The hype, the hope, and the reality of genomic medicine

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Columbia University
Disclosures

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• Research funding provided by Biogen
Genetics
THE FUTURE IS NOW

New breakthroughs can cure diseases and save lives, but how much should nature be engineered?
Genetics
THE FUTURE IS NOW

New breakthroughs can cure diseases and save lives, but how much should nature be engineered?
“We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten.”

Bill Gates
Genomic Testing Clinical Scenarios

• Diagnose symptomatic individuals
  • Prenatal & Postnatal Diseases
  • Cancer (germline and somatic)
  • Cardiac conditions
  • Neurodevelopmental disorders/Seizures
  • Visual impairment

• Predict risk
  • Identify pre-symptomatic individuals
  • Pharmacogenetics

• Screening
  • Carrier Screening
  • Prenatal Screening
  • Newborn Screening
Value of a Genetic Diagnosis

VALUE OF GENETIC TESTS THAT:

- Confirm suspected or established diagnosis
- Inform prognosis
- Support from other families
- Inform reproductive decisions and life planning
- Inform disease management and prevention

CLINICAL ACTIONABILITY:

- Inform reproductive decisions and life planning
- Inform disease management and prevention
- Inform prognosis
- Support from other families
- Confirm suspected or established diagnosis

Lerner et al, Genetic Medicine 2016
Why accurate *predictions* matter

- Tailor health maintenance and prioritize health threats in real time
- Increase alertness/monitoring to maintain health
- Prevent disease, ideally using real time data
- Provide reassurance or decreases ambiguity
- Assist with life planning
- Assist with family planning
Reduced Sequencing Costs Enables Genomic Medicine
Sensitivity of NIPS and First Trimester Serum Screening

- **Trisomy 21**: Serum FTS and NIPT
- **Trisomy 18**: Serum FTS and NIPT
- **Trisomy 13**: Serum FTS and NIPT
NIPS Positive Predictive Value

- Trisomy 13 - NIPT
- Trisomy 13 - Serum FTS
- Trisomy 18 - NIPT
- Trisomy 18 - Serum FTS
- Trisomy 21 - NIPT
- Trisomy 21 - Serum FTS
Fetus at 28 weeks gestation

- Hydropic
- Anatomy scan normal
- Fetal echocardiogram normal
- Irregular heartbeat, physician suspicious of LQT
- No family history of sudden cardiac death/arrest, syncope, seizures
Goal of parents and clinical team was to administer correct neonatal therapy, not termination

Parents highly motivated

Possible diagnosis of LQT or an arrhythmia

After case review by cardiac and prenatal team, agreed to test the fetus (LQT panel)
Result: KCNH2 mutation

- Pathogenic variant in KCNH2 previously reported as *de novo* in a neonate with:
  - Fetal bradycardia
  - Torsades de pointes
  - 2:1 atrioventricular block
  - Infant asymptomatic at 3 months following therapy with propanolol and a pacemaker

- Our patient reported to match this presentation
  - Patient treated with beta blocker and is doing well
Expansion of Newborn Screening

- 0
- 10
- 20
- 30
- 40
- 50
- 60
- 70


Core Conditions  Secondary Conditions

- SCID
- CHD
- Pompe
- MPS-I
- X-ALD
- Tandem Mass
Seizures

• 9 year old female
• Seizures and dyskinesia at birth, microcephaly, intellectual disability
• No known family history of similar symptoms
Positive for a *de novo* 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 if damage has already been done.
The Most Efficient Strategy to a Diagnosis for Many Conditions is Exome Sequencing: Yield by Clinical Indication

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage of Positive Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing (N=21)</td>
<td>55</td>
</tr>
<tr>
<td>Vision (N=60)</td>
<td>48</td>
</tr>
<tr>
<td>Musculoskeletal (N=43)</td>
<td>42</td>
</tr>
<tr>
<td>Skin (N=54)</td>
<td>39</td>
</tr>
<tr>
<td>Nervous system (N=188)</td>
<td>39</td>
</tr>
<tr>
<td>Cardiovascular (N=54)</td>
<td>37</td>
</tr>
<tr>
<td>Metabolic (N=84)</td>
<td>32</td>
</tr>
<tr>
<td>Blood (N=154)</td>
<td>31</td>
</tr>
<tr>
<td>Senile (N=134)</td>
<td>27</td>
</tr>
<tr>
<td>Musculature (N=108)</td>
<td>26</td>
</tr>
<tr>
<td>Genitourinary (N=132)</td>
<td>25</td>
</tr>
<tr>
<td>Growth (N=137)</td>
<td>23</td>
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<tr>
<td>Mucocutaneous (N=173)</td>
<td>23</td>
</tr>
<tr>
<td>Respiratory system (N=32)</td>
<td>22</td>
</tr>
<tr>
<td>Autism spectrum (N=120)</td>
<td>20</td>
</tr>
<tr>
<td>Abdomen (N=14)</td>
<td>18</td>
</tr>
<tr>
<td>Endocrine system (N=62)</td>
<td>14</td>
</tr>
<tr>
<td>Peripheral nerve (N=221)</td>
<td>13</td>
</tr>
<tr>
<td>Neoplasm (N=27)</td>
<td>11</td>
</tr>
<tr>
<td>Other (N=6)</td>
<td>10</td>
</tr>
</tbody>
</table>

Retterer, Genetics in Medicine, 2015
# Diagnostic Yield of Gene Panels

<table>
<thead>
<tr>
<th>Gene Panel Type</th>
<th>N</th>
<th>Overall Dx Yield</th>
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<tbody>
<tr>
<td>Dermatology</td>
<td>68</td>
<td>62%</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>36</td>
<td>61%</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>122</td>
<td>59%</td>
</tr>
<tr>
<td>Renal diseases</td>
<td>107</td>
<td>57%</td>
</tr>
<tr>
<td>Deafness</td>
<td>147</td>
<td>54%</td>
</tr>
<tr>
<td>Vision</td>
<td>418</td>
<td>52%</td>
</tr>
<tr>
<td>Neurology</td>
<td>524</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Syndromic DD/ID</strong></td>
<td></td>
<td>25-47%</td>
</tr>
<tr>
<td><strong>Non-syndromic DD/ID</strong></td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>Dysmorphology-Dysplasia</td>
<td>354</td>
<td>38%</td>
</tr>
<tr>
<td>Primary Immunodeficiencies</td>
<td>196</td>
<td>37%</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>36</td>
<td>36%</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>73</td>
<td>29%</td>
</tr>
<tr>
<td>Hematology</td>
<td>33</td>
<td>24%</td>
</tr>
</tbody>
</table>

Adapted from Saudi Mendeliome Group Study, 2015
### Panels vs Exomes

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
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<tbody>
<tr>
<td>• Cheaper</td>
<td>• Miss novel genes</td>
</tr>
<tr>
<td>• Less (more?) to analyze</td>
<td>• No opportunity to interrogate additional genes for other indications in the future</td>
</tr>
<tr>
<td>• Shorter turnout time</td>
<td></td>
</tr>
<tr>
<td>• No incidental findings</td>
<td></td>
</tr>
</tbody>
</table>

**Diseases for which panels sufficient for most patients**
- Germline cancer
- Cardiac diseases (cardiomyopathies, inherited arrhythmias, aortopathies)
- Hearing loss
- Retinitis Pigmentosa
Publications of Novel Disease Genes Identified from Exome Sequencing

AJHG

Mosaicism and Biallelic Variants in EMCI Identified in Individuals with Global Developmental Delay, Hypotonia, Seizures, and Cardiomyopathy


Neuron

Genes that Affect Brain Structure and Function Identified by Pair Variant Analyses of Mendelian Neurologic Disease


De novo mutations in PURA are associated with hypotonia and developmental delay


De novo POGZ mutations are associated with neurodevelopmental disorders and microcephaly


Mutations in ARID2 are associated with intellectual disabilities


Clinical Case Reports

Loss of function mutation in glutamate pyrocarboxylase transaminase 2 (GPT2) causes developmental encephalopathy


AJHG

De novo mutations in PURA are associated with hypotonia and developmental delay


De novo mutations in PURA are associated with hypotonia and developmental delay


AJHG

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Simons Variation in Individuals Project (Simons VIP)

- Study of monogenic forms of autism to increase homogeneity of subjects to enable more robust and replicable studies of the brain and behavior

**Genes Associated with Features of Autism**

<table>
<thead>
<tr>
<th>ACTL6B</th>
<th>CHAMP1</th>
<th>DYRK1A</th>
<th>KMT2C</th>
<th>PURA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNP</td>
<td>CHD2</td>
<td>FOXP1</td>
<td>KMT2E</td>
<td>REST</td>
</tr>
<tr>
<td>AHDC1</td>
<td>CHD8</td>
<td>GRIN2A</td>
<td>MBDS</td>
<td>SCN2A</td>
</tr>
<tr>
<td>ANK2</td>
<td>CSNK2A1</td>
<td>GRIN2B</td>
<td>MED13L</td>
<td>SETDS</td>
</tr>
<tr>
<td>ANKRD11</td>
<td>CTBP1</td>
<td>HIVEP2</td>
<td>PACS1</td>
<td>SMARCC1</td>
</tr>
<tr>
<td>ARID1B</td>
<td>CTNNB1</td>
<td>HNRNPH2</td>
<td>PBRM1</td>
<td>SMARCC2</td>
</tr>
<tr>
<td>ASH1L</td>
<td>CUL3</td>
<td>KAT6A</td>
<td>POGZ</td>
<td>STXB1</td>
</tr>
<tr>
<td>ASXL3</td>
<td>DDX3X</td>
<td>KATNAL2</td>
<td>PPP2R5D</td>
<td>SUV420H1</td>
</tr>
<tr>
<td>BAF190</td>
<td>DSCAM</td>
<td>KDM5B</td>
<td>PTCHD1</td>
<td>SYNGAP1</td>
</tr>
<tr>
<td>BCL11A</td>
<td>DST</td>
<td>KDM6B</td>
<td>PTEN</td>
<td>TBR1</td>
</tr>
</tbody>
</table>

[Simons VIP Registration: Access all identified genes]
PACS1: bringing families together

• Arg203Trp mutation is associated with autism/intellectual disability/epilepsy
• Associated with congenital heart disease
• Transport protein that mediates the localization and movement of other proteins along the trans-Golgi-network
The mission of SPARK – an online, long-term study – is simple. We want to speed up research and advance our understanding of autism. Help spark better futures for all individuals and families affected by autism.

JOIN SPARK!

SPARKforAutism.org
To recruit, engage, and retain 50,000 individuals with ASD and their biological family members to:

- Identify causes of ASD
- Accelerate clinical research and find new treatments
- Enable genotype-driven research
- WES performed and monogenic causes of autism are CLIA confirmed and returned to families

SPARKforAutism.org
sfari.org/resources/sfari-base
SPARK is returning individual genetic results related to ASD

- Pre-define list of genes that Medical Genetics Committee agrees are established ASD genes, list updated annually (90 genes and CNVs)
- Variants are confirmed in CLIA lab and clinical report issued
- Committee reviews each case prior to returning result
- If participant chooses to receive result, SPARK returns result through a central genetic counselor/geneticist or report to participant’s medical provider
- Centralized expertise that scales
Reinterpretation of Exome Data Has Significant Yield

**INITIAL DIAGNOSTIC YIELD**

- Diagnosis = 25%
- No Diagnosis = 75%

**DIAGNOSTIC YIELD ON REANALYSIS OF NEGATIVE CASES**

- Diagnosis = 51%
- No Diagnosis = 49%

- Known Genes
- Novel Genes
- Candidate Genes
Opportunities and Challenges for Genomic Sequencing

In a study of WGS in 35 NICU patients (Petrikin et al., 2015)

- Diagnostic yield 57% (20/35)
- 65% are due to de novo variants
- Molecular diagnosis had not been considered in the differential diagnosis in 45% (9/20)
- Diagnosis had clinical impact in 65% of diagnosed patients.

Turn around time
Insurance coverage
Need for iterative re-analysis
Deciding what to report
Impact of an Early Diagnosis

Petrikin JE et al., 2015
Impact of an Early Diagnosis

Petrikin JE et al., 2015
Solutions Needed for Clinical Exome/Genome Sequencing

- Turn around time: 2-4 weeks
  - Consolidation of data generation to sites able to do this cost effectively and efficiently
  - Continue family based analyses for now for diseases with high *de novo* frequency
  - Elimination of orthogonal confirmations in some scenarios
  - Automated pipelines for standard analysis
  - Federation of gene/disease experts for difficult interpretations
Solutions Needed for Clinical Exome/Genome Sequencing

- Insurance coverage: for specific clinical scenarios sufficient evidence exists for coverage
  - Major congenital anomaly
  - Neurodevelopmental disorders (ID, autism, epilepsy, myopathy, neuropathy)
  - Early onset hearing/visual impairment
  - Rare presentations
Solutions Needed for Clinical Exome/Genome Sequencing

- Need for iterative re-analysis
  - New methods to identify indels/CNVs
  - Better algorithms to predict pathogenic variants
  - New genes/phenotypic expansion of known genes
  - Better understanding of dual diagnoses

Boycott et al., 2017
• Deciding what to report
  • Need for interaction between clinicians and laboratorians
  • Incorporating patient preferences
  • Especially challenging for fetuses/newborns when phenotype is incomplete
Improving Interpretation of Genomic Data: Integration of multiple data types

- More data on controls
  - Value of data from communities with increased consanguinity
- Constrained/haploinsufficient genes
- Constrained regions of genes/gene families
- Improved methods of predicting functional impact of missense variants
- Improved methods of predicting functional impact of inframe indels
- Three dimensional structure of more proteins and sites of protein protein interaction

- Cells, tissues and timing of expression of all genes
- Binding sites of promoters, enhancers, splice enhancers, RNA binding proteins
- High throughput functional assays
- Use of somatic mutation data
  - 38% of all potentially causative damaging (LGD or D-mis) de novo variants observed in developmental delay cases are located in candidate cancer driver genes
What Do We Miss With Exomes?

- CNVs, re-arrangements
- Indels
- Repeats
- Non-coding regions
- Mosaics (overgrowth, brain malformations, autism)

Jamuar et al., 2014
What Is The Solution?

• Long reads
• Higher read depth
• More even coverage
• Transcriptomes?
  • What is the incremental yield and cost (data generation, analysis and storage)
• Genomes?
  • What is the incremental yield and cost (savings on library prep but increased cost in data generation, analysis and storage)
Variant Classification is Not Uniform, But Converges With Discussion

Classification of the same variant across laboratories

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement</td>
<td>34%</td>
<td>71%</td>
</tr>
<tr>
<td>Discordant</td>
<td>22%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Amendola LM et al., 2016
What Should the Policy Be to Reinterpret Variants/Genomes?

- Whose responsibility?
- How often?
- Who pays?
  - Subscription services to handle reinterpretation?
- Which reclassifications get reported?
- Same policy for retrospective versus prospective cases?
- Same policy for interpretation of exomes/genomes?
  - High yield of reinterpretation over time
Updated variant interpretation available

Private archive of variants identified in lab

Public archive of variants

Larger Data Sets
Machine Learning/Artificial Intelligence

Variant Alert
Updated variant interpretation available

Subscription Service
Genomic Workforce Is Growing, But Not Fast Enough
Future Dissemination of Genomic Medicine

CLINICAL EXPERTISE

ENABLERs
- Educational materials and public education
- Simplified billing/insurance coverage
- Centralized clinical expertise for rare disorders

LAB EXPERTISE

ENABLERs
- Larger datasets of ethnically diverse individuals
- Aggregated disease data
- Automated variant interpretation
- Automated exome/genome interpretation in clinical context
- Automated reinterpretation
Peek Into The Future...

FDA approves 23andMe test for breast cancer gene mutations

Angelina Jolie
Public awareness and education surrounding genetic testing is increasing.

BFOR Study
BRCA founder outreach study; provides genetic testing for common BRCA mutations for women and men of Ashkenazi Jewish ancestry.
# Cost Effectiveness of BRCA screening

## Cost-effectiveness of breast cancer strategies in the United States

<table>
<thead>
<tr>
<th>Testing Strategy</th>
<th>Age range, population</th>
<th>Cost-effectiveness ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Mammography</td>
<td>All ages</td>
<td>&gt;340,000</td>
</tr>
<tr>
<td>BRCA mutation screening</td>
<td>&gt;30, Universal</td>
<td>1.7 million (Myriad)</td>
</tr>
<tr>
<td></td>
<td>&gt;30, Universal</td>
<td>92,000 (Ambry)</td>
</tr>
<tr>
<td></td>
<td>&gt;30, Universal</td>
<td>53,000 (Color Genomics)</td>
</tr>
<tr>
<td></td>
<td>&gt;30, AJ</td>
<td>Cost-saving</td>
</tr>
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</table>
Fine Tuning Risk for BRCA1 Carriers
Improvements in Genetic Risk Calculators

HIGHLY PENETRANT GENES

MODERATELY PENETRANT GENES

POLYGENIC RISK SCORE

COMPOSITE RISK
Personalized Risk App

Analytics
Can adjust data to view risk over lifetime with lifestyle modifications

Dashboard
Receive alerts about scheduling annual health surveillance, news health alerts, etc.

Genetics
Calculate affect of genetic test results on health outcomes

Medical Record
View EMR and other medical record information

Personalized risk app that factors in genetics as well as other risk modifying variables.
Problem List
- Right breast cancer
- High blood pressure
- History of obesity

Annual Health Surveillance
- Mammography/MRI
- Colonoscopy
- Laboratory services
- Weight management

Genetic Test Results
- CHEK2 positive
- KCNQ1 positive

Health Alerts
- Long QT syndrome
- Pharmacogenetics

Support Groups/News Feed

Modern EMR Dashboard
Spinal Muscular Atrophy (SMA)

- Progressive degeneration & loss of spinal cord & brainstem motor neurons
- Muscle weakness, atrophy
- Difficulty breathing, poor weight gain, pneumonia, scoliosis, joint contractures

Age at onset, symptoms, severity and survival vary (types 1, 2, 3, 4)
Most common genetic cause of infant & toddler death

- Incidence: 1 in 6,000 to 1 in 11,000
- Carriers: 1 in 50 to 1 in 60

95%–98% homozygous deletion of Survival of Motor Neuron 1 (SMN1) exon 7

$SMN1$ (5q13)

$SMN2 = SMN1$ homologue
(Both produce SMN, differ by 5 nucleotides)

# genomic copies of $SMN2$ varies (0–5)
$\uparrow SMN2 \approx$ less severe, later onset

$SMN1$

$SMN2$

full-length SMN (100%)

truncated, non-functional SMN (~85-95%)

full-length SMN (~5-15%)
SMN2 copy number modifies SMA phenotype

Figure 3  Diagram of the frequency of patients with type I, type II, and type III SMA versus SMN2 copy number.

Pilot SMA Newborn Screening

Columbia University Medical Center, NY Presbyterian Hospitals, and NYS Newborn Screening Program

Major Goals
- Develop SMN1 assay
- Demonstrate feasibility of high-throughput newborn SMA screening
- Offer screening, assess uptake and outcomes

NY Presbyterian, Morgan Stanley Children’s Hospital
Manhattan
4,400 births/yr

Weill-Cornell Medical Center
Manhattan
5,800 births/yr

Allen Hospital
Upper Manhattan/Bronx
2,000 births/yr
The result of SMA newborn screening

14 months old
Gene Therapy with AAV9 for SMA

Mendell et al NEJM 2017
Conclusions

• Growing number of opportunities for genomic medicine
• Demand will increase as sequencing costs come down and as interpretation improves and is automatable
• Demand will increase as therapies and preventative options are available
• We need scalable solutions with greater centralization of expertise enabled through collaborations of experts and the enable patients
• We must collect evidence distributed across health care systems to support evidence collection
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The Vanech Foundation
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