Bringing Comprehensive Genetic Testing into Routine Medical Practice

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Co-founder, Invitae

The 14th Population Health Colloquium
We’ve come a long way in genetics!

Sickle cell disease was the first genetic medical condition described in the mid-20th century using electrophoresis to identify protein changes that result from underlying change in genetic code.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
<th>Positions to which hemoglobins have migrated</th>
<th>Origin</th>
<th>Hemoglobin types present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle-cell trait</td>
<td>$Hb^S/Hb^A$</td>
<td></td>
<td></td>
<td>S and A</td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>$Hb^S/Hb^S$</td>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Normal</td>
<td>$Hb^A/Hb^A$</td>
<td></td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>

Migration
There's never been a more vibrant discussion about the role of genetics.
Genetics is leaving the age of scarcity and entering an age of abundance...

Genetic testing is in a state of disruption

1) Aggregation of all genetic tests into a low-cost cloud-based information service is underway

2) Incidental findings will rise rapidly with more comprehensive screening leading to “big data” analysis on medical impact

3) Economics will turn the R&D paradigm upside down as the clinical system and the R&D system merge into one
Complimentary DNA Sequencing Strategies:

Screen the genome looking for mutations

Target know genes and mutations for known diseases

find the needle in the haystack

remove the hay from the needle stack
Why focus on rare diseases?

Because rare diseases in aggregate are common (with over 3,000 Mendelian-inherited diseases with known mutations), and common diseases are really a collection of rare diseases with similar phenotype…

…in fact, “common disease” is an oxymoron
Rare diseases are actually common

100% of the population:
• is carrying multiple rare genetic conditions
• carries genetic variations that affects their response to drugs

Up to 5-10% of the population may have a genetic condition, many undiagnosed

• 1 in 500-1,000 has Lynch Syndrome (>300,000)
  Fam Cancer 4:233, 2005
• 1 in 500-1,000 has a cardiomyopathy (>300,000)
  Cardiomyopathy.org
• 1 in 2,000 has Long QT Syndrome (150,000)
  Circulation 120:1761, 2009
• 1 in 500-1,000 live male births result in Klinefelter’s syndrome (>300,000)
  Clin Endocrinol Metab 88: 622 Feb 2003

Every “common” disease is either caused or effected by genetic differences…most of which are not yet known
Nature Genetics 33:177, 2003
Approximately 2% of the population* harbor an actionable genetic disorder: ACMG “must report” list

### Hereditary Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
</tr>
<tr>
<td>MYH-associated polyposis</td>
<td>MUTYH</td>
</tr>
<tr>
<td>Von Hippel Lindau syndrome</td>
<td>VHL</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td>MEN1</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
<td>RET</td>
</tr>
<tr>
<td>Familial medullary thyroid cancer (FMTC)</td>
<td>RET, NTRK1</td>
</tr>
<tr>
<td>PTEN hamartoma tumor syndrome</td>
<td>PTEN</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB1</td>
</tr>
<tr>
<td>Hereditary paraganglioma- pheochromocytoma syndrome</td>
<td>SDHD, SDHAF2, SDHC, SDHB</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>TSC1</td>
</tr>
<tr>
<td>WT1-related Wilms</td>
<td>WT1</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2</td>
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</table>

### Hereditary Cardiovascular Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene(s)</th>
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</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy, dilated cardiomyopathy</td>
<td>MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, MYL2, PRKAG2, GLA, LMNA</td>
</tr>
<tr>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
<td>RYR2</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>PKP2, DSP, DSC2, TMEM43, DSG2, PRKAG2, GLA, LMNA</td>
</tr>
<tr>
<td>Romano-Ward long QT syndromes types 1, 2, and 3, Brugada syndrome</td>
<td>KCNQ1, KCNH2, SCN5A, LDLR, APOB, PCSK9</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td></td>
</tr>
</tbody>
</table>

### Hereditary Connective Tissue Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDS - vascular type</td>
<td>COL3A1</td>
</tr>
<tr>
<td>Marfan syndrome, Loeys-Dietz syndrome, and familial thoracic aortic aneurysms and dissections</td>
<td>FBN1, TGFR1, TGFR2, SMAD3, ACTA2, MYLK, MYH11</td>
</tr>
</tbody>
</table>

### Anesthesia Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant hyperthermia susceptibility</td>
<td>RYR1, CACNA1S</td>
</tr>
</tbody>
</table>

*approximately 6 million in the United States

Source: Green R, et al. American College of Medical Genetics 2013
The Changing Business Model for Genetics

1. Make genetic testing more affordable and accessible than ever before
2. Build a secure and trusted genome management infrastructure
3. Embrace a new global community for sharing genetic information to advance science and medicine

Supreme Court decision opens the door to broad genetic testing
Genomics will create value over the lifetime of a customer
New networks for sharing genetic information will drive clinical utility
Genetics is the future of medicine  
... and we are all connected...

Invitae is a genetic information company focused on bringing comprehensive genome management into routine medical practice.

- More than 100 people joining the movement to reinvent genetic testing
- Clinical laboratories in San Francisco and Santiago Chile
- First-in-kind commercial product launch Nov. 19, 2013 – 218 genes - $1,500

Principal investors
- Baker Brother Investments
- Thomas McNerney Partners
- Randy Scott
- Genomic Health
- Genesys Capital
- Casdin Capital
- Redmile

A team with unparalleled experience
- Lisa Alderson, Commercial Disney, Crossloop, Genomic Health
- Lee Bendegkey, Finance & Legal Incyte, Nuvelo, DNAnexus
- Michele Cargill, Science & Genetics Navigenics, Affymetrix, Celera
- Alex Furman, Software Development Navigenics, Iris Financial Solutions
- Sean George, Technology & Development Navigenics, Affymetrix, Invitrogen
- Jill Hagenkord, Medical Complete Genomics
- Steve Lincoln, Informatics Complete Genomics, Affymetrix, Incyte
- Randy Scott, Strategy Genomic Health, Incyte
- Jon Sorenson, Bioinformatics Pacific Biosciences, Applied Biosystems

Principal investors
To bring comprehensive genetic information into routine medical practice to improve the quality of healthcare for billions of people.

By aggregating the world’s genetic tests into a single service with better quality, faster turnaround time, and a lower price than most single-gene diagnostic tests today.
Invitae’s approach to genetics

- Aggregate multiple genetic tests into a single assay
- Drive down the cost to an affordable price
- Easily customized by each clinician
- Driving ease of use and volume online with full reimbursement support

More affordable than ever before.

One price. Any test, every test.

$1500

Faster time to answers.

2 weeks on average from sample to results.

Flexible test options.

Design your own test or select a curated panel.

Deeper genetic insights.

Choose multi-gene panels or order a free re-requisition.

Confidence and quality.

Our team of genetic experts assures 450x average coverage.

Common feedback – is it too good to be true?
Multiple layers of complexity to solve

Disparate, non-standardized clinical annotation
- Incomplete databases
- 5-20% errors in databases and condition literature
- Unclear condition boundaries
- Multiple aliases
- Subjective pathological determination

Difficult, clinical-grade ‘must have’ targets
- Read-through
- Insertions, deletions, inversions
- Copy number alterations
- Pseudogenes
- Tri/di-nucleotide repeats
- Homopolymers, high GC content regions of interest
- Diagnostic quality sensitivity and specificity
Invitae’s First Commercial Test: Launched Nov. 19, 2013

Designed for oncology and a “long tail” of rare genetic conditions
Analyzing genomes requires a major investment in software & data analysis.

1. Make genetic testing more affordable and accessible than ever before.

- Requisition
- Accession
- Target Prep
- Sequencing
- 1° Analysis
- 2° Analysis
- Clinical Interpretation Delivery
- Portal
- Backoffice
- LIMS
- Production
- Data analysis PIPE
- Variant knowledgebase
- Clinical Report Optimization Process
- Interpretation
- Report Generator
Case Study: Bardet-Biedl Syndrome

Clinical Presentation:

- Two children in a family present with unusual symptoms:
  - Post-axial polydactyl, obesity, and developmental delay
- Doctor suspects Bardet-Biedl Syndrome (BBS) as a possibility
  - Genetically heterogenous, autosomal recessive condition
- Difficult to diagnose due to wide variation in symptoms between and among families and complex genotype
  - 18 associated genes: BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14), WDPCP (BBS15), SDCCAG8 (BBS16), LZFFL1 (BBS17) and BBIP1 (BBS18)

1) GeneReviews PMID: 20301537
Case Study: Bardet-Biedl Syndrome

- Prior to NGS, clinicians tested BBS1 then reflexed to BBS10, then BBS2, and so on.
  - TAT for each was ~30 days.
  - Cost for each was ~$900 for each gene, plus another $1000 each for dup/del testing
  - For genes that only cause a small percentage of BBS, it could take a year and cost up to $20,000 to get a diagnosis.
Case Study: Bardet-Biedl Syndrome:

- **Child A**
  - Doctor orders 13 known BBS genes from Invitae ($1,500)
  - Invitae identifies 2 variants in 2 different genes, **BBS7** and **TRIM32**
  - Each of these genes causes less than 2% of all cases of BBS and historically, would not be tested until more common genes ruled out
- **Child B**
  - To clarify the significance of the 2 candidate variants, the sibling was tested resulting in a single candidate variant in **BBS7**.
- **Parents**
  - Confirmed that they were each carriers for the **BBS7** variant and that it was the likely cause of BBS in this family.
Hereditary cancer
Customized panels for hereditary cancer:

**Products – Hereditary Cancer**
- BRCA1 and 2
- High Risk Panels
- Hereditary Cancer panel – 29 genes

**Target Markets**
- Primary: Medical Geneticists / Genetic Counselors
- Secondary: Medical Oncologists, Surgical Oncologists

**Price:**
- Any Test, Every Test, $1500
BRCA and Women’s Hereditary Cancers

**BRCA 1 & BRCA 2**
- Full Gene Sequencing and Deletion/Duplication
- BRCA 1 & BRCA 2

**High-Risk Hereditary Breast Cancers**
- Full Gene Sequencing and Deletion/Duplication
- 6 Genes associated with hereditary breast and ovarian cancer

**Women’s Hereditary Cancer Panel**
- Full Gene Sequencing and Deletion/Duplication
- 18 Genes associated with hereditary breast, ovarian and endometrial cancer

**Hereditary Cancer Syndromes Panel**
- Full Gene Sequencing and Deletion/Duplication
- 29 Genes associated with hereditary cancer syndromes
- Option to design your own panel

Optional preventative information can be included with any panel for no additional charge
Colon Cancer and Polyposis Syndromes

**Lynch Syndrome**
- Full Gene Sequencing and Deletion Duplication
- 2 Genes associated with Lynch Syndrome

**High-Risk Hereditary Colon Cancers**
- Full Gene Sequencing and Deletion/Duplication
- 7 Genes associated with Colon Cancer or Polyposis Syndromes

**Hereditary Colon Cancer Panel**
- Full Gene Sequencing and Deletion/Duplication
- 14 Genes associated with Colon Cancer or Polyposis Syndromes

**Hereditary Cancer Syndromes Panel**
- Full Gene Sequencing and Deletion/Duplication
- 29 Genes associated with hereditary cancer syndromes
- Option to design your own panel

Optional preventative information can be included with any panel for no additional charge.
Case Study: Hereditary Cancer

- Female ~45y, presenting with breast cancer
- BRCA1/2 Negative
- Consented to biobank a blood sample ~8 years ago

- In this study, shown to be MLH1 positive (Lynch)
- Re-contacted: She had Dx of endometrial cancer in the intervening period
- Additional colonoscopy performed: Positive (polyps found and removed)
Case Study: Incidental Findings

Patients A and B: Both women in their early 60’s with personal histories of cancer.
• Patient A: Breast cancer, Patient B: Gastric cancer

Indication for testing: Rule out hereditary cancer syndromes.
• Order Invitae gene panel

Primary Findings:
• For both patients A and B, primary findings were negative. An established or likely cause of hereditary cancer was not identified.

Secondary Findings:
• Both patients A and B each have a likely pathogenic variant in the KCNE2 gene associated with Long QT Syndrome.
• Patient B is also a carrier for Bardet-Biedl Syndrome, a rare pediatric genetic disorder.
Case Study: Incidental Findings

Genetic cardiac electrophysiology disorder

- Abnormal EKG tracing (ie, prolongation of the QT interval)
- Predisposition to fainting and sudden cardiac death.
- Cardiac events are most common from the pre-teen years through the 20s and are best known for causing sudden death in young athletes.
- 13 subtypes (KCNQ1, KCNQ2, KCNQ3, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1, KCNJ5, KCNE1)5

Inherited cardiac arrhythmias are relatively common

- Prevalence: Inherited cardiac arrhythmias - 1:500, LQTS - 1:3000.
- Hereditary cardiac arrhythmias cause up to 30% of unexplained cardiac death in the young and 10% of sudden infant death syndrome.2,3

Well-established preventative measures for sudden cardiac death.1

- Beta blockers, pacemakers, or defibrillators
- Avoid the ~300 drugs that are contraindicated in patients with LQTS.4
- EKG monitoring during childbirth, surgeries, endoscopies, and dental work.
- Avoiding intense physical activities.
- Postpartum beta blocker treatment.

1. Gene Reviews, PMID 20301308
2. PMID 19322600
3. PMID 15929465
4. www.qtdrugs.org
5. doi:10.1038/ejhg.2013.28
Example of genetic complexity: Cardio Genetics...

1 Hershberger RE, et al; 2013. PMID: 23900355
Patient B also learned that she is a carrier for Bardet-Biedl Syndrome (BBS).
- Symptoms of BBS include polydactyly, obesity, blindness, cognitive defects, and genital/renal abnormalities.

BBS is autosomal recessive, so 50% of her children will also be carriers.
- It is possible for one of her children or grandchildren to have a child affected with BBS, although given how rare the disease is, it is unlikely.
- Most parents of children with BBS wish they had known that they were carriers before having affected children.

In the past, it wasn’t feasible to screen for rare genetic disorders. Now it is.
Genome management for life

One Assay… a lot of potential value to unlock

**Traditional Diagnostic**
- My patient has cancer
- Is it hereditary or sporadic?

**Preventative Diagnostics**
- Surgery
  - Anesthesia reactions
  - Bleeding/clotting
  - Post Op pain management
  - Post Op antibiotics
- Chemotherapy
  - Chemo-related PGx
  - Long QT, Acquired long QT
  - Cardiomyopathies

**Genome Management**
- Comprehensive Genetic Testing
  - Hundreds of genetic conditions come along for free!

- Exploring ways to add value for patients, physicians and researchers

**Comprehensive cancer panel**

**$1,500 Test**

**Multiple conditions analyzed in one test**
Your Genome is Valuable To You And Your Network...
Genetic information is most powerful when shared

- Invitae family history tool available for incorporating family health history will facilitate sharing genetic information in the future
- Infrastructure for improved real-time medical interpretation of variants
- Functionality to help clinicians and patients share information around genetic variation
Sharing genetic info starts with family

I have certain hereditary conditions...how are they segregated throughout my family?

What does it mean for those who have the mutation?

Should I be worried about those individuals?

Cloud-based family history tool available online at www.invitae.com or as an iPad app from the Apple Store
Global opportunity for genome informatics

- Current Direct Sales
- Partners
- 2014 Target Markets
Targeting the “Mendeliome” is now possible

- All known Mendelian-inherited genetic diseases for which mutations are known
  - ~4,400 genes covering full coding sequence and all known HGMD mutations
  - Enormous potential for over 2,000 genes comprising comprehensive disease panels:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult cardio</td>
<td>132</td>
</tr>
<tr>
<td>Ataxia</td>
<td>50</td>
</tr>
<tr>
<td>Brain malformations</td>
<td>80</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>54</td>
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<tr>
<td>Dermatology and neural crest</td>
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<tr>
<td>Dystonia</td>
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<tr>
<td>Endocrinology</td>
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<td>id autism</td>
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<td>Urology</td>
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<td>White matter disease</td>
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<tr>
<td>Other</td>
<td>1074</td>
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</table>
Pace of Development in Genetic Panels

Number of Genes

- Mendeliome: Early access available 2014
- Next Invitae Panels: Early access available 2014
- Current Invitae Panel
- Oncology Panel
- BRCA 1/2: Available now for $1,500

Available now for $1,500
Our core principles

People have a right to self knowledge (their genome)
- Patients should own and control their own genetic information

We require a physician to order and interpret genetic tests
- Let’s help physicians learn how to utilize the genome

Genetic information is more valuable when shared
- We encourage sharing genetic information at the patient’s discretion
- We support the elimination of DNA sequence patents

Decreasing costs will increase both clinical and personal utility
- Payors will find areas of immediate cost savings
- Patients will increasingly be able to afford tests with personal utility
- Physicians will find clinically useful information that rides along for free
Genetic testing has the largest market possible... everyone on the planet.