Precision Medicine

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What is precision medicine?

• Providing the right treatment for the right patient at the right time and engaging the patient in a way that will enable them to maintain and improve their health and the health of their family.
The Cost of Sequencing Has Declined

Cost per Genome

Moore's Law

NIH National Human Genome Research Institute

genome.gov/sequencingcosts

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Columbia University Medical Center
Seizures

• 9 year old female
• Seizures and dyskinesia at birth, microcephaly, intellectual disability
• No known family history of similar symptoms
Positive for a mutation in SLC2A1 Causing GLUT1 deficiency syndrome

• GLUT1 deficiency syndrome is due to the inability to transport glucose to the brain

• Diagnostic Implications:

In individuals with SLC2A1 mutations, a ketogenic diet often improves seizure control and reduces paroxysmal events, although cognitive impairment persists.

Mutation-specific testing for the SLC2A1 mutation showed this was a de novo mutation.
Complexities of Genetic Diagnostics

- Analysis of a genome identifies thousands of genetic variants, many of which have never been observed before.
- The methods used in the lab to generate data and interpret the data are highly complex and still evolving. Changes are made on a quarterly basis and result in significant improvements.
- Limiting patient access to these innovations jeopardizes patients’ health.
• Why a diagnosis matters

• Ends the diagnostic odyssey which may involve invasive/expensive tests
• Prognosis, ability to tailor health maintenance
• Identifies treatment options
• Risk of recurrence, ability to prevent having other affected children if desired
• Closure about how this happened
### Cost Analysis Before WES

- (without including cost of the hospitalization)

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging Cost</td>
<td>$5,979</td>
</tr>
<tr>
<td>Laboratory Tests Cost</td>
<td>$1,221</td>
</tr>
<tr>
<td>Other Testing (including biopsy)</td>
<td>$887</td>
</tr>
<tr>
<td>Genetic testing /Karyotype/ Chromosome microarray</td>
<td>$14,425</td>
</tr>
</tbody>
</table>

**Total Cost** $22,512
## Opportunities in Precision Medicine

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of sequencing a human genome</td>
<td>$22,000,000</td>
<td>$1000 to $5000</td>
</tr>
<tr>
<td>Time to sequence a human genome</td>
<td>2 years</td>
<td>&lt;1 day</td>
</tr>
<tr>
<td>Number of smart phones in the United States</td>
<td>1 million (&lt;2% of population)</td>
<td>160 million (58%)</td>
</tr>
<tr>
<td>Health providers using electronic records</td>
<td>20 % to 30%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Computer power</td>
<td>n</td>
<td>n x 16</td>
</tr>
</tbody>
</table>

Jocelyn Kaiser Science 2015;347:817
Cumulative Risk of Breast and Ovarian Cancer

BRCA1

BRCA2
Clinically Available Molecular Diagnostics along the continuum from health to disease in cancer and cardiovascular disease

<table>
<thead>
<tr>
<th>Time point in clinical decision making</th>
<th>Cancer</th>
<th>Cardiovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk/susceptibility</td>
<td>BRCA1, BRCA2, HNPCC, MLH1, MSH2, TP53, PTEN</td>
<td>Breast, Colon, Sarcomas</td>
</tr>
<tr>
<td>Screening</td>
<td>HPV genotypes</td>
<td>Cervical</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Lymphochip</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Oncotype DX (21-gene assay), MammaPrint (70-gene assay), Her2/neu, ER, PR</td>
<td>Breast</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>Her2/neu, UGT1A1, KRAS, EGFR, Amplichip; DMET</td>
<td>Herceptin, Irinotecan, Cetuximab, Erlotinib, Gefitinib, Various others</td>
</tr>
<tr>
<td>Monitoring</td>
<td>CTCs</td>
<td>Tumor recurrence or progression</td>
</tr>
</tbody>
</table>

What’s next?

• Mutation specific therapy
  – Cystic fibrosis: Ivacaftor/Kalydeco for G551D mutation (1200 patients at cost of $311,000/year)
  – Spinal muscular atrophy

• Gene editing

• Demonstrating cost effectiveness

• Predictive testing
  – Will need real time measurement of disease progression with biomarkers
Ivacaftor (Kalydeco) for treatment of cystic fibrosis

- Drug for patients with one mutation-G551D (affects 4% of all ~70,000 cases of CF)
- Identified in small molecule screen as VX-770
- Mechanism of action: binds and opens CFTR channel protein
- Outcomes
  - Improvement of lung function
  - Changes in CF respiratory symptoms
- Cost of drug: $311,000 per year
Proprotein convertase subtilisin/kexin type 9 (PCSK9)

- Involved in high cholesterol
- Genetically identified in individuals with high and low cholesterol
- Drugs that block PCSK9 lower LDL cholesterol to prevent hyperlipidemia
  - Monoclonal antibodies decreases bad cholesterol
Precision Medicine Through Life

Decision support tools:

- Assess risk
- Refine assessment
- Predict/diagnose
- Monitor progression
- Predict events
- Inform therapeutics

Sources of new biomarkers:

Baseline risk:
- Stable genomics
  - Haplotype mapping
  - Gene sequencing
  - Single-nucleotide polymorphisms

Preclinical progression:
- Dynamic testing
  - Gene expression
  - Proteomics
  - Metabolomics
  - Clinical risk models

Disease initiation and progression:
- Therapeutic decision support

Disease burden
Cost
1/reversibility

Time

Disease process

Personal health plan

How Genomic Medicine Is Used in the Pipeline to Develop New Treatments

Identify/validate gene targets

Identify lead compounds

Improve efficacy and safety

Target patients

Target identification

Target validation

Lead development

Preclinical

Clinical

Market

Genomics

Eliminate targets

Validate leads

Select patients

Genomic medicine

Gene editing as a treatment for genetic diseases

- DNA is inserted, replaced, or removed from a genome by programmable nucleases
- Targeted therapies aimed at disease mechanisms based on knowledge of genetic basis of disease
Challenges Ahead

- Interpretation of variants is challenging
  - Minority populations must be better represented
- Need to share data yet protect privacy
- Cost of sequencing is still high because of monopolies in the market
The Cost of Sequencing Is Not Declining
Challenges Ahead

• Interpretation of variants is challenging
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• Need to share data yet protect privacy
• Cost of sequencing is still high because of monopolies in the market
• Access to testing is not universal
• Clinical utility/cost effectiveness must be demonstrated but will take a long time
• Low genomic literacy of the public
• Insufficient genomic work force to deliver patient care
Insufficient Number of Medical Geneticists

![Bar chart showing the number of board certificates issued for Clinical Genetics and Cardiology from 2004 to 2013. The chart indicates a significant increase in 2013, with the total number of certificates reaching 8,104.](image-url)
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- Threats of FDA regulation could be paralyzing
- Many disorders are new, and developing understanding of disease mechanism/treatment will take time and resources for research
NIH Funding is Declining

NIH funding, FY 1950–2019

in thousands of constant 2013 BRDPI adjusted dollars

Source: NIH funding figures through FY 2014 are based on total budget authority. Projected NIH funding figures for FY 2015 through FY 2019 are based on data from the Congressional Budget Office.
Conclusion

• There are important opportunities to improve the health of the country and decrease health care costs and allow us to lead the world in innovation, but this will require investment to realize our potential