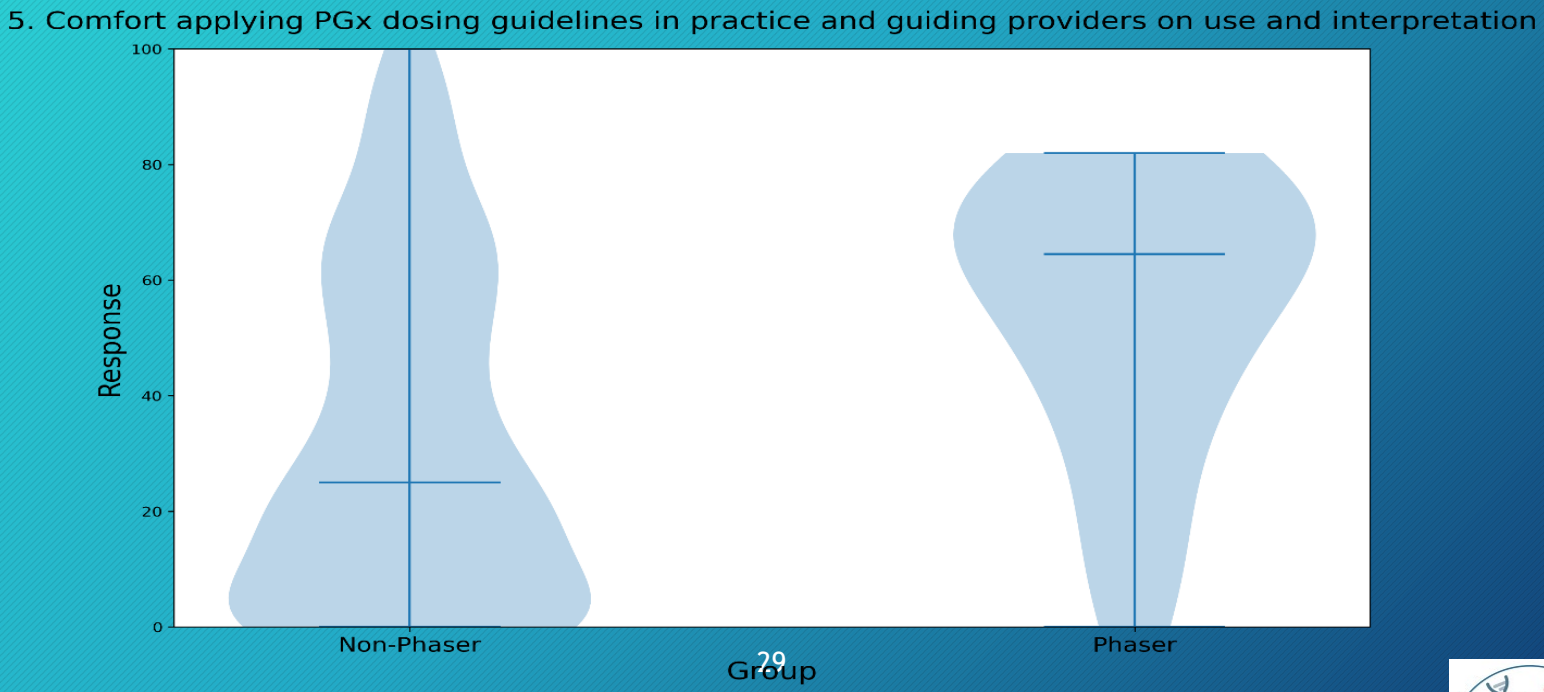

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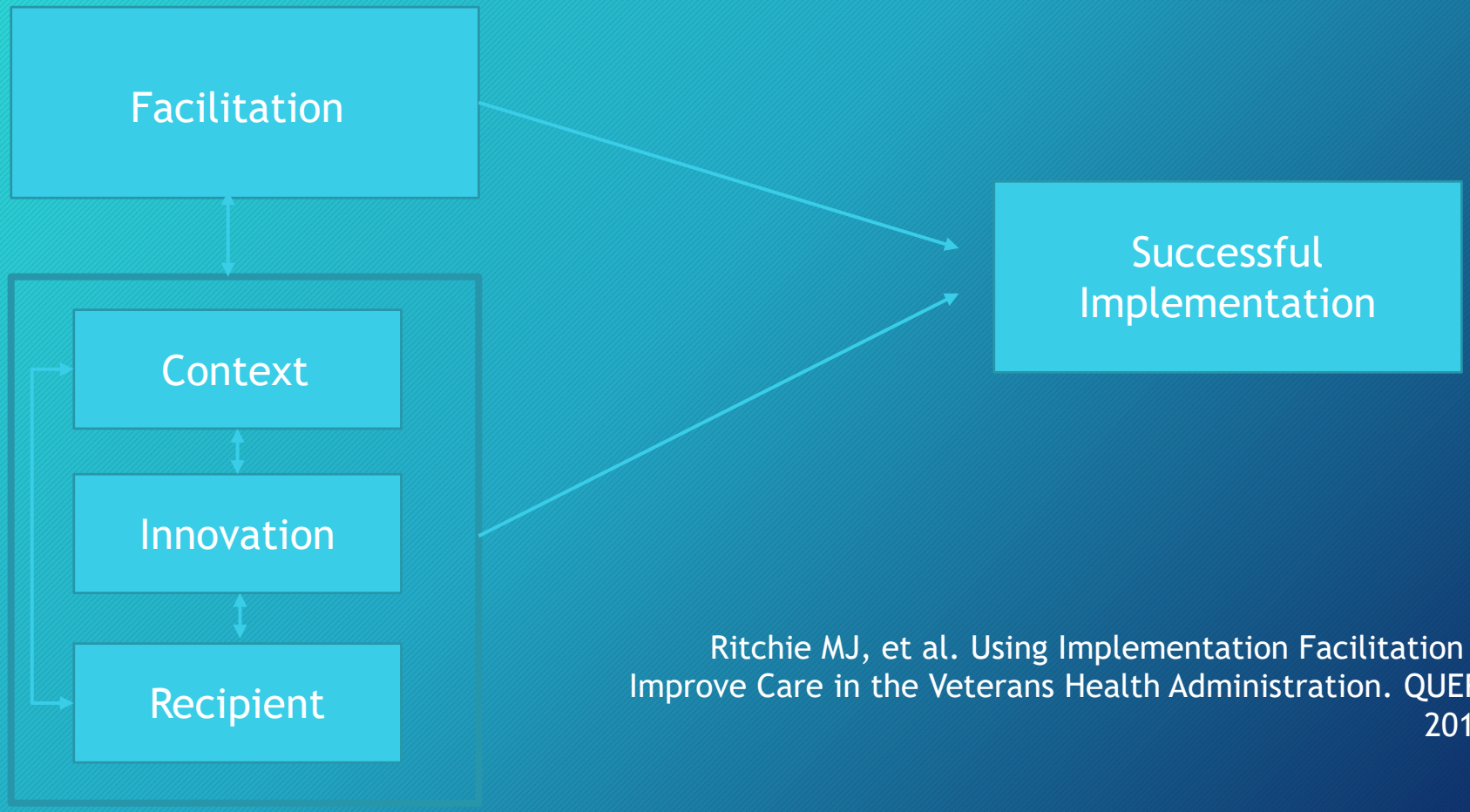
i-PARIHS Framework



Ritchie MJ, et al. Using Implementation Facilitation to Improve Care in the Veterans Health Administration. QUERI, 2017.

Align the Health-system in the Precision Medicine Space

- The Q behind the Q
- Informatics
- Pathology and laboratory services
- Healthsystem priority: pharmacogenomics versus inheritable disease (or both?)
- Definition of ”pharmacogenomics”
  - Germline pharmacogenes
  - Precision oncology

Align the Health System in the Precision Medicine Space

- Infrastructure should support all of precision medicine
  - Cloud computing versus cluster computing?
  - Genomic data infrastructure in electronic health record?
  - Interoperability?
  - Reference laboratories: inhouse or external vendor?
  - Supporting software?

Align the Health System in the Precision Medicine Space

While the cost of sequencing has decreased, infrastructure needs to support continue:

- Cost to the patient – payer coverage of genomic testing
- Cost to store genomic data e.g., cluster versus cloud computing
- Cost of software to support integration of genomics into care e.g., structured data, clinical decision support, interoperability with vendors
- Cost to support biobanking - sample procurement and storage
- Cost for personnel e.g., workforce education, informed consent, building informatics and other infrastructure, etc.

Summary

- Clinical utility---as it relates to pharmacogenomics---is broad and not well defined, making it challenging to assess
- Costs related to pharmacogenomics implementation often extend beyond testing
- Access to pharmacogenomics testing impacts both its clinical utility and clinician self-efficacy