Realizing a Lifetime of Genomically Informed Care

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Top Topic Perspective

- Genomic Medicine
- Personalized Medicine
- Individualized Medicine
- Precision Medicine
Genomic Medicine

- Includes
  - Traditional single gene disorders (genetics)
  - Analysis of the whole genome (genomics)
  - Analysis of subsets of the whole genome
    - Exome sequencing
    - Pharmacogenomics
  - Family History
Personalized Medicine-Definition

- “...use of information and data from a patient’s genotype, or level of gene expression to stratify disease, select a medication, provide a therapy, or initiate a preventative measure that is particularly suited to that patient at the time of administration”
  - Wikipedia
Genomic Medicine ≠ Personalized Medicine

“Personalized medicine is the practice of clinical decision-making such that the decisions made maximize the outcomes that the patient most cares about and minimizes those that the patient fears the most, on the basis of as much knowledge about the individual’s state as is available.”

Personalized vs. Precision Medicine

• Clinicians practice personalized medicine (and always have)
• Currently—Intuitive medicine
  o Care for conditions that can be diagnosed only by their symptoms and only treated with therapies whose efficacy is uncertain and watching for empiric response.
  o Empiric ‘trial and error’
• Future—Precision medicine
  o the provision of care for diseases that can be precisely diagnosed, whose causes are understood, and which consequently can be treated with rules-based therapies that are predictably effective.
  o Expect genomics to play a key role in this

Adapted from The Innovator’s Prescription A Disruptive Solution for Healthcare. Christensen, Grossman and Hwang, 2009
Value in Healthcare
What is Value?

• Crudely can be thought of as a relationship between outcomes and cost of care

• Patient centered outcomes would include
  o Medical outcomes (treatment, prevention, safety)
  o Service outcomes (number of visits, disruption of life routine)
  o Information?
    ▪ Highly valued in genetics
    ▪ Difficult to value economically
    ▪ Personal utility vs. control of health care costs

• In general we do a poor job measuring cost of services
## Value Plot

<table>
<thead>
<tr>
<th>Medical and/or Service Outcomes</th>
<th>Cost of care decreased</th>
<th>Cost of care unchanged</th>
<th>Cost of care increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Unchanged</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Worsened</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
</tbody>
</table>
Value in the United States

Health-Care Spending and Health Outcomes, 2009 or Most Recent Year

<table>
<thead>
<tr>
<th>Country</th>
<th>Health expenditures per Capita (US$PPP)</th>
<th>Life expectancy (years)</th>
<th>Infant mortality (deaths per 1,000 live births)</th>
<th>Potential years of life lost (years per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>$7,538</td>
<td>77.5 (17)</td>
<td>6.7 (17)</td>
<td>4565 (17)</td>
</tr>
<tr>
<td>Norway</td>
<td>$5,063</td>
<td>80.6 (8)</td>
<td>2.7 (6)</td>
<td>2799 (6)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>$4,627</td>
<td>82.2 (2)</td>
<td>4.9 (12)</td>
<td>2660 (4)</td>
</tr>
<tr>
<td>Canada</td>
<td>$4,079</td>
<td>80.7 (7)</td>
<td>5.1 (16)</td>
<td>3365 (12)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>$4,063</td>
<td>80.2 (10)</td>
<td>3.8 (10)</td>
<td>2767 (3)</td>
</tr>
<tr>
<td>Austria</td>
<td>$3,970</td>
<td>80.5 (9)</td>
<td>3.7 (6)</td>
<td>3619 (8)</td>
</tr>
<tr>
<td>Ireland</td>
<td>$3,753</td>
<td>79.9 (12)</td>
<td>3.1 (5)</td>
<td>3164 (10)</td>
</tr>
<tr>
<td>Germany</td>
<td>$3,737</td>
<td>80.2 (10)</td>
<td>3.5 (7)</td>
<td>3134 (9)</td>
</tr>
<tr>
<td>France</td>
<td>$3,696</td>
<td>81.0 (6)</td>
<td>3.8 (10)</td>
<td>3344 (11)</td>
</tr>
<tr>
<td>Belgium</td>
<td>$3,677</td>
<td>79.8 (14)</td>
<td>3.4 (6)</td>
<td>3587 (16)</td>
</tr>
<tr>
<td>Denmark</td>
<td>$3,540</td>
<td>78.4 (15)</td>
<td>4.0 (12)</td>
<td>3410 (14)</td>
</tr>
<tr>
<td>Sweden</td>
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<td>2.5 (1)</td>
<td>2541 (1)</td>
</tr>
<tr>
<td>Australia</td>
<td>$3,353</td>
<td>81.5 (3)</td>
<td>4.1 (14)</td>
<td>2823 (7)</td>
</tr>
<tr>
<td>U.K.</td>
<td>$3,129</td>
<td>79.7 (15)</td>
<td>4.7 (15)</td>
<td>3391 (13)</td>
</tr>
<tr>
<td>Finland</td>
<td>$3,068</td>
<td>79.9 (12)</td>
<td>2.6 (2)</td>
<td>3552 (15)</td>
</tr>
<tr>
<td>Italy</td>
<td>$2,870</td>
<td>81.5 (3)</td>
<td>3.7 (8)</td>
<td>2699 (5)</td>
</tr>
<tr>
<td>Japan</td>
<td>$2,729</td>
<td>82.7 (1)</td>
<td>2.8 (2)</td>
<td>2587 (2)</td>
</tr>
</tbody>
</table>

Note: Rankings are shown in parentheses for the health outcomes indicators. Source: OECD.
Value in Genetics

• With few exceptions little information
  • Challenge of disorders rare individually but common in aggregate
  • No concerted effort to generate evidence of benefit

• Health care system moving to value-based assessments

• Have to determine how to assess the value of WGS

• Potential to reuse genomic information over a lifetime?
Genomics over the Lifespan

Advantages

- Cost spread out over lifetime of care
- Avoids need to repeat testing
- Information can be used as soon as it is needed
- More precise pharmacologic therapy
  - Avoid adverse events
  - Choose best tolerated most effective therapy
## Genomics over the lifespan

### Sequencing as screening
- Sequencing done at some point for everyone
  - Newborn?
- Advantages
  - Sequence available when it’s needed
  - Public Health approach
- Disadvantages
  - Large up front cost
  - Fewer indications for use in infancy and childhood
  - Changing technology

### Sequencing for indication
- Sequencing performed for a medical indication
- Advantages
  - Sequence immediately useful
  - Sequence available for use for rest of lifespan
- Disadvantages
  - Takes time to obtain sequence
  - May not be available when needed (medications)
  - Not everyone would get sequenced
Genomics over the lifespan

- Prenatal
  - Prenatal screening
  - Known genetic disease in family
- Diagnosis
  - Fetal growth issues
  - Malformations
Newborns

- Newborn screening
  - Replace analyte screening?
  - Genomic approaches for some screened disorders
    - Deafness
    - Immunodeficiency
  - Expand to additional diagnoses
- Neonatal illnesses
  - Malformations
  - Severe illness
Children

- Medications
- Anesthesia associated risks
- Diagnosis
  - Autism/Developmental Delay
  - Malformations
  - Neurologic disease
Young Adults

- Medications
- Risk for adult-onset disorders
  - Individualized prevention
- Preconceptional genetic testing
- Diagnosis
  - Rheumatologic disease
  - Cancer
  - Early-onset adult disorders
Older Adults

- Pharmacogenomics
- Individualized prevention
- Diagnosis
- Genomically informed disease management
- Prognosis
- Interpretation of somatic genome (cancer)
# Genomics over the Lifespan

## Advantages
- Cost spread out over lifetime of care
- Avoids need to repeat testing
- Information can be used as soon as it is needed
- More precise pharmacologic therapy
  - Avoid adverse events
  - Choose best tolerated most effective therapy

## Questions
- Storage of information
- Information available wherever patient receives care
- Evidence of benefit (or lack thereof)
- Updating information
- Presentation of information when needed at point of care
- Discrimination
Storage
Storage

- Whole genome consists of over 6 billion base pairs
- Cost of storage significant
  - Cheaper to keep in the DNA molecule?
- Do we need to store everything?
Storage—other approaches

**Exome**
- Consists of the DNA in genes and regulatory regions
- 1.5% of the whole genome
- Contains most of what is clinically relevant currently

**Limitations**
- Most of the exome is still not clinically useful
- Current approaches to exome sequencing miss 10-15% of exome
- Other parts of the genome will have clinically important information
Concept

- Clinical ‘exome’
  - Store only the information that has evidence of clinical effectiveness
    - Subset of exome
    - All information of potential clinical relevance
    - As more information is accumulated about can add additional genes/variants to the clinical ‘exome’
    - All genomic information is added if clinically useful
<table>
<thead>
<tr>
<th>Criteria:</th>
<th>Clinical Utility</th>
<th>Clinical Validity</th>
<th>Unknown Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bins:</strong></td>
<td>Bin 1 Medically actionable incidental information</td>
<td>Bin 2A Low risk incidental information</td>
<td>Bin 2B Medium risk incidental information</td>
</tr>
<tr>
<td><strong>Examples:</strong></td>
<td>BRCA1/2, MLH1, MSH2, FBN1, NF1</td>
<td>PGx variants and common risk SNPs</td>
<td>APOE Carrier status for recessive Mendelian disorders</td>
</tr>
<tr>
<td><strong>Estimated number of genes/loci:</strong></td>
<td>10s (eventually 100s – 1000s)</td>
<td>1000s</td>
<td>10s</td>
</tr>
<tr>
<td><strong>Alleles that would be reportable (YES) or not reportable (NO) in a clinical context</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known deleterious</td>
<td>YES</td>
<td>YES/NO</td>
<td>YES/NO</td>
</tr>
<tr>
<td>Presumed deleterious</td>
<td>YES</td>
<td>N/A</td>
<td>YES/NO</td>
</tr>
<tr>
<td>VUS</td>
<td>NO</td>
<td>N/A</td>
<td>NO</td>
</tr>
<tr>
<td>Presumed benign</td>
<td>NO</td>
<td>N/A</td>
<td>NO</td>
</tr>
<tr>
<td>Known benign</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

N/A: not applicable; VUS: Variant of uncertain significance

1 Reporting through decision making with an appropriate provider if elected by the patient.
2 By definition, variants in genes with unknown implications could not be considered deleterious.
3 By definition, SNPs or PGx variants will either be present or absent.
4 Variants in genes with unknown clinical implications would not be reported; however, they may serve as an important substrate for research, potentially uncovering new disease genes.
Availability of Information

- Genomic information must be available whenever needed
- Currently difficult to move patient-specific information between different health systems

Solutions

- National electronic health record or information exchange
- Centralized genomic data repository
  - Trusted broker
  - Secure Cloud based
  - Certified EHRs access through secure app or portal
- Personal responsibility
  - Flash drive
  - Genomic “credit card”
  - Implant
Evidence

- At present few examples of clinical utility
  - Pharmacogenomics
  - Rare, single-gene conditions
- Anticipate rapid increase in knowledge—if data can be aggregated
- Need a centralized way to accumulate and store information to facilitate research on clinical utility
- Could also allow rapid annotation of genome from a variety of sources
- Would need to develop standardized policies, sustainable funding and interoperability with clinical EHRs
eMERGE Network
The ClinGen Resource-Aims

- Develop a standardized infrastructure for data acquisition, submission and public access for a clinical genomic variation database
- Submit genotype and phenotype data into a public database for clinical and research communities
- Implement sustainable expert clinical level curation systems for human genomic variants
- Maintain active collaborations with other groups and initiatives seeking to improve patient care
Discrimination

- Has been of great intellectual concern
- Few examples of discrimination in health care or employment
- Legislation to protect against genetic discrimination at state and national level
- Still significant concern from patients and providers
Strategy

**6 Quality Outcomes**
- Avoid adverse effects events
- Improve patient physiologic function
- Relieve patient signs and symptoms
- Improve patient well-being and functioning
- Achieve patient satisfaction
- Minimize the cost of care

Implementation Research

Basic genetic/genomic and other knowledge

Intelligent filter

Informatics, just-in-time education, care processes, clinical decision support, etc.

Ready for Prime Time

Intervention
Realizing Precision Medicine

• Many challenges
  • Storage of information
  • Communication of information across different care delivery systems
  • Defining clinical contexts where specific information could be used
  • Updating information as new knowledge emerges
  • Models of care delivery
  • Measurement of costs and outcomes (value)

• How can we individualize this at the point of care?
Mass Customization

Create your own personal apparel!
Evolution to Mass Customization

19th Century
CRAFT
- high quality
- customized, but at high cost
- limited distribution

20th Century
MASS PRODUCTION
- low cost
- wide distribution, but lower quality

21st Century
MASS CUSTOMIZATION
- customized
- high quality
- low cost
- wide distribution

SOURCE: Candace Keaton Rylander, Texas Comptroller of Public Accounts.
Problems with Mass Customization in Medicine

- Evidence for therapies is almost exclusively population-based
  - FDA drug approval requires this to determine efficacy
- Current EHR systems do not support aggregation of relevant patient data at the point of care
- Number of data elements surpasses human cognitive capacity
- Limited ability to collect outcomes data from real world to determine effectiveness of personalized interventions
- Traditional methods of disseminating knowledge (e.g. conferences, journals) not supportive of this approach
A (near) Future View
Antiretroviral therapy

- Nevirapine
  - HSR in ~6% of patients
  - Risk factors
    - CD4 count
    - Sex
    - Asian ethnicity
    - HLA-B*35:05 status
  - How to implement?
CDS Computerized Order Entry for Nevirapine

**Information needed**
- Ethnicity
- Drug allergies
- Sex
- Pregnant (if female)
- Interacting medications
- CD4 count

**HLA-B*3505 genotype**

**Information complete?**

**Adverse Reaction algorithm**

**Alert!!**
Patient is at high risk for hypersensitivity reaction. Recommend alternative treatment.

Click here for recommended alternatives

more...
CDS Computerized Order Entry for Tegretol

**Information needed**
- Treatment indication
- Asian Ethnicity
- Drug allergies
- Gender
- Pregnant (if female)
- Interacting medications
- CD4 count

**HLA-B*15:02 genotype**

- +Asian

**Information complete?**
- Yes
  - **Adverse Reaction algorithm**
  - **ALERT!!**
    - Patient is at high risk for Stevens-Johnson syndrome.
    - Recommend alternative treatment.
    - Click here for recommended alternatives
    - more...

- No
  - Provider prompted to obtain needed information
Pharmacogenomics

2010

Carbamazepine (Tegretol) Sensitivity

Pharmacologic agent: Carbamazepine (Tegretol) carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia.

**WARNING: SEVERE DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE:**
Severe, life threatening skin reactions, including fatal cases, have occurred in patients treated with carbamazepine. These have included cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. In countries with primarily Caucasian populations, the incidence is 1-5 per 10,000 new users. The rate approaches 10 times higher in Asian and Asian Indian populations. This higher risk is due to the presence of the HLA-B*1502 allele in much higher frequencies in these populations.

Pharmacogenomic information: Patients who carry the HLA-B*1502 allele are at high risk for developing severe hypersensitivity skin reactions to carbamazepine. Patients of Asian ethnicity should be screened for this HLA type prior to initiation of carbamazepine. FDA has revised the boxed warning to reflect this risk.

**Action:**
- Screening for the HLA-B*1502 allele should be performed in patients of Asian ethnicity prior to starting carbamazepine. If this is present an alternative medication is indicated unless the benefits of carbamazepine clearly outweigh the risks.

**Reference/Resources**

General drug information obtained from RxList: [http://www.rxlist.com/tegretol-drug.htm](http://www.rxlist.com/tegretol-drug.htm)
The Future is Now

- Pharmacogenomics is being implemented in a number of health care systems
- Clinical Decision Support tied to physician order entry in regular use for allergies, drug interactions
- CDS does improve care, but subject to alert fatigue and override
- Requires physician to have done evaluation and place an order
- How can we use information more dynamically?
Dynamic EHR Mining

- Use documentation of medical care in EHR to trigger search of genomic data
- ‘Genome first’ diagnosis
- Focus on conditions with high genetic burden
- Avoids the need to recognize that a genetic test (or result) is needed
- Can provide a shortcut for the diagnostic odyssey
Example

- A newborn infant fails hearing screening test and is referred for confirmatory testing
  - EHR ‘captures’ failed screening test and order for referral to audiology
  - Triggers algorithm (2/3 of congenital deafness is genetic)
  - Interrogate sequence (more likely orders sequencing from newborn blood spot)
    - Look at all genes known to cause deafness
Example

- At audiology referral infant has been identified to have 2 mutations in the Connexin-26 gene.
  - Autosomal recessive non-syndromic hearing loss
- Value?
  - Parents at 25% chance for recurrence
  - No other medical issues to investigate
  - Able to be treated with cochlear implant
At age 6 child becomes ill with fever and right lower quadrant abdominal pain

Diagnosed with acute appendicitis and prepared for surgery

EHR recognizes diagnosis and order for surgery

System identifies that the child has had genomic sequencing
  • Interrogates for genes associated with malignant hyperthermia
Example continued

- Deleterious mutation identified in $RYR_1$
- Anesthesiologist alerted to avoid certain muscle relaxants and to have appropriate dose of Dantrolene ready for administration
- In post-op period codeine is ordered for pain control
- Computerized order entry CDS interrogates $CYP_{2D6}$ genotype to inform appropriate dose or alternative medication
What’s Needed

- EHR that can capture or transform medical ‘transactions’ as structured data
  - Standardized across all EHRs
- Storage of relevant genomic information in a system that can interact with EHR
  - Prebuilt clinical triggers message the genomic storage
  - Preconstructed algorithms assess the genes relevant for clinical trigger
    - Alternatively all algorithms are run once sequencing is done and answers are available in EHR when needed
  - Relevant answers are returned to clinicians at appropriate time in clinical workflow
- Information is regularly updated as new knowledge is generated
Role of the Patient

- At present the only consistent agent in the US healthcare system
- Have the most to gain by effective use of genomic information
- Have more time than health care providers
- How can we empower patients to be effective partners in managing genomic information?
PCORI Contract

- Enhancing Genomic Laboratory Reports to Enhance Communication and Empower Patients
- 3 year contract funded through PCORI Communication and Dissemination funding opportunity
Specific Aims

- **Specific Aim 1** Develop a genomic laboratory report with advanced functionality including point of care education and clinical decision support. Development will use providers and parents of affected patients to provide feedback on the desired elements for the provider and patient views and the usability of the report.

- **Specific Aim 2** Deploy the report for patients and families and their providers. The report will be presented to clinicians in the electronic health record and to patients either through a secure patient portal or by giving access to parts of the electronic medical record.

- **Specific Aim 3** Study the impact of the tool from the perspective of providers and family of affected patients.
Genomic Test Report Development Flow Chart

Individual Patient Interviews (n=15)

Combined patient/provider report acceptable?

Yes → Revise report based on patient/provider feedback

No → Present revised patient report to patient focus group (n=16)

Present revised patient report to patient focus group (n=16)

Revise & reiterate as needed

Final Patient Report

Individual Provider Interviews (n=10)

Combined patient/provider report acceptable?

Yes → Present to patient focus groups (n=16)

Present to patient focus groups (n=16)

Show results & reiterate as needed

Final Combined Report

No → Present revised provider report to providers (n=6)

Present revised provider report to providers (n=6)

Revise & reiterate as needed

Final Provider Report
Key Outcomes

- Identify key opportunities, barriers and generalizable principles
- Extend to other sequencing efforts
- Utilize patient portals, mobile technologies and other emerging strategies
- Test effectiveness compared to usual care
Conclusions

- Genomics is moving into practice
- Potential is large but need evidence and effective implementation
- Neither patients nor providers are adequately prepared to use most genomic information at present
- Health care system will need to undergo a re-engineering to successfully utilize genomic information
Thank you and Questions