

Genome-friendly Connected Care

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PREDICT helps match patient with proper drug

BY: KATHY WHITNEY

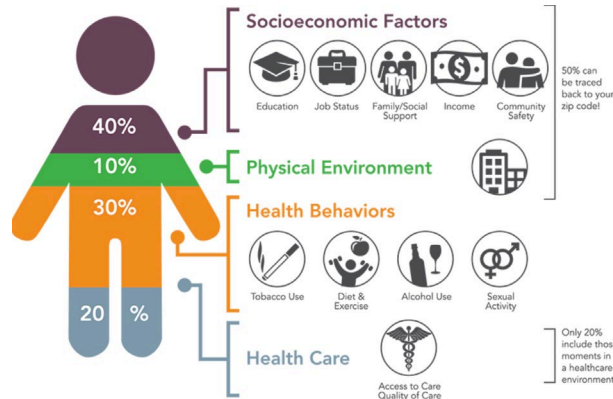
10/28/2010 - Had Scyble Van Cleve, a spry 83-year-old from Brentwood, had her heart procedure done a month ago instead of one week ago, she would have been prescribed the standard dose of clopidogrel, a blood thinner used to prevent blood clots from forming around her coronary stents.



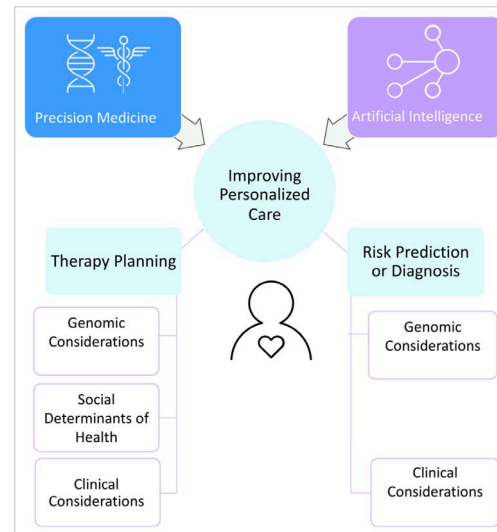
Scyble Van Cleve, right, is the first patient at Vanderbilt to benefit from a new program that puts genetic information in the patient's medical records to help physicians like John McPherson, M.D., choose the drug and dose that will benefit them the most. (photo by Susan Umy)

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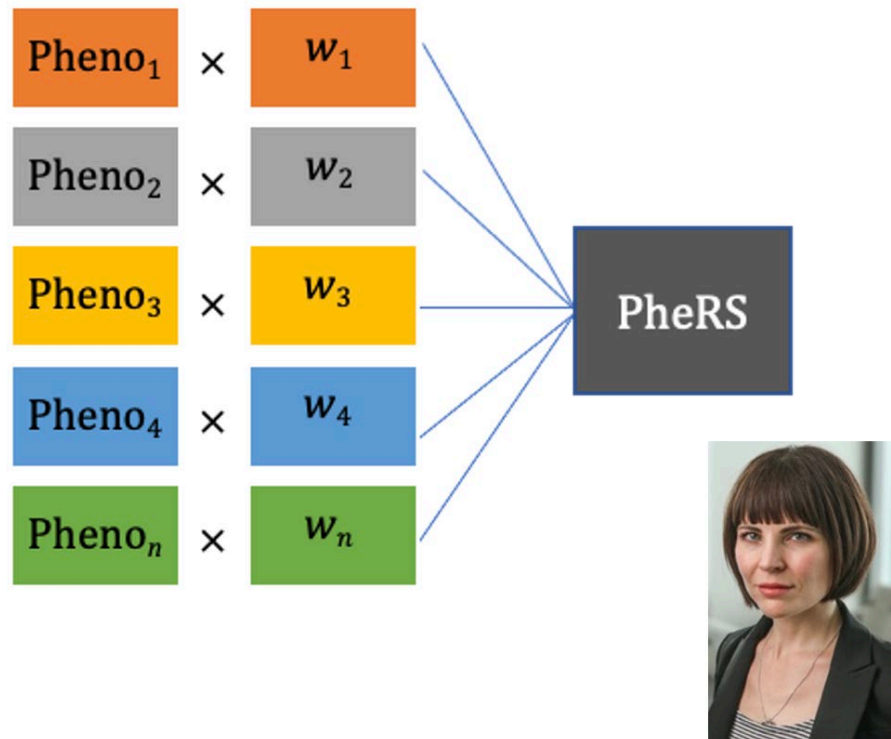
Where is Medicine Going?



Source: Institute for Clinical Systems Improvement, Going Beyond Clinical Walls: Solving Complex Problems (October 2014)

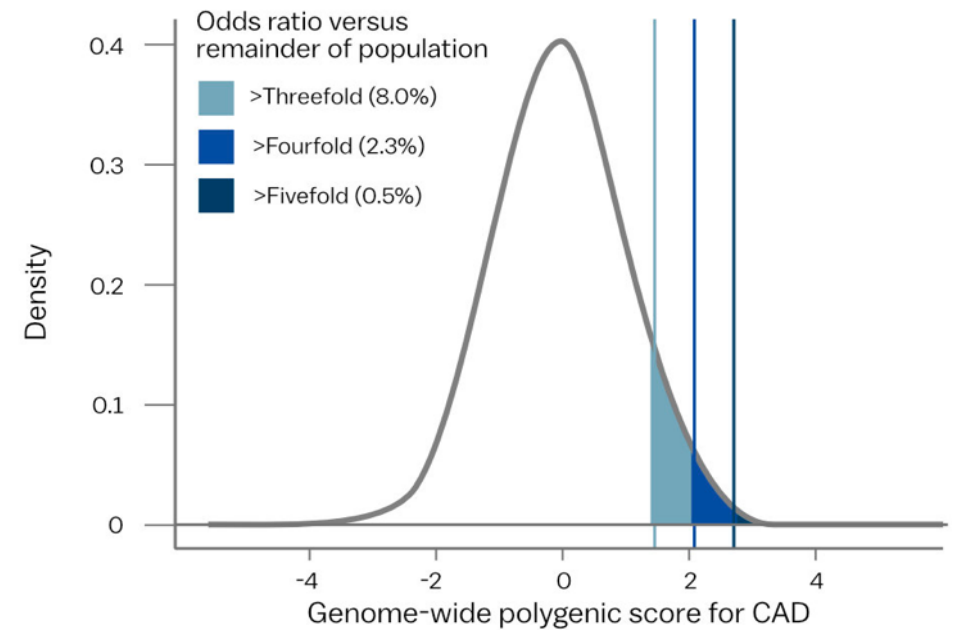


Advances in Prediction



Science, 2018

Polygenic scores signal increased risk for coronary artery disease



Source: Nature Genetics

Khera et al, Nature Genetics, 2019

Literature Supporting Personalization

Proposed Healthy Adult Screening Program

Box 2 | Suggested Tier System for Genomics-Based Screening Programs

TIER 1

- Lynch syndrome-associated genes (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
- Hereditary Breast and Ovarian Cancer (HBOC)-associated genes (*BRCA1, BRCA2*)
- Familial hypercholesterolemia (FH)-associated genes (*LDLR, APOB, PCSK9*)

TIER 2

- Genes with unknown or low penetrance
- Genes with a less well-established knowledge base
- Efficacious interventions available
- Follow-up confirmatory tests available
- Examples including but not limited to *PALB2*, hereditary hemochromatosis, malignant hyperthermia, hypertrophic cardiomyopathy, long QT syndrome, pharmacogenomic variants

SOURCE: PSWG Working Group, 2018.

Murray and Khoury, NAM 2018

Genomics sensitive preventative care workflows

Topic	Due Date	Frequency
New data from outside sources		
Allergies, Medications, and Immunizations need attention. Go Reconcile		
Potassium Level	Overdue since 3/4/1957	1 year(s)
eGFR/Creatinine Level (Estimated Glomerular Filtration Rate (e...))	Ordered on 1/5/2021	1 year(s)
HIV Screening	Overdue since 3/4/1957	Once
Hepatitis C Screening	Overdue since 3/4/1957	Once
Chlamydia Screen	Overdue since 3/4/1973	1 year(s)
Zoster Vaccine (1 of 2)	Overdue since 3/4/2007	Imm Details
CRCS: Colonoscopy	Overdue since 2/1/2019	10 year(s)
Obesity Intervention	Overdue since 1/22/2020	1 year(s)
Upcoming		
DTaP, Tdap and Td Vaccines (3 - Td)	Next due on 7/11/2022	Imm Details
BCS: Mammogram	Next due on 10/24/2022	2 year(s)
CCS: Pap + HPV	Next due on 5/15/2024	5 year(s)
Lipid Panel	Next due on 10/28/2025	5 year(s)

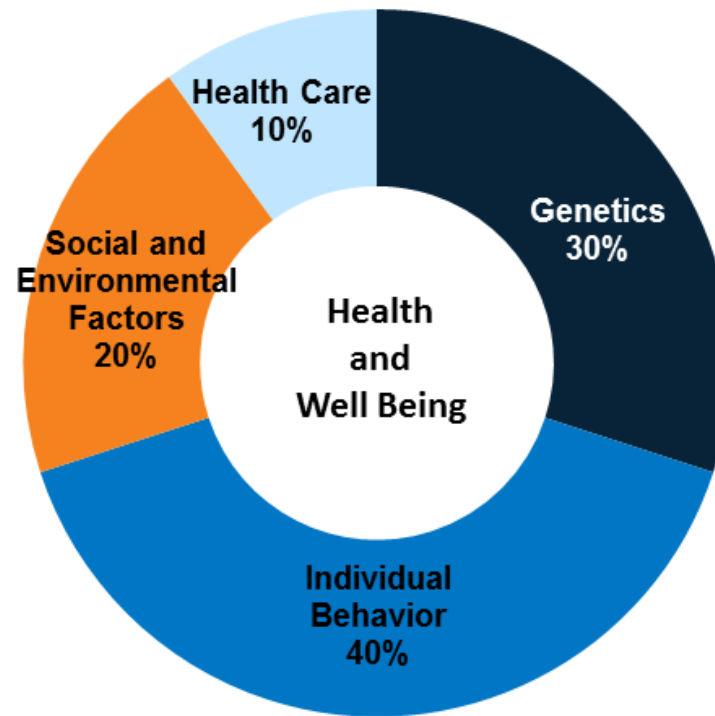
Adjust colonoscopy frequency & age of onset

Add MRI + adjust frequency

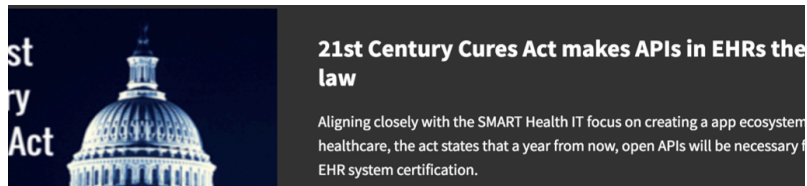
Adjust lipid frequency and lipid-lowering targets

Figure 2

Impact of Different Factors on Risk of Premature Death



SOURCE: Schroeder, SA. (2007). We Can Do Better — Improving the Health of the American People. *NEJM*. 357:1221-8.



Title I: Innovation Projects

- \$4.8 Billion to NIH for Precision Medicine (\$1.45B Moonshot (\$1.8B), Brain Initiative (\$1.5B)
- \$1B over 2 years for grants to states to supplement abuse prevention and treatment activities

Title II: Discovery

- Supporting Young Emerging Scientists
- NIH Strategic Planning
- Facilitating use of data for research

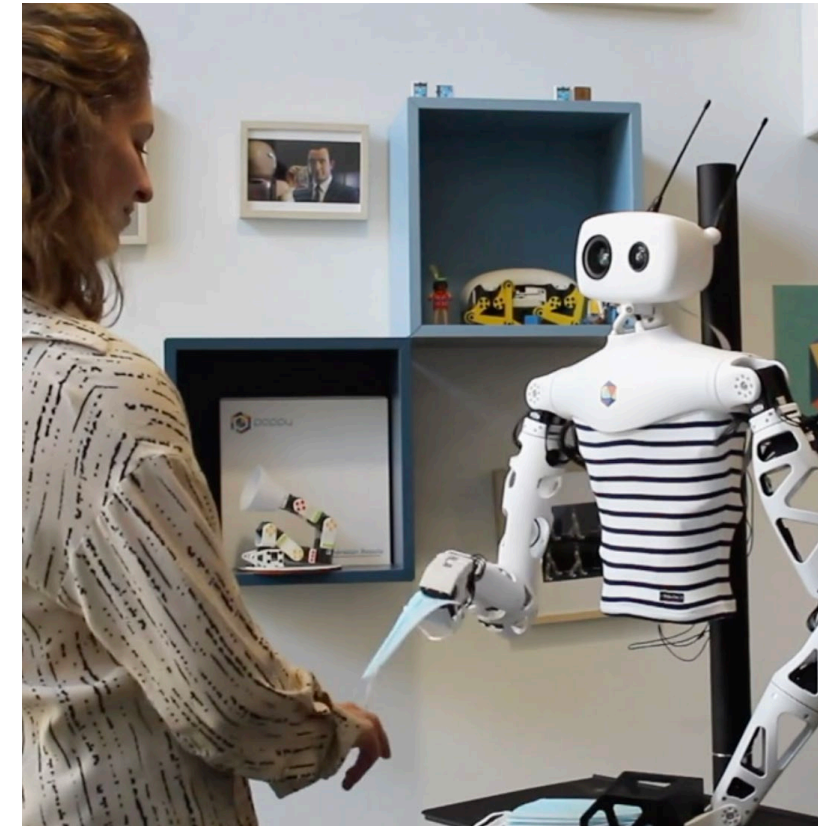
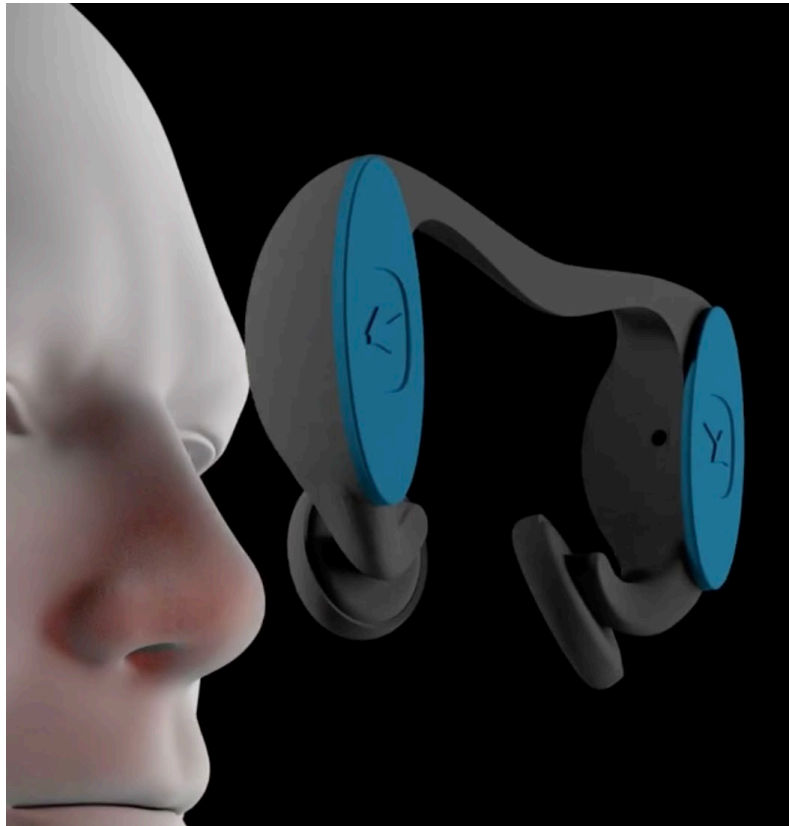
Title III: Development

- Patient-focused drug development
- Patient access to Therapies and Information
- Modern trial design and evidence development
- Advancing new therapies

Title IV: Delivery

- Interoperability
- Information Blocking
- Leverage EHR to support participatory medicine

<https://www.nihcollaboratory.org/Pages/>



Enabling Platforms

Specific Drug Gene Interactions

- [Citalopram \(Celexa\) – CYP2C19](#)
- [Clopidogrel \(Plavix\) – CYP2C19](#)
- [Codeine – CYP2D6](#)
- [Escitalopram \(Lexapro\)- CYP2C19](#)
- [Fluvoxamine \(Luvox\) – CYP2D6](#)
- [Ondansetron \(Zofran\) – CYP2D6](#)
- [Paroxetine \(Paxil\)- CYP2D6](#)
- [Sertraline \(Zoloft\)- CYP2C19](#)
- [Simvastatin \(Zocor\) – SLCO1B1](#)
- [Tacrolimus \(Prograf\) – CYP3A5](#)
- [Thiopurine \(Purinethol, Imuran, Tabloid\) – TPMT](#)
- [Tramadol \(Ultram\) – CYP2D6](#)
- [Voriconazole \(Vfend\) – CYP2C19](#)
- [Warfarin \(Coumadin\) – CYP2C9 / VKORC1 / CYP4F2](#)

BestPractice Advisory - Johnson, Kevin B

Critical (1)

Drug-Gene Interaction

Voriconazole Rapid Metabolizer

Genetic testing has been performed and indicates this patient may be at risk for toxicity or non-response to voriconazole (Vfend).

This patient has been tested for CYP2C19 variants, and the results indicate this patient is predicted to be a rapid metabolizer of voriconazole. This patient is at **risk for non-response voriconazole**. Please consult a clinical pharmacist or infectious disease specialist for recommended dose adjustments or alternative antifungal therapy.

<https://www.mydruggenome.org/dgi/voriconazole/>

The Vanderbilt P&T Committee has approved this recommendation based on the detailed review of the literature and consensus guidelines.

Remove the following orders?

Remove	Keep	voriconazole (VFEND) 200 mg/5 mL (40 mg/mL) oral suspension oral, Every 12 hours scheduled, First Dose today at 1000
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Apply the following?

Order	Do Not Order	E-Consult service Pharmacy Pharmacogenomics
Order	Do Not Order	Inpatient Consult to Infectious diseases, General
Order	Do Not Order	Inpatient Consult to Pediatric Infectious disease, General

Acknowledge Reason

Pursuing Alternate Dose Previously tolerated dose Discussed with Specialist Other (specify)

Accept

VUMC: Current Capabilities

My Health at Vanderbilt

Kevin My Record Appointments Messaging Billing Resources Settings Kevin B Johnson Log Out Ver en Español

My Genetic Profile

This page shows what we know about your genes, including how they might affect the way you respond to certain medications and whether you are predisposed to certain conditions. Always speak to your doctor before making any changes to your medications.

Genetic Findings of Interest

This section contains genetic testing findings related to your health that might require special attention.

Tacrolimus - Intermediate metabolizer Prograf	Tacrolimus (sounds like "tah-CRAH-hi-mus") is a type of medicine called an immunosuppressant. Other names for tacrolimus include Prograf® (brand name) and FK-506. An immunosuppressant lowers the activity of the immune system. Your genes can affect how well tacrolimus works. This genetic test identifies how well you may respond to a standard dose of tacrolimus. The results of your test show that your genes increase your risk for a negative outcome. Talk with your doctor about the best plan for you. More information...
Voriconazole - Rapid metabolizer Vfend	Voriconazole (sounds like "vohr ih korr' uh zoh") is a medicine used to treat serious fungal infections. Your genes can affect how well the drug works. This genetic test identifies how well you may respond to voriconazole. Based on the results of your test, your genes increase your risk for a negative outcome. Talk with your doctor about the best plan for you. More information...

myDRUG GENOME The right drug, the right dose, the first time.

Drug-Gene Interactions (DGIs) FAQ Meet the Team Contact Us

Using Genetics to Personalize Treatment

My Drug Genome

My Drug Genome is your resource to learn about how genetics may affect the way medications work and how genetic results can be incorporated into personalized patient care. Part of personalized medicine means ensuring that patients receive the right dose of the right medication for them.

What is PREDICT?

The Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment (PREDICT) initiative empowers patients and doctors with the genetic information needed to anticipate and prevent adverse drug reactions or lack of effectiveness based on genetic information specific to each patient tested.

Why now?


Genetic variation is an increasingly well-recognized contributor to variability in drug response and adverse drug reactions. The Food and Drug Administration (FDA) recognizes many of these associations. Currently at least 70 drugs have pharmacogenomic information in their FDA labels that affects prescribing.

What is the goal of PREDICT?

The long-term goal of PREDICT is to incorporate clinically actionable genetic data into the VUMC electronic medical record and implement guidance for clinical decisions utilizing those pharmacogenomic results.

What is tested through PREDICT?

Using one blood test, patients are *genotyped* for 39 common polymorphisms within 8 genes associated with drug absorption, distribution, metabolism, and excretion. This single genetic test has repeated utility over the lifetime of the patient. Currently, the test provides data pertinent to 16 drugs, with additional drug-gene interactions continuously being added to the program. When new content is added, re-ordering as a non-duplicative test is possible. Only results for genes that have been reviewed and approved as actionable by Vanderbilt's Pharmacy and Therapeutics subcommittees will be released into the patient chart.



Rules supporting clinical recommendations for *CYP2C19* Alleles - Citalopram



localhost:8083/tbl/predict_2020_jun_2.editor#predict_2020_jun_2:DGI10poor_metabolizer

TopBraid EDG™ Enterprise Data Governance

PREDICT 2020 Jun

Layouts Panels Undo Hello, Administrator

Taxonomy Dashboard Settings Users Import Transform Export Reports Workflows Tasks Comments Manage

Taxonomy Concepts x Concept Search x

Quick search

Citalopram poor metabolizer

- *2/*2
- *2/*3
- *2/*4
- *2/*4B
- *2/*6
- *2/*8
- *3/*3
- *3/*4
- *3/*4B
- *3/*6
- *3/*8
- *4/*4
- *4/*4B
- *4/*6
- *4/*8
- *4B/*4B
- *4B/*6
- *4B/*8
- *6/*6
- *6/*8
- *8/*8

Citalopram poor metabolizer

hidden label: DGI10|poor_metabolizer

type: DGI Rule

Clinical Recommendations

Adult Recommendation: *	Increased risk for adverse drug reaction. Consider a 50% reduction of recommended starting dose OR alternate SSRI.
Pediatric Recommendation:	Increased risk for adverse drug reaction. Consider a 50% reduction of recommended starting dose OR alternate SSRI.
Custom Adult Recommendation :	CITALOPRAM interpretation: Poor metabolizer. Increased risk for adverse drug reaction. Consider a 50% reduction of recommended starting dose OR alternate SSRI. Visit https://www.mydruggenome.org/dgi/citalopram/ for more information.
Custom Pediatric Recommendation:	CITALOPRAM interpretation: Poor metabolizer. Increased risk for adverse drug reaction. Consider a 50% reduction of recommended starting dose OR alternate SSRI. Visit https://www.mydruggenome.org/dgi/citalopram/ for more information.

Escitalopram CDS in Adult with Actionable *CYP2C19*

CYP2C19
Phenotype

Associated Risk

Evidence Link

Remove orders

Apply orders

Acknowledgment

Critical (1)

⚠ Drug-Gene Interaction

Escitalopram Poor Metabolizer

Genetic testing has been performed and indicates this patient may be at risk for adverse events or non-response to escitalopram (Lexapro).

This patient has been tested for *CYP2C19* variants and results indicate this patient is predicted to be a poor metabolizer of escitalopram. This patient is at **increased risk for adverse events** due to elevated escitalopram plasma levels.

Consider:
(1) 50% reduction of recommended starting dose (and titrate to response) **OR**
(2) Select alternative therapeutic agent not predominantly metabolized by *CYP2C19*. Sertraline and citalopram are not appropriate alternatives, as they are *CYP2C19* substrates.

Appropriate alternatives and dose should consider the type and severity of the condition. Please consult a clinical pharmacist for more information.

<https://www.mydruggenome.org/dgi/escitalopram/>

The Vanderbilt P&T Committee has approved this recommendation based on detailed review of the literature and consensus guidelines.

Remove the following orders?

Remove

Keep

escitalopram (LEXAPRO) 5 mg/5 mL oral solution
Starting today at 0935

Apply the following?

Order

Do Not Order

buPROPion (immediate release and sustained release formulations)

Order

Do Not Order

DULoxetine (CYMBALTA) DR capsule

Order

Do Not Order

FLUoxetine (PROzac) capsule

Order

Do Not Order

FLUoxetine (PROzac) oral liquid

Order

Do Not Order

fluvoxamine (LUVOX) tablet

Order

Do Not Order

Pharmacy consult for Pharmacogenomics

Acknowledge Reason

Previously tolerated

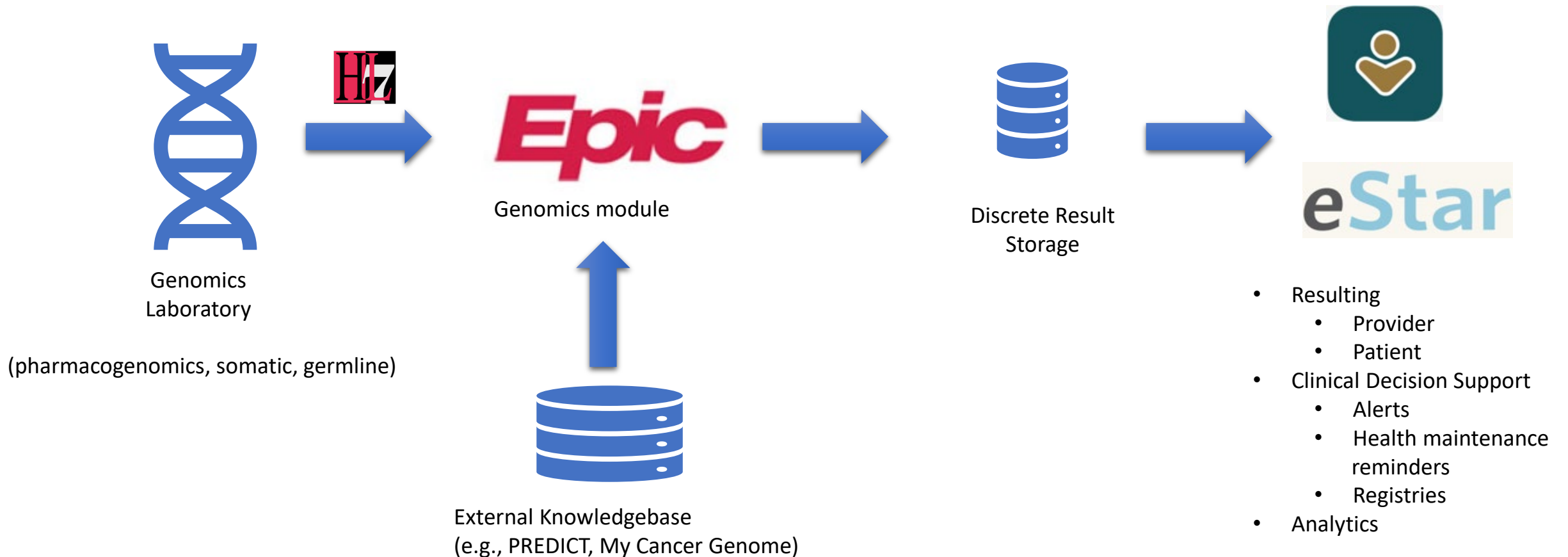
Failed other treatments

Adjusting dose

Other: Please specify

✓ Accept

Epic Genomics Module





A Vision

Questions that we should anticipate

Which drug will be most effective in my patient?

Should I be considering genetic testing? If so, what test?

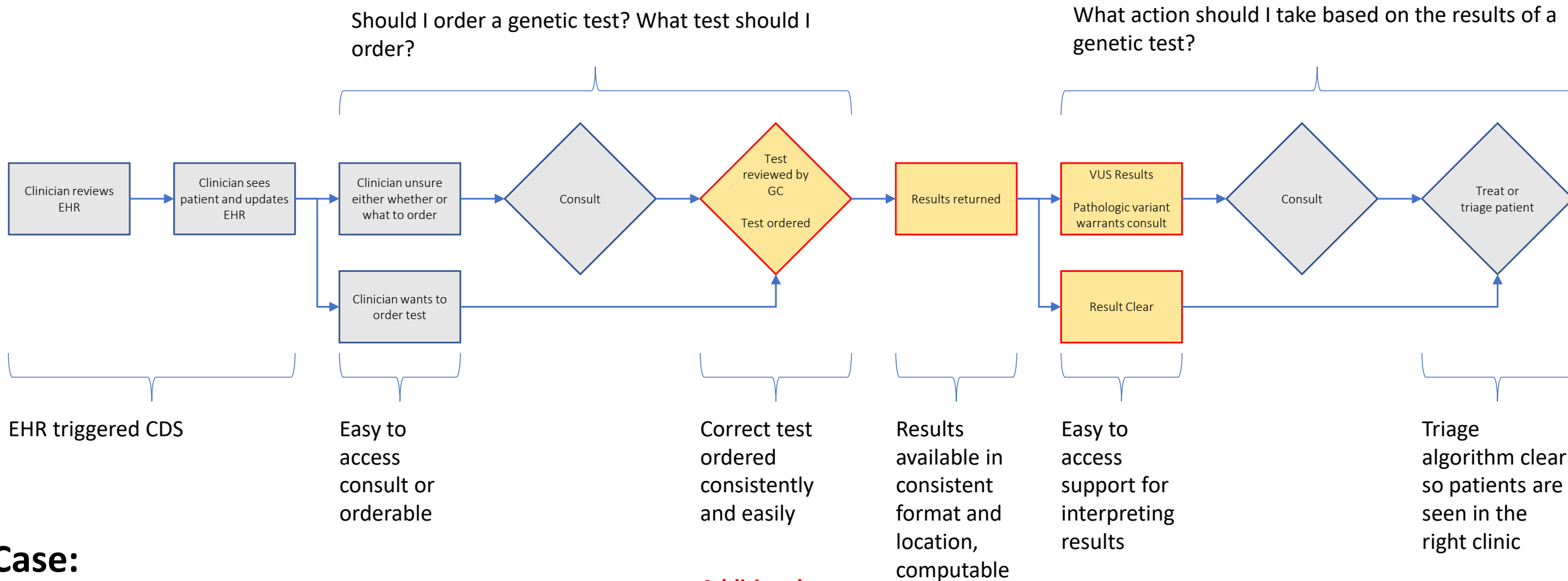
How do I interpret these test results? They don't have clinical meaning? What does indeterminate mean?

The literature isn't specific to my patient. What have other patients like her at Vanderbilt experienced with this condition and this treatment?

Is there a clinical trial for my patient out there?

What is the best way to treat my patient's tumor?

Workflow supported by technical foundation:



EHR triggered CDS

Easy to access consult or orderable

Correct test ordered consistently and easily

Results available in consistent format and location, computable

Easy to access support for interpreting results

Triage algorithm clear so patients are seen in the right clinic

Additional panels in house

Scale Epic genomics module and Tempus

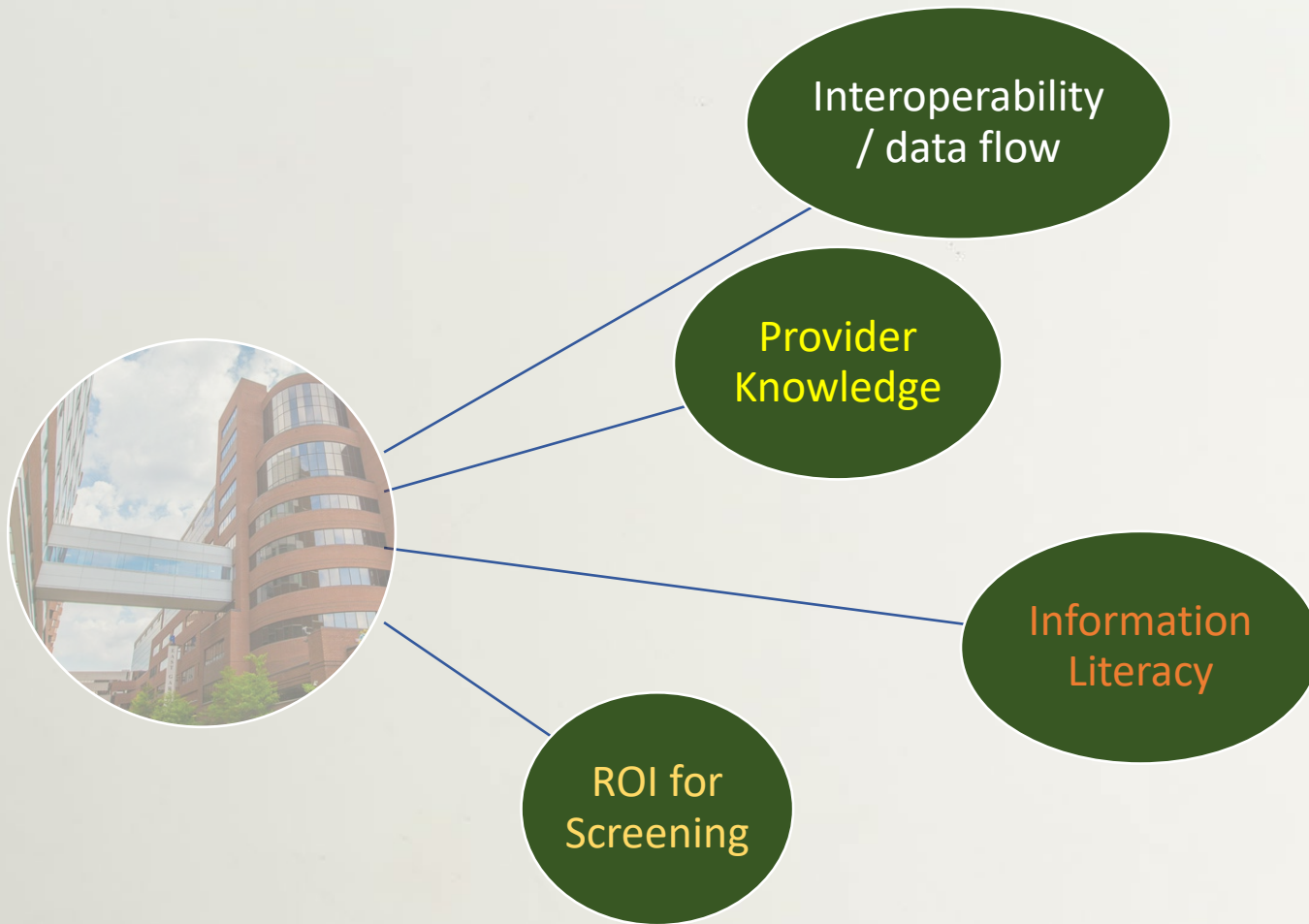
Expand E-consult launched

Case:
19 year-old woman evaluated in primary care after spontaneous pneumothorax with a heart murmur. The clinician suspects Marfan syndrome.

Translating PheRS or Related techniques

- Technical requirements:
 - Large, identified, full-text EHR
 - Syndrome features organized into an ontology
 - *Concept-indexed EHR documentation*
- Challenges:
 - Algorithm refinement to reduce manual review
 - Patients may not have appropriate clinical relationships established

Health System Challenges

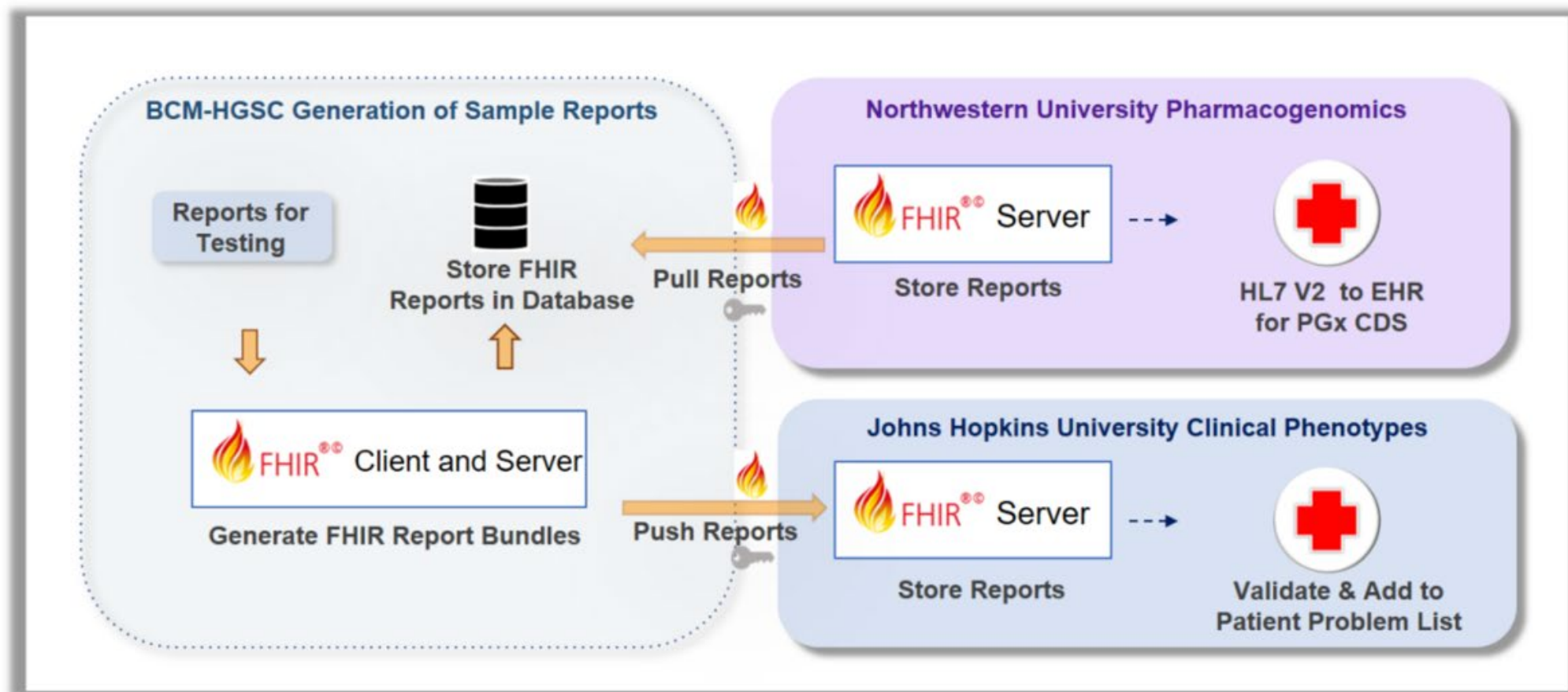


- Computable data from outside labs
- Recontact as information changes
- Understanding the nomenclature
- Addressing family concerns
- Consistent knowledge representation
- Understandable to the lay public
- Quality evaluation studies
- Payor and self-insured party support

“Data in motion”: HL7 FHIR Genomics

Transmission standard for sequencing data

Figure 1: Baylor College of Medicine Human Genome Sequencing Center Demonstration Project



Daily Living Challenges

Equity

Literacy

Fear and
Misinformation

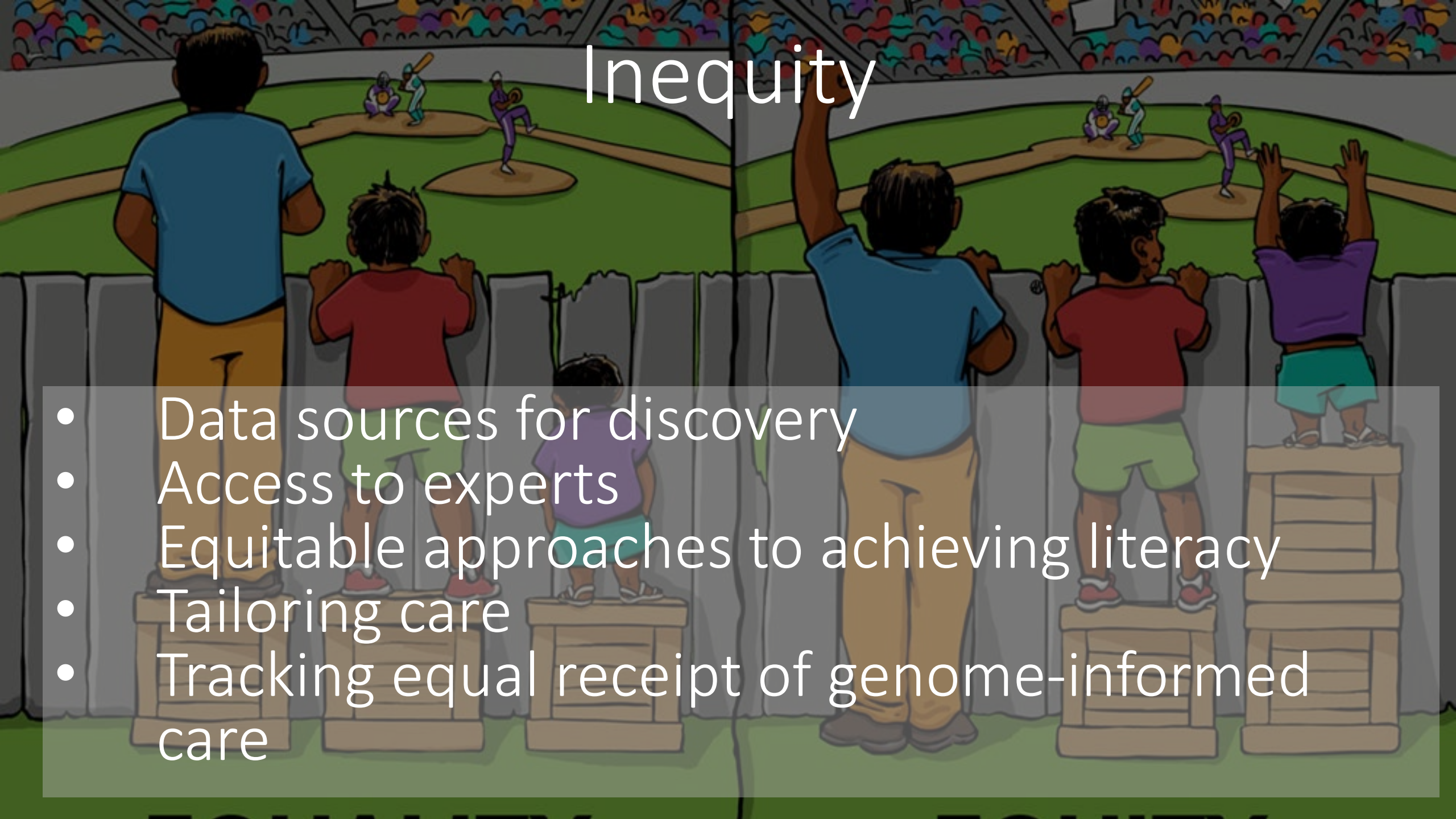
Life
Integration

- Access to tailored care/ trial options
- Recontact as information changes
- Mitigating biases in data
- Understanding the nomenclature
- Addressing family concerns
- Concerns about experimentation
- Concerns about job retention and insurability
- Technology literacy
- Recontact over time



Inequity

- Data sources for discovery
- Access to experts
- Equitable approaches to achieving literacy
- Tailoring care
- Tracking equal receipt of genome-informed care



How Do We Lesson Genetic Discrimination Fears?



U.S. Equal Employment Opportunity Commission

MENU

Fact Sheet: Genetic Information Nondiscrimination Act

This guidance document was issued upon approval of the Chair of the U.S. Equal Employment Opportunity Commission.

OLC Control Number: EEOC-NVTA-0000-4

Concise Display Name: Fact Sheet: Genetic Information Nondiscrimination Act

Issue Date: 09-09-2014

General Topics: ADA/GINA

Summary: This document provides basic information about the Genetic Information Nondiscrimination Act, including the definition of genetic information under the law.



What Can/Should We Automate?



Summary: What Research/Development is Necessary

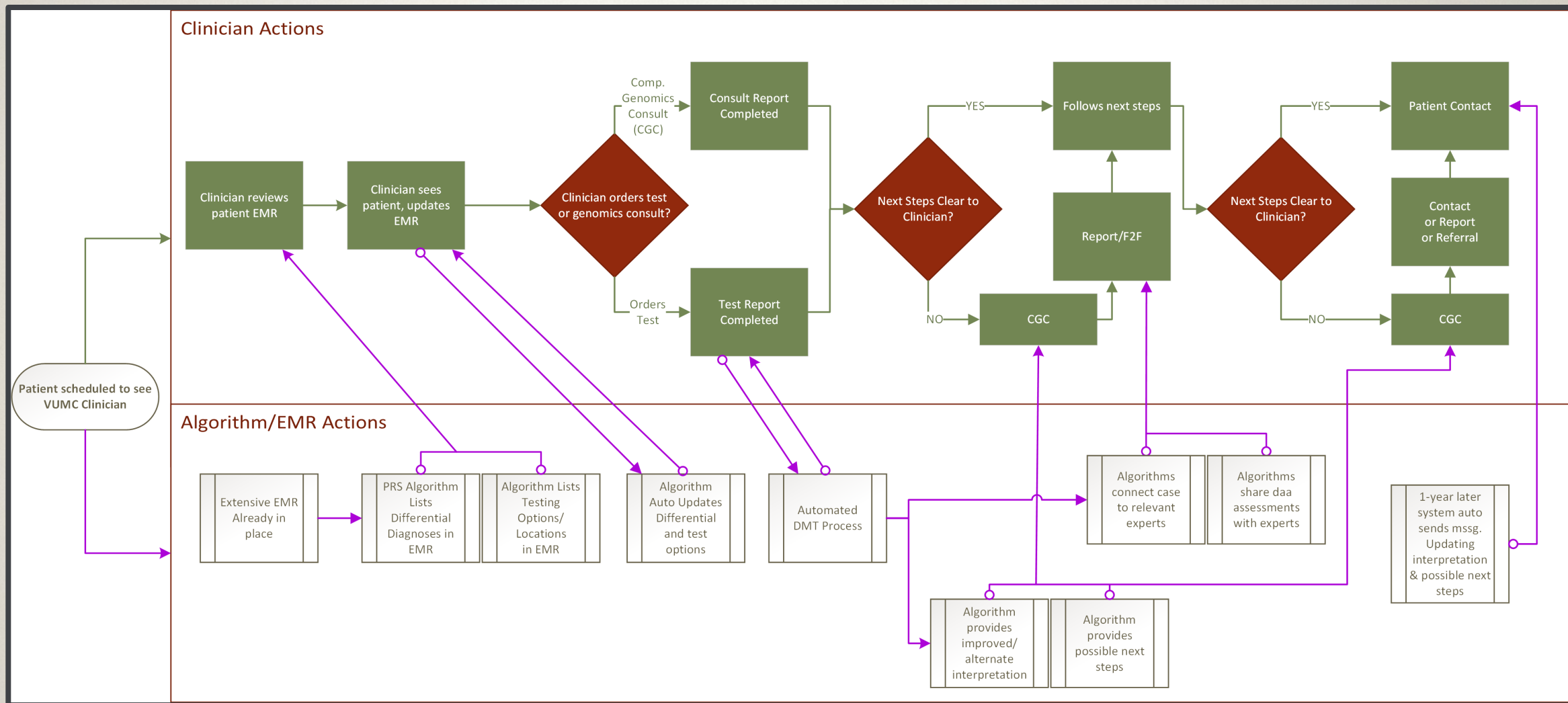
- Literacy
- Expanding ClinVar, dbGaP, EGA
- Standards for genomic interoperability from external labs into the EHR
- ROI for sequencing in support of both screening and diagnosis
- More experts available for clinicians

- Literacy
- Tools and pilots of innovation solutions
- Patient understanding of genomic medicine in general
- Patient understanding of genomic risk
- Equitable approaches to genomic literacy
- More expertise available for everyone else



"The future is here
- it's just not
evenly distributed"

William Gibson



Future Tech

- Non-invasive prenatal testing over amniocentesis and CVS
- Expanded pediatric screening for genetic risk/protection variants