Applying Genomic Intelligence (and Decision Support) at the Point of Care

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Conflict of Interest

Andrew G Ury, M.D.
Dr. Ury is the CEO of ActX, Inc.

Wade Schulz, M.D.
Dr. Schulz is a consultant for Hugo Healthcare, a patient-centered research platform.
Agenda

• Wade Schulz
  – Implementing Precision Medicine at the Bedside
• Andrew Ury
  – Why Genomics and the Barriers to Clinical Use
  – Genomics and the EHR
• Wade Schulz
  – Yale New Haven Health – Implementation Use Case
  – Yale New Haven Health – Predictive Modeling for Genomic Screening
Learning Objectives

• Define the challenges of implementing genomics and precision medicine within an electronic health record

• Appraise the potential of genomics and precision medicine when integrated into normal physician workflow

• Describe genomics and genomic decision support to improve patient outcomes in behavioral health, cardiology, infectious disease, and pediatrics.

• Evaluate which aspects of germline precision medicine are practical to do today
Speaker Introductions

• Andrew Ury, M.D.
  • CEO and Founder of ActX
  • Founded the first commercial EHR, Practice Partner
  • Twice vice chair of the EHRA
  • CCHIT, NQF

• Wade Schulz, M.D., PhD.
  • Clinical Fellow
  • Senior Solution Architect at Yale New Haven Health
  • Lead for computational health at Yale New Haven Health
  • Consulting director of data science at National Center for Cardiovascular Disease, Beijing, China
Human Genetics – an as yet Unfulfilled Promise for Patient Care

• 2003 – entire human genome sequenced
• Since 2003 sequencing costs drop by a factor of 100,000
• An explosion in medical knowledge occurs
• But for a large majority of physicians, very few changes in clinical practice

• Ref: NHGRI https://www.genome.gov/sequencingcosts/
Why Genomics?

20-75%
Average response rates to medications

2M
Americans hospitalized yearly from adverse drug reactions

82K
Cancers in US per year are hereditary

Precision Medicine
“Applying genomic and molecular data to better target health care treatments and disposition to a particular disease or condition”

Ref: FDA Center for Drug Evaluation and Research, PhRMA, ACS
Goal of Precision Medicine
Genomics at the Bedside

How can we increase the accessibility and impact of clinical genetic testing?
Areas Where Genomics is Having a Medical Impact

- Oncology (cancer)
  - Sequencing of tumors to help select which medications to use
- Testing of high risk adult patients
  - E.g. BRCA\textsubscript{1} and BRCA\textsubscript{2}
- Rare pediatric genetic disorders
- Pregnancy
  - Pre-natal carrier screening and NIPT
- Selected pharmacogenomics (for a few medications at a time)
Progress but most daily medical practice unaffected

• With the exception of a few specialties, when physicians see patients, there have been only small changes in the last 25 years in the impact of genetics on their practice.
Busy Clinician Perspective when they get a Genetics Report

- Pressed for time and often not a genomics expert
- *From insurance pay:* focused on variants; not very useful clinically. If pharmacogenomics, PDF will get buried and be hard to use.
- *From DTC:* hard to sort through and not very helpful clinically.
- *From patient pay:* long PDF report or unfamiliar third party website.
- Visits can be **stressful** for non-experts (and even sometimes for experts)
# Report vs. Actionable Information

## Pathologist Interpretation:
No variants of established pathologic significance are identified by sequencing; however, a low frequency variant (5%) is identified in a splice site of DNMT3A, which may be pathologic.

### Level 1 Variants (Diagnostic, Prognostic, or Therapeutic Significance)
No level 1 variants identified.

### Level 2 Variants (Variants with Unknown Clinical Significance, May Be Related to Disease)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant location, SNP#</th>
<th>HGVS Names</th>
<th>Variant Type</th>
<th>Allele Freq</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNMT3A</td>
<td>chr2:25467023</td>
<td>NM_022552.4</td>
<td>Splice Site</td>
<td>5.0</td>
<td>Splice site variant, usually significant, with a single report of specific variant in association with acute myeloid leukemia. Likely related to this patient’s disease.</td>
</tr>
</tbody>
</table>

### Level 3 Variants (Variants with Unknown Clinical Significance, Unlikely Related to Disease)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant location, SNP#</th>
<th>HGVS Names</th>
<th>Variant Type</th>
<th>Allele Freq</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF3R</td>
<td>chr1:36939463</td>
<td>c.447G&gt;C p.Glu149Asp</td>
<td>Missense</td>
<td>52.0</td>
<td>Probable polymorphism unrelated to disease.</td>
</tr>
</tbody>
</table>

## Description of Variant Classification:
- Level 1 variants include those that have diagnostic, prognostic, or therapeutic significance. Level 2 variants have unknown significance, but may be relevant to the patient’s diagnosis. Level 3 variants are either benign or have not been documented and have no known effect. Additional mutations, including those that are known normal polymorphisms, known benign variants, or are due to analytic artifact can be found within the VarBase patient profile.
- Details about specific variants can be found at the VarBase database by using the “VarBase ID” that begins with “vb” followed by a series of numbers.
Dilemma for Clinicians

- How to take effective action?
  - Become an expert
  - Refer to medical geneticist or genetic counselor
    - Useful in many situations, however
    - Few adult medical geneticists (30 new ones / year for the USA)
    - Genetic counselors are helpful but in limited supply and cannot provide clinical care
    - Genetics referral won't help with medications
    - Still need to provide some education to the patient even if referred
  - Find another way
“Finding another way” is Challenging

• There is a “last mile” barrier
• Physicians cannot learn the meaning of genetic results like they do other test results because genetic knowledge is too large and dynamic
  • Too many variants, too many conditions, too much dynamic knowledge
Genomic Information is Currently Delivered to Physicians via PDF’s

• Useful for clinical genomic testing mostly focused on one or two genes at a time
  • Similar to other traditional medical tests
  • But still leads to long, hard to interpret, PDF’s
• Does not scale to the modern era of hundreds or thousands of targeted genes
• Does not scale to large numbers of medications
• PDF’s can rapidly become obsolete as our knowledge changes
Translational Barrier

• Bringing research into practice at scale has to overcome a “translational” knowledge barrier

• The way through the translational barrier is computerized decision support at the point of care
  • Genomic Decision Support
Electronic Health Records (EHRs) are Key

- Genomic decision support at the point of care, seamlessly integrated into a physician’s normal tool, the EHR, is the way for genomics to become part of normal clinical practice

Problem- EHR Architecture is not Well Suited for Genomics

- **Data storage**
  - Granular data per patient normally quite limited
  - Not prepared for hundreds of thousands or millions of variants per patient

- **Decision support**
  - EHR Rules engines not well suited for genetics
    - Cannot handle tens of thousands of important variants – which grows daily
    - Cannot handle complex rules needed because genetics and biology are “messy”

- **Processing**
  - Intensive processing resources not usually available

Ref: Genetics in Medicine 15, 779–785 (2013)
Solution – Integrated Web Service

• An EHR integrated web based service for Genomics
  • Easy to integrate into existing EHRs
  • Handles huge genomic data sets
  • Provides real time decision support
  • Includes extensive content
• Delivers the power of a secure Cloud

Ref: Genetics in Medicine 15, 779–785 (2013)
Example...

1. Patient visits Physician
2. Prescription written
3. Alert! Based on her genes, patient likely to suffer severe side effects
4. Treatment altered
Example...

1. Patient visits MD

2. MD views gene risk profile in EHR

3. Patient has 70% lifetime risk of colorectal cancer

4. Preventative screening ordered
Demonstration
EHR’s and Genomics

• Many major EHR’s are partnering for Genomic Decision Support

Ref: www.actx.com/info/partners
Methodology

• Focus on Actionable Genomics --- where there is sufficient evidence that the doctor and patient can do something

• Evidence based on the original literature, with advice from leading medical geneticists

• Frequent re-analysis of the genetic data

• Web Service in a secure cloud – handling knowledge curation, genomic data storage, processing to support real time clinical decision support
Methodology

- Be part of normal clinician workflow
- Work in the background
- Import clinical genetic data in standard formats
- Customizable content
- Offer optional genetic testing
Potential Screening Results Today

- Focus on actionable genomics
- 90% of patients have a potential drug genomic interaction
  - The average is 6-7 potential drug genomic interactions per patient
- 3 - 4% of patients have an actionable, evidence based, serious, medical risk based on their genomics
- 20% or more of patients have genomic risk factors
- 60% or more are carriers

  - Ref: multiple studies including Geisinger ACMG 2016 conference
Clear Patient Impact

• Examples of real outcomes:
  • Patient with refractory depression who was treated with SSRI’s that had no efficacy based on the patient’s genetics
  • Avoiding Steven Johnson syndrome in a patient given Carbamazepine
  • Hereditary Hemochromatosis in an undiagnosed symptomatic 52 yo female
Clear Patient Impact (cont.)

• Alpha1 Antitrypsin Deficiency in a 23 yo smoker
• Malignant Hyperthermia variant in a 25 yo who has not yet had major surgery
• Brugada Syndrome in a patient with EKG abnormalities previously believed to be benign
Yale New Haven Health

Yale Center for Genome Analysis (YCGA) (Yale West Campus)

Tumor Profiling Laboratory (Anatomic Pathology)

Molecular Diagnostics Laboratory (Laboratory Medicine)
YNHH Genomic Health Initiatives

• Expand access to genetic testing
  • Genetics/West Campus: Whole exome/genome sequencing
  • Anatomic Pathology: Solid tumor panels
  • Clinical Pathology: Hematologic malignancy panels, non-NGS testing

• Several clinical areas of interest
  • Pediatric exome sequencing / rare diseases
  • Oncology sequencing
  • Pharmacogenomics
Requirements for Point of Care Genomic Results

• Speed/availability of testing
• Correlation of outcome/phenotype with genotype
• Usable results with information at time of care
• Clinical champions interested in pharmacogenomic testing
Clinical Rollout

Clinical Departments
- Psychiatry
- Anesthesia / Pain Management
- Infectious Disease
- Cardiology

Rollout Considerations
- Care Workflow
- Existing Testing
- Support Capacity
- Clinical Evidence / Indications
Experience Implementing a Point of Care Genomics Platform

- Approximate 8 week deployment timeline
  - 6 week deployment timeline for EHR build / vendor integration
  - 2 week validation of full round testing and integration
- Close collaboration between IT, laboratory, and pharmacy
  - LIS build team
  - EHR integrations team
  - Local laboratory managers and reference laboratory
  - Pharmacy system leaders and IT build team
  - Vendor support (EHR, pharmacogenomics platform)
Integrating Informatics and Clinical Testing

• System-funded initial rollout
• Randomized trial to assess outcomes / cost effectiveness
• Capture of additional genotype / phenotype data to support research studies
• Development of screening models / protocols for routine testing
Clinical Trial - Psychiatry

- Many variant/drug interactions in database for commonly prescribed psychiatric medications

- Pharmacokinetics well-described, with some evidence to support use (but in small / international studies)

- **Hypothesis**: Pharmacogenomic testing in patients with newly diagnosed depression will lead to fewer medication failures and side effects compared to standard of care.
  
  - Randomize patient to standard of care vs with pharmacogenomics
  
  - Assess number of medications, adverse events, and time to improved symptoms between groups
When to Test?
Artificial Intelligence and Genomic Decision Support
Artificial Intelligence and Genomic Decision Support

Demographics → Encounter History → Medical History → Prescription History → Laboratory Results

AI Profile → New Encounter → Likelihood of New Prescription
Assisting Clinical Practice with AI

Patient has Clinical Encounter

AI-Driven Pharmacogenomic Screening Order

Pharmacogenomics Result Obtained

Point-of-Care Gene/Medication Alert to Provider

Patient has Next Clinical Encounter
Moving Beyond Pharmacogenomics

• Carrier testing
• Genetic trait reporting
• Decreased exome/genome turnaround time

• Associated questions / concerns
  • Reimbursement
  • Patient privacy (GINA limitations)
  • Analytic capacity for large scale clinical testing
Conclusions

• Integrating genomics into routine clinical care is an important step to advance the promise of precision medicine

• Identifying tools that can fit provider workflow and provide complex interpretative data at the point of care may reduce the barrier to integration

• Point of care genomic workflows can be efficiently integrated into existing EHR platforms

• Many opportunities to develop translational research projects and improve clinical care with genomics and point of care results
Questions

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