Genome-friendly Connected Care

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Where is Medicine Going?
Advances in Prediction

Polygenic scores signal increased risk for coronary artery disease

Source: Nature Genetics

Khera et al, Nature Genetics, 2019
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


Genomics sensitive preventative care workflows

**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

- Genetics: 30%
- Individual Behavior: 40%
- Social and Environmental Factors: 20%
- Health Care: 10%

Enabling Platforms
Specific Drug Gene Interactions

- Citratozym (Citrate) – CYP2C19
- Clopidogrel (Plavix) – CYP2C19
- Coenzyme – CYP2D6
- Escitalopram (Lexapro) – CYP2C19
- Flavoxamine (Lactus) – CYP2D6
- Ondansetron (Zofran) – CYP2D6
- Paroxetine (Paxil) – CYP2D6
- Zolpidem (Ambien) – CYP2C9
- Zolpidem Tartrate – SCAD21B
- Tacrolimus (Prograf) – CYP3AS
- Trizivirine (Truvada) – TRRA1
- Tranquilizers (Trifluoperazine) – CYP2D6
- Voriconazole (Vfend) – CYP2C9
- Warfarin (Coumadin) – CYP2C9 / VKORC1 / CYP4F2

VUMC: Current Capabilities
Rules supporting clinical recommendations for **CYP2C19 Alleles - Citalopram**

- **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](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](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**
Epic Genomics Module

Genomics Laboratory
(pharmacogenomics, somatic, germline)

Genomics module

External Knowledgebase
(e.g., PREDICT, My Cancer Genome)

Discrete Result Storage

• Resulting
  • Provider
  • Patient
• Clinical Decision Support
  • Alerts
  • Health maintenance reminders
  • Registries
• Analytics

eStar
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:

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

Interoperability / data flow

Provider Knowledge

Information Literacy

ROI for Screening

• 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

- 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

- 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?

Fact Sheet: Genetic Information
Nondiscrimination Act

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