Whole Genome Sequencing for Treating Complex Neurological Patients

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Disclosures

HudsonAlpha is a not-for-profit 501(3)c and is the sole owner of the Smith Family Clinic for Genomic Medicine, LLC. and the Clinical Services Laboratory, LLC. both of which charge for clinical services.

Howard Jacob is a Founder, Major Shareholder and Chief Scientific Officer of Envision Genomics, Inc. Envision works with hospital systems and large clinics to implement genomic medicine. None of this talk has Envision data or discusses Envision offerings, other than Envision uses HudsonAlpha’s Clinical Services Laboratory, LLC.

Overview of my talk

- The human genome will change how doctors practice medicine
- How we are changing medicine today in our community!
- Where genomic medicine can go
Mapping completed in 2002. Took 10 Years and ~$1B
Has been largely a research tool.
Sequence technology became major focus of field & created a "technology rat race"—if you have genomic technology, you are under constant pressure to get the next best technology.
Today we can do clinical Whole Genome sequencing has utility in most specialties and the NICU

Medicine is about averages

Adults: Take 2 aspirin
Shaq = 4 aspirin
Danica = 1 aspirin

Evolution of Genomics & Genomic Medicine
HudsonAlpha Faculty

17 Faculty, 115 scientists (209 total employees)

- Leading genomics research environment: NIH Undiagnosed Disease Network (UDN), Clinical Sequencing Exploratory Research (CSER), Oncology Research Information Exchange Network (ORIEN), St. Jude’s Life program.
- Expertise in clinical application of genomic medicine: Smith Family Clinic, CAP/CLIA MDx lab
- We already practice medicine using genomic data derived knowledge

4th Largest sequencing capacity in US
1st in sequencing quality in head-to-head comparision

www.smithfamilyclinic.org
Genomic Medicine is a Team Sport

Families Referring Physicians
Smith Family Clinic for Genomic Medicine
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Kelly East
Whitney Kelley
Meagan Cochran
Carol Aiken
Stefanie Frey
Elizabeth Coffey

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Inna Vaemkova
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Building Genomic Medicine

For physicians, there are 69,104 clinical genetic testing products available in the US with ten new tests entering the market each day. These tests range in complexity from single gene tests to whole genomic sequencing.

The core problems facing health plans is lack of clarity around what they are paying for with genetic testing, ambiguity on clinical utility, and concern about paid amounts for the testing, as the current 69,104 genetic tests are represented by only 200 billing codes.

Why Rare Disease Matters to Your Clinic (1/2)

- Institute of Medicine just reported 5% of diagnoses are errors – on average physician makes 62 misdiagnoses per year!
- "Five steps to diagnosis: pre-pre-analytic, pre-analytic, analytic, post-analytic, and post-post-analytic phases."
- "The pre-pre-analytic phase, which involves clinician test selection and ordering, has been identified as a key point of vulnerability in the work process due to the large number and variety of available tests, which makes it difficult for non-specialist clinicians to accurately select the correct test or series of tests (Hickner et al., 2014; Laposata and Dighes, 2007)."
- "The task of selecting the appropriate diagnostic testing is challenging for clinicians, in part because of the sheer volume of choices." There are 70,000 gene tests in the market.
- "Choosing the appropriate test requires understanding the patient’s history and current signs and symptoms, as well as having a sufficient suspicion or pre-test probability of disease or a condition (see section on probabilistic reasoning) (Pauker and Kassirer, 1975, 1980; Sox, 1986)."
- 10% of deaths and 6% to 17% of admissions due to misdiagnosis.
- Leading reason for malpractice claims.

Current standard of care: gene panels

- Primarily used to confirm a suspected diagnosis
- Expensive per gene/variant test
- Panels always out of date due to new gene/variant role in disease discovery
- New panels/updates to panels require validation
- Combined Neurology Panel:
  - Today: 556 genes
  - Includes 90 genes not shown to be pathogenic in 2015
- Whole Genomes—future-proofing

Why Rare Disease Matters to Your Clinic (2/2)

Molecular diagnostic testing is expected to improve patient management and outcomes. The potential advantages of molecular diagnostics include: (1) providing earlier and more accurate diagnostic methods, (2) offering information about disease that will better tailor treatments to patients (3) reducing the occurrence of side effects from unnecessary treatments, (4) providing better tools to for the monitoring of patients for treatment success or disease recurrence, and (5) improving patient outcomes and quality of life.

Idiopathic nature: masks the prevalence of rare disease. As each differential diagnosis goes down a different path and often settles on the closest match—masking the real diagnosis. Colleagues will not have seen this type of case either—creates a gap in knowledge to make the correct diagnosis.

IOM definition of Diagnostic Error: the failure to (a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient.

NEUROLOGY: WHEN TO CONSIDER GENOMIC TESTING

- Developmental Delay
- Seizure Disorder
- Ataxia
- Cognitive & Motor Delay
- Early-onset Dementia
- Neuropathy
- Myopathy
- Cerebral Palsy
- Autism
- Hypotonia
Clinical Sequence Exploratory Research

- NHGRI-funded consortium (9 institutions) generating and using sequencing data in a variety of clinical contexts
- Consortium aims to determine best practices when doing genomic medicine, and incorporate genomics into the current clinical workflow
- How does the return of diagnostic and secondary genetic results affect patient/family health and well-being? Clinical outcomes?

Developmental Delay/Intellectual Disability (DD/ID)

- 1-2% of children exhibit one or more DD/ID-associated symptoms
- Impaired cognition
- Failure to meet developmental milestones
- Congenital heart defects
- Craniofacial and skeletal abnormalities
- Severe autism
- Seizures

The vast majority of these problems have genetic cause

CSER Project Status

Enrollment began June 2013
Data through June 2017

- Individuals sequenced/analyzed: 1,283
- Families sequenced/analyzed: 455
- Affected individuals sequenced/analyzed: 494
- Parents sequenced/analyzed: 789

Return of results: 1,220 individuals (432 families)
Case Study 1

De novo pathogenic variant in MECP2 leads to atypical Rett syndrome

11 y.o. female with severe ID, speech delay, seizures, stereotypic behaviors

Case Study 2

3 year old female
- Severe ID
- Hypertonia
- History of infantile spasms
- Brain MR suggestive of white matter volume loss and decreased size of corpus callosum

SLC1A4

- Detected paternally inherited variant in SLC1A4 (sodium-dependent amino acid transporter, GLu258Lys)
- SLC1A4 associated with spastic tetraplegia, thin corpus callosum, progressive microcephaly (autosomal recessive)
- GLu258Lys described as a disease allele in the literature
- Proband phenotype matches: infantile spasms, severe ID, microcephaly, white matter loss, corpus callosum abnormalities
- Observed 60X in gnomAD in a heterozygous state (47 times in Ashkenazi Jews family is of Jewish descent)

Variation in the second SLC1A4 allele?
Case Study 3

- 18 year old male
- Moderate ID
- Seizures
- chr2:166870255delA
- SCN1A
- L1224R fsX34
- Pathogenic
- Dravet Syndrome

Pharmacogenomics

- Drug toxic but beneficial
- Drug toxic but NOT beneficial
- Drug NOT toxic and NOT beneficial
- Same diagnosis, same prescription

Why Learn about Adverse Drug Reactions (ADR)?
- Over 2 MILLION serious ADRs yearly
- 100,000 DEATHS yearly
- ADRs 4th leading cause of death ahead of pulmonary disease, diabetes, AIDS, pneumoonia, accidents and automobile deaths
- Ambulatory patients ADR rate—unknown
- Nursing home patients ADR rate—35% yearly
Sam Herrin not diagnosed for years!

- Misdiagnosed in 2001
- Diagnosed in 2013
- $3M wasted
- Made him sicker.
Trial and Error is Paid for!

The UDN will compare EXOME and GENOME sequencing
Hypothesis: Genome increases diagnosis rate 25%

So… Why aren’t care providers doing this?
So why is everyone doing whole exome?

- Believed to me more accurate than WGS
- Believed to resolve/diagnose as many cases as WGS
- Believed to be cheaper than WGS
- Believed to be easier than WGS for providers to use (fewer variants to deal with)

WGS: The best WES test available

40X Whole Genome Sequencing Provides the Most Complete Coverage of the Exome (2 Models)

This graph shows the percent of all reference transcripts covered at quality (20x, Q20) plotted against the percent of target transcripts covered. E.g. a minimum % coverage of 100% means the entire exonic region of the transcript was covered at 20X. Transcripts were either mapped to UCSC RefSeq Exons or the BCM Exome.

Green bars represent data from an exome performed by Baylor College of Medicine Medical Genetics Lab. Yellow bars represent a 30x genome generated at HudsonAlpha on the MiSeq II sequencer and represents the sequencing conditions used by HudsonAlpha CSL. Blue bars represent a 40x genome generated at HudsonAlpha on the HiSeq X sequencer. Transcripts were analyzed down to minimum coverage of 50%.

Minimum % Coverage Per Transcript (20X, Q20)

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WGS Provides Superior Clinical Utility

Comparison of the diagnostic yield of WGS and WES

Unique opportunity to compare and contrast WES and WGS findings used by the same clinical sites. HudsonAlpha is the sequencing center for all WGS in the UDN.

- 67% (47) of the 70 UDN WES cases without a diagnosis rendered a primary finding (P, LP, VUS) when analyzed using WGS.
- One case had a pathogenic structural variant identified & confirmed by a clinical site.
- Where we have the data we could see that the WES had been undertaken between 2012 and 2016 (3 had a subsequent 2015 or 2016 reanalysis)

Others Find the Same Benefits

<table>
<thead>
<tr>
<th>Approach</th>
<th>Disorder</th>
<th>n</th>
<th>MDx rate</th>
<th>Site/Ref</th>
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<td>34%</td>
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<td>ID – CSER</td>
<td>240</td>
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<td>42-62%</td>
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<td>Autism spectrum disorder</td>
<td>170</td>
<td>42.4%</td>
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<td>Hereditary spastic</td>
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<td>44%</td>
<td>Garvan Institute/2716996</td>
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<tr>
<td></td>
<td>Hereditary spastic</td>
<td>9</td>
<td>44%</td>
<td>Garvan Institute/2716996</td>
</tr>
<tr>
<td></td>
<td>Various – genetics</td>
<td>190</td>
<td>45%</td>
<td>HudsonAlpha/ -</td>
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<td>35</td>
<td>57%</td>
<td>Children’s Mercy, Kansas City/25937031</td>
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<td></td>
<td>Neurodevelopmental disorders</td>
<td>15</td>
<td>73%</td>
<td>Children’s Mercy, Kansas City/25473036</td>
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<td></td>
<td>AD Polycystic kidney disease</td>
<td>28</td>
<td>85%</td>
<td>Garvan Institute/27169907</td>
</tr>
</tbody>
</table>
The test that keeps on giving

RE-ANALYSIS

- CSER Research Program at HudsonAlpha
  - Previously undiagnosed genomes:
    - New analytical methods, newly published information
    - Whole genome sequencing 11% provided a diagnosis when reanalyzed one year later

- Undiagnosed Disease Network (UDN)
  - Baylor using Exomes 5% increase in diagnoses when reanalyzed a year later.
  - HudsonAlpha—redoing whole genome on previous exomes – 16% increase in diagnosis

- Pharmacogenomics
  - Available for the rest of the patient’s life
  - Better Quality by the right drug at the right dose at the right time.
  - Real-time always up to date

So why is everyone doing whole exome?

- Believed to me more accurate than WGS
  - WGS is a more accurate exome test than WES!
- Believed to resolve/diagnose as many cases as WGS
  - WGS solves more in first pass
  - WGS solves more on re-analysis

- Believed to be cheaper than WGS
- Believed to be easier than WGS for providers to use (fewer variants to deal with)

Reflex from WES to WGS cost consideration

A common money saving hypothesis used by healthcare systems is that MDx should start with WES or panel testing and only reflex to WGS if those fail to render a diagnosis. However, the lowering prices for WGS and greater diagnostic rate suggest starting with WGS.

Illustration:

- Based on reported MDx rates reflex to WGS would be required in ~70% of WES cases (i.e. 30% WES MDx success rate).
- Using $6,500 WGS and $5,000 WES per sample price points and for 100 patients (with 70% WES MDx rate) it would cost:
  - $650,000 for WGS first versus $955,000 for WES with WGS reflex.
  - 1.5x as much for the WES with a WGS reflex plan as compared to the WGS first approach.
- You need to have an 77% WES MDx success
### Prices for single tests and common drugs

<table>
<thead>
<tr>
<th>Common Tests/Medicines/Procedures</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crestor 1 year supply</td>
<td>$3,200</td>
</tr>
<tr>
<td>Xarelto 1 year supply</td>
<td>$4,500</td>
</tr>
<tr>
<td>3 Pharmacogenetic tests Quest (3 Variants)</td>
<td>$975</td>
</tr>
<tr>
<td>Pediatric echocardiogram</td>
<td>$4,050</td>
</tr>
<tr>
<td>Pediatric MRI</td>
<td>$4,400</td>
</tr>
<tr>
<td>CT Abdomen &amp; Pelvis with contrast</td>
<td>$3,900</td>
</tr>
<tr>
<td>Adalimumab, two weekly, 1 year supply</td>
<td>$24,800</td>
</tr>
<tr>
<td>Clinical WGS with Sanger Confirmation</td>
<td>$6,500</td>
</tr>
</tbody>
</table>

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  - WGS solves more on re-analysis
- Believed to be cheaper than WGS
  - Doing WGS first saves 32%
- Believed to be easier than WGS for providers to use
  (fewer variants to deal with)
VUS

- Everyone worries about having too many VUSs with WGS
- It is critical to define a VUS:
  - In research there are millions of VUSs with WGS and thousands with WES.
  - Clinically, VUSs are believed to be causally related based on the Lab Director's interpretation. Does not match ACMG guidelines.
  - The number of VUSs will be slightly higher, but also increases the rate of diagnosis.

Clinical Report

Primary  Secondary  PGx

Secondary Findings

Glycogen storage disease
Tay-Sachs disease
Polycystic kidney disease
Wilson disease
Breast cancer
Colorectal cancer
Cardiomyopathy
Carnitine deficiency
Prenatal screening
Long QT syndrome
Charcot-Marie-Tooth
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- Believed to be cheaper than WGS
  - Doing WGS first saves 32%
- Believed to be easier than WGS for providers to use
  (fewer variants to deal with)
  - With the right tools, WGS is not harder AND increases rate of diagnoses.

EVERY PHYSICIAN HAS A CASE OR A FEW CASES WHERE THE CLINICAL PICTURE DOES NOT MATCH THE DIAGNOSIS—GENOMICS OFFERS A SOLUTION. HOW & WHEN TO DEPLOY?
Randomized Case Control Studies

- Determine the average response
- Not enough people on the planet to test every DNA variant in a Randomized Case Control Study
- Need new ways to demonstrate relevance for an individual patient—How?
CAN SALT CAUSE HYPERTENSION?

As an analogy, on a population level, NaCl has the same effect as the SNPs associated with hypertension do.

1000’s of variants from research studies
WHAT ABOUT THE ETHICS?

Perspective Matters
Summary

• Whole Genome Sequencing has utility for Neurologist today!
  • More accurate than WES
  • Reduce misdiagnoses
  • Every physician has a case
  • HudsonAlpha here to help

Let’s Change Medicine!