Using Genome Sequencing in the Clinic will Change How You Practice Medicine, Educate and Conduct Research

Howard J. Jacob, Ph.D.
Executive Vice President Genomic Medicine
Chief Genomic Medicine Officer
Faculty Investigator
@hudsonalpha
@howardJacob_phd
Overview of my talk

• Genome sequencing is transitioning from being a research tool only. To a clinical tool with research application.

• Genomics will impact all aspects of an Academic Health Center

• Late adopters will have bigger challenges from clinical care, education and research.

  • Non-academic health centers are going to move into genomic medicine and this will create new competition.

• I spent 16 years on the Executive Faculty at the Medical College of Wisconsin.
Completed in 2002. Took 10 Years and ~$1B

Has bee largely a research tool. If you have genomic technology, you are under constant pressure to get the next best technology.

Today we can do a NICU case in 4 to 5 days.
Charting a course for genomic medicine from base pairs to bedside - 2011

- “The routine use of genomics for disease prevention, diagnosis and treatment will require a better understanding of how individuals and their healthcare providers assimilate and use such information.”

- Eric D. Green, Mark S. Guyer & National Human Genome Research Institute
Care Redesign
What Data Can Really Do for Health Care

Amy Compton-Phillips, MD Executive Vice President and Chief Clinical Officer for Providence St. Joseph Health; NEJM Catalyst Lead Advisor for Care Redesign

Biggest Opportunities for Use of Data in Health Care

What are the top three biggest opportunities for the use of data in health care?

- Care coordination: 81%
- Improved decision support: 79%
- Predictive analytics: 68%
- Precision medicine: 45%
- Reduced fraud and abuse: 14%
- Data is not useful in health care: 1%

What do you consider the top three most useful sources of health care data today and in 5 years?

- Clinical data: 95% today, 82% in 5 years
- Cost data: 56% today, 58% in 5 years
- Claims data: 45% today, 32% in 5 years
- Patient-generated data: 30% today, 40% in 5 years
- Pharmaceutical data: 25% today, 17% in 5 years
- Patient preference data (e.g., HCAHPS): 21% today, 23% in 5 years
- Genomic data: 17% today, 40% in 5 years

There are significantly fewer clinicians than executives and clinical leaders who consider predictive analytics as one of the top three.

Clinical leaders: 80%
Executives: 76%
Clinicians: 58%

Base = 682 (Multiple responses)
NEJM Catalyst (catalyst.nejm.org)
© Massachusetts Medical Society
The Transition to Clinical Sequencing

- Illumina estimates that 300,000+ exomes have been sequenced for clinical purposes.

- Whole Genome Sequencing is coming.

- Where is your clinical sequence data?

- Academic medical centers that did not biobank missed the GWAS and current research sequencing programs.

- Those that enter clinical sequencing late will miss the next research wave. Clinical sequencing will be the start for clinical research in the future.
- Leading genomics research environment: NIH Undiagnosed Disease Network, Clinical Sequencing Exploratory Research (CSER), Oncology Research Information Exchange Network (ORIEN)
- Expertise in clinical application of genomic medicine: Smith Family Clinic, CAP/CLIA MDx lab
  - We already practice medicine using genomic data derived knowledge
Four Missions

Missions in Genetics and Genomics

Clinical Genomics

Research

Education

Economic Development
Unique Relationships with Industry – Associate Companies

Biotech companies (genomics, genetics, drug development, medical devices, diagnostics) co-located on campus

March 2016
Disclosures

The following relationships exist related to this presentation:

• Executive Vice President, Chief Genomic Medical Officer and Faculty Investigator for HudsonAlpha Institute for Biotechnology

• We see patients at The Smith Family Clinic for Genomic Medicine, LLC. We sequence clinical genomes at The HudsonAlpha Clinical Services Laboratory, LLC.

• Co-Founder & Chief Scientific Officer for Envision Genomics
Education Outreach
Educational Outreach

the expertise to reach any audience across any platform

around any biotech topic

Total Outreach

public
teachers
students
digital downloads

107,500
191,070
318,916
619,090

2012 2013 2014 2015
Research
HudsonAlpha Faculty

17 Faculty, 115 scientists (209 total employees)
“Healthcare” in America

The world’s fifth largest economy!

Based on being sick
Runs on averages
Is make a lot of misdiagnoses
Medicine is Practiced on Average

Adults: Take 2 aspirin

Shaq = 4 aspirin
Danica = 1 aspirin

Out of 6 billion chemical units in their DNA
They differ at only 4M to 6M places
DNA: the molecule of life

Trillions of cells

Each cell:
- 46 human chromosomes
- 2 meters of DNA
- 3 billion DNA subunits (the bases: A, T, C, G)
- Approximately 30,000 genes code for proteins that perform most life functions
Building Genomic Medicine

**PILOT CLINICAL PROJECTS:**
- Rare Disease:
  - Clinical Seq. Exploratory Research (NIH funded)
  - Undiagnosed Disease Network (NIH funded)
  - Pilot with Children’s of Alabama Hospital
- WGS Pilot with State of Ala City of Huntsville Insight Genome®

**Cancer Screening:**
- Information is Power

**IPG NX other Disease Risks:**
- Insight Genome®

**DISCOVERY PROJECTS:**
- ENCODE and the NIH
- ORIEN Avatar Research
- Gabriella Miller and the NIH

**FOUNDATION PROJECTS:**
- Ethics:
  - Ethics in Workplace Genomics
  - Ethics of Adoption
- **Software for Patients and Providers:**
  - Genome Gateway®
  - Codiecemes

**EDUCATION PROJECTS:**
- Biotech Public Classes
- Touching Triton® Interactive Game
- Genomics and Your Practice
- Clinic Afterhours
- Middle and High School Curricula
- Teacher and Student Internships
- Fieldtrips and Summer Camps
- iPhone Apps: iCell® and Genome Cache®
Multiple Opportunities

- Rare disease, NICU, Cancer, Cardiovascular, Neurology, PGNX—medically relevant
- Better Quality/Happier Families.
- Creates revenue/value on fee for service and ACOs
- Crosses all specialties
- Positions Health System for population health
- Market differentiator. Creates ability to lead.
Want to Know My Future?

New genetic tests can point to risks—but not always a cure

By Bonnie Rochman

www.time.com
PATIENT STORIES
Debra Jenkins

“my daughter, thankfully, was negative”
What if we screened all women (and men) 30 years old were screened for free?
Positive Results

- No reported fhx: (26%)
  - BRCA2
  - CHEK2
  - RAD50
  - PMS2

- Some fhx: (31%)
  - TP53
  - CHEK2
  - BRCA2
  - PALB2
  - PMS2
  - BRIP1

- Strong fhx: (41%)

- Unknown fhx: (2%)
57% WOULD DISCOVER THEY ARE AT RISK FOR BREAST/OVARIAN CANCER WHEN THEY GET IT!
Pharmacogenomics

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

Pharmacogenomics: The Promise of Personalized Medicine
FDA-approved medications (n = 1,200)
- 7% Affected by actionable pharmacogenes
- 93% Not affected by actionable pharmacogenes

Prescriptions in the United States (n = 4 billion)
- 18% Affected by actionable pharmacogenes
- 82% Not affected by actionable pharmacogenes
IMPRECISION MEDICINE
For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. **ABILIFY** (aripiprazole)
   Schizophrenia

2. **NEXIUM** (esomeprazole)
   Heartburn

3. **HUMIRA** (adalimumab)
   Arthritis

4. **CRESTOR** (rosuvastatin)
   High cholesterol

5. **CYMBALTA** (duloxetine)
   Depression

6. **ADVIL DISKUS** (fluticasone propionate)
   Asthma

7. **ENBREL** (etanercept)
   Psoriasis

8. **REMICADE** (infliximab)
   Crohn’s disease

9. **COPAXONE** (glatiramer acetate)
   Multiple sclerosis

10. **NEULASTA** (pegfilgrastim)
    Neutropenia

*For a full list of references, see Supplementary Information at go.nature.com/4dr78R.*

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**Nature (2015)**
Panels are the Standard of Care

• To confirm a suspected diagnosis
• Expensive per gene/variant test
• Panels always out of date
  • Combined Neurology Panel:
    • Today: 556 genes
    • Includes 90 genes not shown to be pathogenic in 2015
• New panels require validation
• Whole Genomes—future-proofing
Sam Herrin not diagnosed for years!

- Misdiagnosed in 2001
- Diagnosed in 2013
- $3M wasted
- Made him sicker
Exome sequencing  Whole Genome Sequencing
40X Whole Genome Sequencing Provides the Most Complete Coverage of the Exome (2 Models)

This graph shows the percent of the 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 40x genome generated at HudsonAlpha on the HiSeq X sequencer and represents the sequencing conditions used by HudsonAlpha CSL. Blue bars represent a 30x genome generated at HudsonAlpha on the HiSeq X sequencer. Transcripts were analyzed down to minimum coverage of 50%.

The HAIB 40X covered more transcripts than WES at every point analyzed for both exome targeted strategies.

Minimum % Coverage Per Transcript (20X, Q20)
Comparison of the diagnostic yield of WGS and WES

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).
Published MDx rates for WGS and WES

<table>
<thead>
<tr>
<th>Approach</th>
<th>Disorder</th>
<th>n</th>
<th>MDx rate</th>
<th>Site</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>WES</td>
<td>Various</td>
<td>250</td>
<td>25%</td>
<td>Baylor College Medicine</td>
<td>24088041</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>2,000</td>
<td>25%</td>
<td>Baylor College Medicine</td>
<td>25326635</td>
</tr>
<tr>
<td></td>
<td>Intellectual disability</td>
<td>100</td>
<td>27%</td>
<td>Radboud, Nijmegen</td>
<td>24896178</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>3,040</td>
<td>29%</td>
<td>GeneDx</td>
<td>26633542</td>
</tr>
<tr>
<td></td>
<td>Intellectual disability</td>
<td>1,133</td>
<td>27%</td>
<td>DDD STUDY, UK</td>
<td>25529582</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>43</td>
<td>33%</td>
<td>TRANSLAD, France</td>
<td>26757139</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>362</td>
<td>29%</td>
<td>FORGE, Canada</td>
<td>26283276</td>
</tr>
<tr>
<td>WGS</td>
<td>Intellectual disability</td>
<td>50</td>
<td>42-62%</td>
<td>Radboud, Nijmegen</td>
<td>24896178</td>
</tr>
<tr>
<td></td>
<td>Autism spectrum disorder</td>
<td>170</td>
<td>42%</td>
<td>HSC, Toronto</td>
<td>27525107</td>
</tr>
<tr>
<td></td>
<td>Various - genetics</td>
<td>23</td>
<td>36%</td>
<td>MCW</td>
<td>Bick et al</td>
</tr>
<tr>
<td></td>
<td>neurodevelopmental</td>
<td>15</td>
<td>73%</td>
<td>Children’s Mercy, Kansas City</td>
<td>25473036</td>
</tr>
<tr>
<td></td>
<td>Various - NICU</td>
<td>35</td>
<td>57%</td>
<td>Children’s Mercy, Kansas City</td>
<td>25937001</td>
</tr>
<tr>
<td></td>
<td>Various - Pediatric</td>
<td>100</td>
<td>34%</td>
<td>Toronto</td>
<td>Stavropoulos et al</td>
</tr>
<tr>
<td></td>
<td>AD Polycystic kidney disease</td>
<td>28</td>
<td>86%</td>
<td>Garvan Institute</td>
<td>27165007</td>
</tr>
<tr>
<td></td>
<td>Hereditary spastic paraplegia</td>
<td>9</td>
<td>44%</td>
<td>Garvan Institute</td>
<td>27679996</td>
</tr>
<tr>
<td></td>
<td>ID – CSER</td>
<td>240</td>
<td>40%</td>
<td>HudsonAlpha</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Various – genetics</td>
<td>190</td>
<td>46%</td>
<td>HudsonAlpha</td>
<td>-</td>
</tr>
</tbody>
</table>

Typical MDx rates are lower for WES than WGS in the literature.
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**
Access to high-quality genomic testing
Clinical Sequencing Exploratory Research

North Alabama Children’s Specialists (Dr. Martina Bebin)

Univ of Louisville (Dr. Kyle Brothers)

Patient recruitment, consent, phenotyping, and return of results

Effects of genomic results on study participants

150 Diagnoses!

HudsonAlpha Institute

Genomic data generation and analysis

Using next generation sequencing to genetically diagnose children with Developmental Delay/Intellectual Disability (DD/ID): 1-2% of children
Before the visit…

Onboarding

Value of establishing relationship with patient

Obtain physician referral and medical records, even for elective patients

Use of online Genome Gateway software for information gathering, education and communication
Profile Information

Questionnaires

Recent Messages

Learning

Files
Clinical Report

Primary

Clinical Indications
Xylo. Rare referral for evaluation of autism spectrum disorder and dysorphic features.

Result Summary for Primary Findings
The following variant(s) were identified in the gene(s) related to the indication for testing. These results are summarized in the table below:

<table>
<thead>
<tr>
<th>Gene &amp; Transcript</th>
<th>Location</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Disease or Phenotype</th>
<th>Inheritance of Disease</th>
<th>Variant Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC6A3, NM_003733.2</td>
<td>Exon 1</td>
<td>c.920G&gt;A</td>
<td>Heterozygous</td>
<td>Autism spectrum disorder</td>
<td>Autosomal Recessive</td>
<td>Likely Pathogenic</td>
</tr>
<tr>
<td>UNC13D, NM_020292.2</td>
<td>Exon 6</td>
<td>c.575G&gt;C</td>
<td>Heterozygous</td>
<td>Hypotonia, with microcephaly, dysmorphic features, and intellectual disability</td>
<td>Autosomal Recessive</td>
<td>Likely Pathogenic</td>
</tr>
</tbody>
</table>

Other Variants of Medical Significance (Secondary Findings)
The following variant(s) were identified in the gene(s) related to the indication for testing. These results are summarized in the table below:

<table>
<thead>
<tr>
<th>Gene &amp; Transcript</th>
<th>Location</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Disease or Phenotype</th>
<th>Inheritance of Disease</th>
<th>Variant Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZC7H5D2, NM_021827.3</td>
<td>Exon 5</td>
<td>c.233C&gt;G</td>
<td>Heterozygous</td>
<td>Hypotonia, with microcephaly, dysmorphic features, and intellectual disability</td>
<td>Autosomal Recessive</td>
<td>Likely Pathogenic</td>
</tr>
</tbody>
</table>

Interpretation and Recommendation Summary for Primary Findings
The patient is heterozygous for a potentially clinically significant variant in SLC6A3. There is a single published report (Rivera RK, 2015) linking this gene with risk for autism spectrum disorder, which is part of this patient’s clinical presentation.

The patient is heterozygous for a potentially clinically significant variant in UNC13D. Variants in this gene are associated with hypotonia, infants, with psychomotor retardation and characteristic facies 2 (OMIM #516887), which is part of this patient’s clinical presentation.

These results should be interpreted in the context of the patient’s medical evaluation, family history, and racial/ethnic background. Please note that variant classification and/or interpretation may change over time as more information becomes available. Interpretation of genome sequencing data is recommended on an annual basis and may be requested by a medical provider. For questions about this report, or for assistance in locating nearby genetic counseling services, please contact the Clinical Services Lab.

Secondary

Pharmacogenomic Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Guidelines</th>
<th>Gene</th>
<th>Variant</th>
<th>Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxapine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clomipramine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>desipramine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nefazodone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>venlafaxine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interpretation and Recommendations for Pharmacogenomic Findings
The Pharmacogenomics report is restricted to genetic variants that have been curated by PharmGKB as meeting the highest standard for evidence (category designated 1A), supporting a variant–drug association. All PharmGKB variants at the TA level of evidence are included in this pharmacogenomics report except the CYR6305 variant and variants in the gene ILK, IL33, and CCR5. When two or more variants are reported within the same gene, all of the variants may come from one parent on the same chromosome (in cis). Alternatively each parent may contribute at least one of the variants (in trans). We are not able to determine whether the variants are in cis or trans. The table above details the variants found in CYR6305 for this patient. For dosing guidelines please use the links below.

PGx

HudsonAlpha Institute for Biotechnology
NEUROLOGY: WHEN TO CONSIDER GENOMIC TESTING

- Developmental Delay
- Seizure Disorder
- Ataxia
- Cognitive & Motor Delay
- Early-onset Dementia
- Neuropathy
- Myopathy
- Cerebral Palsy
- Autism
- Hypotonia
Congenital Heart Defects

- Most common birth defect
- Present in approximately 1% of live births
- >50% occur as an isolated defect
- Over 500 syndromes can include CHD
Congenital Heart Defects - Syndromic

- Often associated with other congenital anomalies or neurodevelopmental phenotypes

- Some defects are pathognomonic for a certain syndrome

- Recurrence risk depends on inheritance pattern and if variant(s) were inherited or *de novo*

<table>
<thead>
<tr>
<th>Inheritance Pattern</th>
<th>Recurrence Risk for Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal</td>
<td>&gt;1% (if not inherited)</td>
</tr>
<tr>
<td>Autosomal Dominant</td>
<td>50% if inherited, &gt;1% if <em>de novo</em></td>
</tr>
<tr>
<td>Autosomal Recessive</td>
<td>25%</td>
</tr>
<tr>
<td>X-Linked</td>
<td>50% for males if maternally inherited</td>
</tr>
</tbody>
</table>
“Making difficult cardiac diagnoses in the past required sending patient specimens to out of state laboratories that would send back complicated, difficult to interpret reports, several weeks later. Now, I can send the patients and their families to The Smith Family Clinic for comprehensive testing and diagnosis. It's fabulous being able to tell my patients they can go to a clinic that is staffed with highly-experienced genetics and genomics experts, right in our own backyard”

A Vasquez, MD
The Heart Center, Huntsville Hospital
Fee-For-Service
• Nearly all payors surveyed reported that treatment for patients with rare diseases is relatively more expensive compared to treatments for other patients with more common diseases (95% in the US, 100% in the UK) and costs are also rising more rapidly (90% in the US, 85% in the UK).

• More visits to specialists (95% in the US, 95% in the UK)

• More mental health support needed (90% in the US, 75% in the UK)

Source: Rare Disease Impact Report: Insights from patients and the medical community. Shire

Your patients stay in your system and see your specialists
Fee-for-Service Economic Model

Use Case: Average cost for the work up of a new patient with a rare, undiagnosed $20,000 in billable/reimbursed services for labs, x-rays, MRI, professional fees, etc.

- Making a diagnosis drives the need for follow-up care

- Patients are likely to obtain follow-up care where the diagnosis is made, allowing hospitals/health systems to keep patients requiring specialty care.

- Strategy: recruit patients with rare, undiagnosed, or misdiagnosed disease in revenue generating specialties and sub-specialties of interest. Analogous to building primary care within the community
Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders

Sarah E. Soden,1,2,3,4 Carol J. Saunders,1,2,3,4 Laurel K. Willig,1,2,3 Emily G. Farrow,1,2,3,4 Laurie D. Smith,1,2,3 Josh E. Petrikin,1,2,3 Jean-Baptiste LePichon,1,2,3 Neil A. Miller,1,2 Isabelle Thiffault,1,3,4 Darrell L. Dinwiddie,5,6 Greyson Twist,1 Aaron Noll,1 Bryce A. Heese,2,3 Lee Zellmer,1,4 Andrea M. Atherton,1,2,3 Ahmed T. Abdelmoity,2,3 Nicole Safina,2,3 Sarah S. Nyp,2 Britton Zuccarelli,2 Ingrid A. Larson,1,2 Ann Modrcin,2,3 Suzanne Herd,1,2 Mitchell Creed,1 Zhaohui Ye,7 Xuan Yuan,7 Robert A. Brodsky,7 Stephen F. Kingsmore1,2,3,4

Neurodevelopmental disorders (NDDs) affect more than 3% of children and are attributable to single-gene mutations at more than 1000 loci. Traditional methods yield molecular diagnoses in less than one-half of children with NDD. Whole-genome sequencing (WGS) and whole-exome sequencing (WES) can enable diagnosis of NDD, but their clinical and cost-effectiveness are unknown. One hundred families with 119 children affected by NDD received diagnostic WGS and/or WES of parent-child trios, wherein the sequencing approach was guided by acuity of illness. Forty-five percent received molecular diagnoses. An accelerated sequencing modality, rapid WGS, yielded diagnoses in 73% of families with acutely ill children (11 of 15). Forty percent of families with children with nonacute NDD, followed in ambulatory care clinics (34 of 85), received diagnoses: 33 by WES and 1 by staged WES then WGS. The cost of prior negative tests in the nonacute patients was $19,100 per family, suggesting sequencing to be cost-effective at up to $7640 per family. A change in clinical care or impression of the pathophysiology was reported in 49% of newly diagnosed families. If WES or WGS had been performed at symptom onset, genomic diagnoses may have been made 77 months earlier than occurred in this study. It is suggested that initial diagnostic evaluation of children with NDD should include trio WGS or WES, with extension of accelerated sequencing modalities to high-acuity patients.
# ACO & Managed Care Economic Model

<table>
<thead>
<tr>
<th>Envision Genomics Offering Can:</th>
<th>Improve Care Quality &amp; Outcomes</th>
<th>Reduce Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End Diagnostic Odysseys</strong></td>
<td>Significantly reduce the “sick cycle” for the patient &amp; family</td>
<td>Eliminate serial, expensive patient visits &amp; procedures</td>
</tr>
<tr>
<td><strong>Avoid Unnecessary/ Multiple Diagnostic Tests</strong></td>
<td>Inform physician test selection, a key point of vulnerability in the pre-analytic treatment phase</td>
<td>WGS is a single test that can be used throughout a patient’s lifetime</td>
</tr>
<tr>
<td><strong>Allow Preventative Care to be Practiced</strong></td>
<td>Creates a genomic blueprint to guide care</td>
<td>Eliminate unwarranted procedures/therapeutics/diagnostic tests</td>
</tr>
<tr>
<td><strong>Reduce Rate of Misdiagnosis/Accelerate Time to Diagnosis</strong></td>
<td>Reduce readmission rate</td>
<td>Eliminate expensive hospital stays</td>
</tr>
<tr>
<td><strong>Inform Treatment/Therapeutic Decisions</strong></td>
<td>Choose most effective drug/therapeutic first, avoid adverse drug reactions</td>
<td>Avoid the administering of ineffective, potentially dangerous expensive specialty pharmaceuticals</td>
</tr>
<tr>
<td>Common tests/medicine/procedures</td>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Crestor 1 year supply</td>
<td>$3,200</td>
<td></td>
</tr>
<tr>
<td>Xarelto 1 year supply</td>
<td>$4,500</td>
<td></td>
</tr>
<tr>
<td>3 Pharmacogenetic tests Quest (3 variants)</td>
<td>$975</td>
<td></td>
</tr>
<tr>
<td>Pediatric echocardiogram*</td>
<td>$4,050</td>
<td></td>
</tr>
<tr>
<td>Pediatric MRI*</td>
<td>$4,400</td>
<td></td>
</tr>
<tr>
<td>CT Abdomen &amp; Pelvis with contrast*</td>
<td>$3,900</td>
<td></td>
</tr>
<tr>
<td>Adalimumab, two weekly, 1 year supply</td>
<td>$24,800</td>
<td></td>
</tr>
<tr>
<td>Clinical WGS with Sanger Confirmation</td>
<td>$6,500</td>
<td></td>
</tr>
</tbody>
</table>

Medicine in general is expensive; WGS is not particularly so these days.
Impact of Diagnostic Error

- Institute of Medicine just reported 5% of Diagnoses are errors = on average physician makes 62 misdiagnoses per year!
- 10% of deaths and 6% to 17% of admissions due to misdiagnosis.
- Leading reason for malpractice claims.
- One test—good for the rest of their patients’ lives—better medicine each year!
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?
Summarizing polygenic risks for complex diseases in a clinical whole-genome report

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**Purpose:** Disease-causing mutations and pharmacogenomic variants are of primary interest for clinical whole-genome sequencing. However, estimating genetic liability for common complex diseases using established risk alleles might one day prove clinically useful.

**Methods:** We compared polygenic scoring methods using a case-control data set with independently discovered risk alleles in the MedSeq Project. For eight traits of clinical relevance in both the primary-care and cardiomyopathy study cohorts, we estimated multiplicative polygenic risk scores using 161 published risk alleles and then normalized them using the population median estimated from the 1000 Genomes Project.

**Results:** Our polygenic score approach identified the overrepresentation of independently discovered risk alleles in cases as compared with controls using a large-scale genome-wide association study data set. In addition to normalized multiplicative polygenic risk scores and rank in a population, the disease prevalence and proportion of heritability explained by known common risk variants provide important context in the interpretation of modern multilocus disease risk models.

**Conclusion:** Our approach in the MedSeq Project demonstrates how complex trait risk variants from an individual genome can be summarized and reported for the general clinician and also highlights the need for definitive clinical studies to obtain reference data for such estimates and to establish clinical utility.

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**Key Words:** clinical whole-genome sequencing; common complex disorders; polygenic score; risk alleles
Exhibit D:
Average Annual Health Insurance Premiums and Worker Contributions for Family Coverage, 2006-2016

Insurance Coverage for WES/WGS

Summary:
- Over 30 million lives total now have coverage for exome ~10% of the US population.

- All policies above covered WES in some “medically necessary” cases, but considered WGS “experimental or investigational” in all cases.

- “Experimental or investigational” is defined: “The evidence is insufficient to determine the effects of the technology on health outcomes”

- Many policies cite several references showing the efficacy getting a diagnosis. Most papers used exomes.
The Spend is in the Wrong Place

~$40M to build infrastructure
Summary

Whole Genome Sequencing has utility today!
• More accurate than WES
• Reduce misdiagnoses
• Every physician has a case
• Get "your" genomic data back!

Don’t invest in CAPEX; Invest in Genomes
At 1,000 clinical genomes a year consider bringing in house.
Will require Pathology and Genetic to work together

It is Economical—Cardiology, Neurology, Undiagnosed, high end patients AND fewer misdiagnoses! Feeds your sub-specialties—Market differentiator. More genomes more research

Let’s make WGS the first best test and deploy genomics across all our hospitals. Better care, less costs.
  Population health—genome physical
  Executive health
  Your healthcare plan