Innovations and learnings in genetic testing:
improving access to actionable information and
potential precision medicine opportunities

SWAROOP ARADHYA, PH.D., FACMG
HEAD, GLOBAL MEDICAL AFFAIRS
Disclosures

AFFILIATIONS

Current position:
Dr. Swaroop Aradhya is currently an employee and stockholder of Invitae, a genomic information company in San Francisco, California

Current academic and community involvement:
Adjunct Clinical Associate Professor, Stanford University School of Medicine
Investigator, ClinGen Resource (US)
Business advisory council, International Society for Prenatal Diagnosis

Past engagements:
GeneDx, Angsana, Agilent, Affymetrix
Reduction in cost of sequencing and rapid increase in tests and scale

Falling fast

In the first few years after the end of the Human Genome Project, the cost of genome sequencing roughly followed Moore’s law, which predicts exponential declines in computing costs. After 2007, sequencing costs dropped precipitously.

Cost of genome sequencing.

Moore’s law for computing costs.

Next generation sequencers enter the market.

The price of sequencing a whole human genome hovers around $5,000 and is expected to drop even lower.

GTR Data

20K

10K

10

1


Tested Conditions

Tested Genes

BRCA1/BRCA2 panels

Genomic testing labs

Mitochondrial genome tests

Cancer/somatic tests

Human genome and Whole exome tests

CGH tests

Pharmacogenetics

Single gene tests
Evolving paradigms in clinical genomics

- The genomics ecosystem is dynamic and changing rapidly due to next-generation sequencing, bioinformatics, and large scale genomics projects
- Better understanding of genetic variants and monogenic and polygenic causes of disease
- Opportunities for precision medicine are arising through interactions among stakeholders
Presentation Outline

1) How is NGS technology and systematic variant interpretation improving our ability to find molecular diagnoses? What is the added clinical sensitivity from identifying rare genetic causes of hereditary disease and expanding genotype-phenotype correlations?

2) Are existing practices for genetic testing keeping up with technology and its capabilities to find answers? Unbiased genetic testing in specific cohorts has shown that existing clinical criteria for genetic testing inadvertently exclude a large pool of individuals who do have hereditary disease and should qualify for appropriate molecular testing.

3) What is the scope for clinical actionability and precision medicine based on genomic information? It is becoming evident that early genetic testing for certain hereditary disorders can guide clinical management decisions and reduce morbidity considerably.
Advantages and nuances of NGS technology used in clinical genomics

- **Not all NGS is the same**: there is variation among labs in terms of pairing NGS chemistry with bioinformatics and performing primary data analysis.
- Highly automated and quality-controlled next-generation sequencing coupled tightly with custom bioinformatics algorithms enable essential transparency.
A rigorous approach to clinical-grade NGS-based genetic testing

- NGS assay is carefully customized to assess clinically important variants
  - 50x minimum, 350x average depth of coverage. Virtually no sequence gaps
  - Optimized capture and analysis of difficult regions (e.g., SMN1)
  - Comprehensive coverage of all major relevant genes in requested panels
  - Accurate copy number calling (deletion/duplication analysis)
  - Confirmation with PacBio/Sanger sequencing or MLPA/array CGH
Capturing the full spectrum of molecular genetic variation

- A broad range of clinically important variants can be identified in a single NGS assay. This requires careful customization of the NGS chemistry and bioinformatics. **Simultaneously identify SNVs, small and large indels, CNVs, mosaic variants.**
Sensitively detecting intragenic copy number variants by NGS

- NGS depth-of-coverage–based exonic deletion/duplication analysis is very reliable
  - **More accurate** because of alignment and sequencing. Statistical algorithm calculates not only probability of abnormal copy number but also probability of normal copy
  - **Consistency** in data quality across samples in a single sequencing run is paramount
  - Sequence and copy number from a single assay → reduced cost + one sample
Sensitively detecting intragenic copy number variants by NGS

- Prevalence of intragenic deletions/duplications poorly understood
  - Because Invitae’s test examines copy number for virtually every exon in ~1500 disease genes, we evaluated the prevalence of CNVs in clinically tested individuals
  - CNVs are highly prevalent among clinically significant variants (~9%) and among individuals with positive reports (~10%)
  - These types of events are typically not detected by whole-genome microarrays (CMA) due to insufficient resolution

<table>
<thead>
<tr>
<th>Intragenic CNV analysis in ~143,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with CNVs among all individuals tested</td>
</tr>
<tr>
<td>% with CNVs among individuals with at least one reported variant</td>
</tr>
<tr>
<td>% with CNVs among individuals with a LP/P variant of any type</td>
</tr>
<tr>
<td>% of all variants that were CNVs</td>
</tr>
<tr>
<td>% of all reported variants that were CNVs</td>
</tr>
<tr>
<td>% of all variants classified as LP/P that were CNVs</td>
</tr>
</tbody>
</table>

Truty R et al. *Genet Med* 2019
Sensitively detecting intragenic copy number variants by NGS

Prevalence and properties of intragenic copy-number variation in Mendelian disease genes

Rebecca Truty, PhD1, Joshua Paul, PhD1, Michael Kennemer, MS1, Stephen E. Lincoln, BS1, Eric Olivares, PhD1, Robert L. Nussbaum, MD, FACMG1,2 and Swaroop Aradhya, PhD, FACMG1

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CNVs detected by Invitae in 143,515 individuals in 1,507 genes

- Reported events: 2,844 (1,237 unique)
- Confirmation by orthogonal method: 98%

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-Exon</td>
<td>75%</td>
</tr>
<tr>
<td>Single Exon</td>
<td>25%</td>
</tr>
<tr>
<td>Deletions</td>
<td>1,810 (64%)</td>
</tr>
<tr>
<td>Duplications</td>
<td>1,034 (36%)</td>
</tr>
</tbody>
</table>
Technically complicated genotypes: repetitive sequences

- Some genes have complex architecture and need sophisticated solutions

**Bioinformatics screen:** sequencing reads from both PMS2 and PMS2CL aligned to PMS2 only

**Sequence variants**

**Non-benign variants detected**

**Deletion/duplication variants (CNVs)**

**MLPA confirmation of deletion/duplication variants**

**Sanger sequencing of LR-PCR products of PMS2 and PMS2CL is performed to determine the location of variants.**

**Align reads derived from both SMN1 and SMN2 to SMN1 only**

**Call variants with several different starting ploidies**

**Use SMN1/2 gene determining variant to call SMN1 and SMN2 exon 7 specific copy number**

**SMN1 CN = 2**

**SMN2 CN = 2**
Technically complicated genotypes: split-read detection

- Rare intragenic structural rearrangements can be detected via NGS

TP53 partial Exon 11 deletion
Part II

- How is NGS technology and systematic variant interpretation improving our ability to find molecular diagnoses? What is the added clinical sensitivity from identifying rare genetic causes of hereditary disease and expanding genotype-phenotype correlations?

- 2) Are existing practices for genetic testing keeping up with technology and its capabilities to find answers? Unbiased genetic testing in specific cohorts has shown that existing clinical criteria for genetic testing inadvertently exclude a large pool of individuals who do have hereditary disease and should qualify for appropriate molecular testing.

- What is the scope for clinical actionability and precision medicine based on genomic information? It is becoming evident that early genetic testing for certain hereditary disorders can potentially guide precision medicine and reduce morbidity considerably.
Genetic testing guidelines and their limitations

- Historically, because of high costs and limited access, genetic testing was triaged to those deemed most likely to benefit from it. This was implemented via stringent clinical criteria established by various organizations (NCCN, Medicare and Medicaid, etc) to narrow referrals to people with likely genetic causes of disease.

- Guidelines also recommend analysis of a limited number of genes. NGS became available and costs decreased, clinicians began using expanded multi-gene panels rather than narrowly testing a small number of key genes, e.g., for breast cancer. What is the added benefit from expanded testing approach over single-gene testing?

- Based on clinical criteria defined by professional guidelines, are patients with suspected hereditary disease being referred for genetic testing equitably so that they may benefit from it where possible?
Multi-gene panels vs single-gene testing: cancer

- With the rapid expansion of NGS, clinicians have been migrating towards multi-gene panels rather than using traditional single-gene testing.
- Many cancer genes outside core panels have management guidelines.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Genes in Panels</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBOC</td>
<td>Narrow BRCA1, BRCA2, 19 gene list: ATM, BRCA1, BRCA2, BRI1P, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53</td>
</tr>
<tr>
<td>Prostate Ca</td>
<td>Narrow BRCA1, BRCA2, 12 gene list: ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53</td>
</tr>
<tr>
<td>CRC</td>
<td>Narrow: EPCAM, MLH1, MSH2, MSH6, PMS2, 19 gene list: APC, AXIN2, BMPR1A, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, SMAD4, SMAD6, STK11, TP53</td>
</tr>
</tbody>
</table>

Positive Yield (P/LP) in 125,648 Patients with Different Cancer Indications

- HBOC
  - N=3,679
  - Positive Yield: 0.22%
- Prostate Ca
  - N=109,527
  - Positive Yield: 0.67%
- CRC
  - N=6,017
  - Positive Yield: 4.5%
- Non-Oncology (Background)
  - N=10,104
  - Positive Yield:
    - 2 or 5 genes: 5.00%
    - 12 or 19 genes “Guidelines Panels”: 10.00%
    - 47 gene “Common Hereditary Cancers”: 15.00%
Multi-gene panels vs single-gene testing: epilepsy

- 30 genes explained 80% of diagnoses in epilepsy cohort. ~16% were non-SNVs
- If only SCN1A, MECP2, or other single genes were analyzed, would miss many diagnoses
Guidelines criteria: data from individuals with HBOC (Study 1)

- In 4,196 Medicare patients with breast cancer, we found that positive results were nearly as high in patients who did NOT meet criteria for testing as in patients who met criteria.


Breast cancer testing guidelines out of date, missing genetic screening, study says

By Susan Scotti, CNN

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Guidelines criteria: data from individuals with HBOC (Study 1)

- Retrospective analysis of a consecutive series of Medicare patients undergoing genetic testing based on personal and family history of breast and gynecologic cancer.
- Ordering clinicians indicated whether patients did or did not meet established criteria for BRCA1/2 genetic testing.
- Among 4196 unique Medicare patients, the rate of P/LP variants in a large panel of ~38-40 genes for the patients who met criteria for genetic testing was 10.5%, and for those who did not, was 9% (p = 0.26).
- Positive rates for a panel analyzing only BRCA1 and BRCA2 were also similar among the two groups (3.2% vs 1.9%, respectively)

Table 1: Positive rates identified in BRCA1/BRCA2 and a large, pan-cancer gene panel for in-criteria and out-of-criteria patients.

<table>
<thead>
<tr>
<th>BRCA1 and BRCA2 only</th>
<th>Pan-cancer panel (up to 80 genes)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient meets criteria (3,549)</td>
<td>Patient meets criteria (3,549)</td>
</tr>
<tr>
<td>Patient does not meet criteria (647)</td>
<td>Patient does not meet criteria (647)</td>
</tr>
<tr>
<td>Positive result</td>
<td>Positive result</td>
</tr>
<tr>
<td>3.2%</td>
<td>10.5%</td>
</tr>
<tr>
<td>1.9%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

Guidelines criteria: data from individuals with HBOC (Study 2)

- A study of ~1000 patients with a personal history of breast cancer using Invitae’s 80-gene cancer panel showed that ~8.6% of patients received positive diagnostic results.

- Of patients who met NCCN guidelines with test results, 9.39% had a P/LP variant compared to 7.9% of patients who did not meet guidelines. This difference is NOT statistically significant, suggesting that NCCN guidelines are too restrictive.

Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle?

Peter D. Beitsch, MD¹; Pat W. Whitworth, MD²; Kevin Hughes, MD³; Rakesh Patel, MD⁴; Barry Rosen, MD⁵; Gia Compagnoni, MD⁶; Paul Baron, MD⁶; Rache Simmons, MD⁷; Linda Ann Smith, MD⁸; Ian Grady, MD⁹; Michael Kinney, MD¹⁰; Cynara Coomer, MD¹¹; Karen Barbosa, DO¹²; Dennis R. Holmes, MD¹³; Eric Brown, MD¹⁴; Linsey Gold, MD¹⁴; Patricia Clark, MD¹¹; Lee Riley, MD, PhD¹⁶; Samuel Lyons, MD¹⁷; Antonio Ruiz, MD¹⁸; Sadia Kahn, DO¹⁹; Heather MacDonald, MD¹⁹; Lisa Curcio, MD¹⁹; Marv Kay Hardwick, MD¹⁹; Shan Yane, PhD²²; Ed D. Esplin, MD, PhD²³; and Robert L. Nussbaum, MD²²
Guidelines criteria: data from individuals with HBOC (Study 2)

- Pathogenic/Likely Pathogenic mutations in most genes other than *BRCA1/2* in HBOC have NCCN management guidelines
Revision of guidelines

Consensus Guideline on Genetic Testing for Hereditary Breast Cancer

Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly
Guidelines criteria: data from individuals with prostate cancer (Study 3)

- A study of 3607 men with a personal history of prostate cancer was conducted by Invitae. Among these individuals, 17.2% had a molecular diagnostic result, and 37% of these patients did not qualify for NCCN criteria for testing.

- The top 10 genes with positive variants as a percentage of men tested were as follows: BRCA2 (4.74%), CHEK2 (2.88%), ATM (2.03%), MUTYH (2.37%), APC (1.28%), BRCA1 (1.25%), HOXB13 (1.12%), MSH2 (0.69%), TP53 (0.66%), and PALB2 (0.56%).

JAMA Oncology | Original Investigation

Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines

Piper Nicolosi, PhD; Elisa Ledet, PhD; Shan Yang, PhD; Scott Michalski, MS, LCGC; Brandy Freschi, MS, CGC; Erin O’Leary, MS, CGC; Edward D. Esplin, MD, PhD; Robert L. Nussbaum, MD; Oliver Sartor, MD
Part III

- How is NGS technology and systematic variant interpretation improving our ability to find molecular diagnoses? What is the added clinical sensitivity from identifying rare genetic causes of hereditary disease and expanding genotype-phenotype correlations?

- Are existing practices for genetic testing keeping up with technology and its capabilities to find answers? Unbiased genetic testing in specific cohorts has shown that existing clinical criteria for genetic testing inadvertently exclude a large pool of individuals who do have hereditary disease and should qualify for appropriate molecular testing.

- What is the scope for clinical actionability and precision medicine based on genomic information? It is becoming evident that early genetic testing for certain hereditary disorders can potentially guide precision medicine and reduce morbidity considerably.
### Scope for clinical actionability from genetic testing

Among rare cancers, specific germline variants can be often be found in genes associated with guidelines-recommended clinical management.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Total Patients</th>
<th>Positive Patients (%)</th>
<th>Total P/LP Variants</th>
<th>P/LP variants in genes within guidelines panels</th>
<th>P/LP variants in genes outside guidelines panels</th>
<th>P/LP outside guidelines panels that would change management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>933</td>
<td>115 (12%)</td>
<td>122</td>
<td>69 (57%)</td>
<td>53 (43%)</td>
<td>50 of 53 (94%)</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>223</td>
<td>67 (30%)</td>
<td>71</td>
<td>50 (70%)</td>
<td>21 (30%)</td>
<td>20 of 21 (95%)</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>693</td>
<td>96 (14%)</td>
<td>101</td>
<td>83 (82%)</td>
<td>18 (18%)</td>
<td>18 of 18 (100%)</td>
</tr>
<tr>
<td>Renal Cancer</td>
<td>949</td>
<td>266 (28%)</td>
<td>294</td>
<td>204 (69%)</td>
<td>90 (31%)</td>
<td>89 of 90 (99%)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>423</td>
<td>68 (16%)</td>
<td>71</td>
<td>39 (55%)</td>
<td>32 (45%)</td>
<td>30 of 32 (94%)</td>
</tr>
</tbody>
</table>
Scope for clinical actionability from genetic testing

- A variety of **neuromuscular disorders have been targeted for therapy development**, e.g., spinal muscular atrophy, Duchenne muscular dystrophy and Charcot-Marie-Tooth disease.

- High diagnostic yield from **genetic testing can facilitate access to therapies**

- Identifying that a muscular dystrophy diagnosis due to **DMD mutations is actionable → exon skipping therapy. Due to SMA deletion → Spinraza**

<table>
<thead>
<tr>
<th>NEUROMUSCULAR DISORDER</th>
<th># OF PATIENTS</th>
<th>% CASES WITH POS DIAGNOSTIC RESULT</th>
<th>% OF DIAGNOSIS DUE TO CNVs</th>
<th>% OF DIAGNOSIS DUE TO SNVs</th>
<th>GENES WITH THE HIGHEST DIAGNOSTIC YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscular Dystrophy</td>
<td>903</td>
<td>295 (32.67%)</td>
<td>69 (23.39%)</td>
<td>226 (76.61%)</td>
<td>DMD (62.9%), DYSF (5.9%), CAPN3 (5.1%)</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth</td>
<td>1640</td>
<td>504 (30.73%)</td>
<td>299 (59.33%)</td>
<td>205 (40.67%)</td>
<td>PMP22 (59%), MFN2 (9.7%), GJB1 (8.7%), MPZ (7.5%)</td>
</tr>
<tr>
<td>SMA</td>
<td>3891</td>
<td>803 (20.64%)</td>
<td>803 (100%)</td>
<td>0 (0%)</td>
<td>SMN1 (100%)</td>
</tr>
</tbody>
</table>

Winder et al. Manuscript submitted 2019
Scope for precision medicine from genetic testing: epilepsy

- **33% of individuals** with positive reports had results related to precision medicine in a cohort of ~10000 patients with epilepsy.

- Nearly **half of positive molecular diagnoses with precision medicine implications** were related to contraindications for anti-epileptic drugs, largely due to variants in **SCN1A**.

- **10% of molecular diagnoses** were related to **biochemical disorders** with available therapies.

- **40% of molecular diagnoses invoked indications** for specific anti-epileptic drugs (e.g., Vigabatrin for spasms in TSC).

- Another **21% of individuals** had positive molecular diagnoses in **genes with emerging association** with precision medicine implications.
Presentation Outline

1) How is NGS technology and systematic variant interpretation improving our ability to find molecular diagnoses? There is considerable additional clinical sensitivity from identifying exonic deletions and duplications and other types of variants as rare genetic causes of hereditary disease

2) Are existing practices for genetic testing keeping up with technology and its capabilities to find answers? Unbiased genetic testing in specific cohorts has shown that existing clinical criteria for genetic testing inadvertently exclude a large pool of individuals who do have hereditary disease and should qualify for appropriate molecular testing. And that multi-gene expanded panels can provide important answers beyond canonical genes.

3) What is the scope for clinical actionability and precision medicine based on genomic information? It is becoming evident that early genetic testing for certain hereditary disorders can potentially guide precision medicine and reduce morbidity and mortality.
Appendix slides
Advantages and nuances of NGS technology used in clinical genomics

- Invitae has invested significant technical and medical expertise and financial resources to build NGS infrastructure that can process thousands of samples each day. Transparent quality monitoring processes built by Invitae engineers ensure consistency, low error rate, and fast turn-around time for clinical samples.

- Scale reduces cost per sample through higher throughput and efficiency. It is eminently possible to create a genetic test with the highest quality at low cost.
Sensitively detecting intragenic copy number variants by NGS

 Compound heterozygous deletions in CLN3

 Heterozygous partial gene duplication in STXBP1
Technically complicated genotypes: split-read detection

- Rare intragenic structural rearrangements can be detected via NGS

- Example: Deletion affecting two neighboring exons – missed by most del/dup methods, but detected by split-read detection
Technically complicated genotypes: mosaic variants

Investigated mosaicism uncovered through gene panel testing results in 472,991 individuals. 1606 different genes represented. 20 million single gene tests. (Truty et al. ACMG conference 2019)

- Found 2,459 mosaic variants in 286 genes: 2107 SNVs, 282 small indels, 70 CNVs. Observed allele balance range of 7% - 40%. Confirmed qualitatively by PacBio seq.

- 40% of mosaic variants classified as LP/P = ~1% of positive results
Key Points

1) How is NGS technology and systematic variant interpretation improving our ability to find molecular diagnoses? What is the added clinical sensitivity from identifying rare genetic causes of hereditary disease and expanding genotype-phenotype correlations?

- Important to ensure technical sensitivity to full spectrum of clinically important variants. **Intragenic deletions and duplications add ~7-20% clinical sensitivity**
- Clinical interpretation of observed variants should be evidence-based, systematic, and consistent. Recognizing impact of certain variants through
- Clinical examples: larger panels for breast cancer, neuromuscular disorders, or epilepsy provide additional and actionable value beyond core genes
Multi-gene panels can provide a high diagnostic yield

- Multi-gene panels provide high diagnostic yield in various hereditary cancer syndromes, beyond HBOC.

<table>
<thead>
<tr>
<th>SELECT EXAMPLES OF ONCOLOGY MULTI-GENE PANELS</th>
<th># OF PATIENTS</th>
<th>% CASES WITH POS DIAGNOSTIC RESULT</th>
<th>% OF DIAGNOSIS DUE TO CNVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitae Multi-Cancer Panel</td>
<td>73,977</td>
<td>10.49</td>
<td>7.26</td>
</tr>
<tr>
<td>Invitae Common Hereditary Cancers Panel (Breast, Gyn, Gi)</td>
<td>118,346</td>
<td>8.98</td>
<td>7.45</td>
</tr>
<tr>
<td>Invitae Breast and Gyn Cancers Panel</td>
<td>37,046</td>
<td>8.74</td>
<td>7.75</td>
</tr>
<tr>
<td>Invitae Colorectal Cancer Panel</td>
<td>13,973</td>
<td>7.96</td>
<td>11.54</td>
</tr>
<tr>
<td>Invitae Pancreatic Cancer Panel</td>
<td>8,162</td>
<td>6.54</td>
<td>6.74</td>
</tr>
<tr>
<td>Invitae Thyroid Cancer Panel</td>
<td>2,095</td>
<td>4.06</td>
<td>5.88</td>
</tr>
<tr>
<td>Invitae Hereditary Paraganglioma-Pheochromocytoma Panel</td>
<td>1,971</td>
<td>19.63</td>
<td>10.34</td>
</tr>
<tr>
<td>Invitae Renal/Urinary Tract Cancers Panel</td>
<td>4,604</td>
<td>4.11</td>
<td>11.11</td>
</tr>
<tr>
<td>Invitae Prostate Cancer Panel</td>
<td>5,544</td>
<td>7.72</td>
<td>5.84</td>
</tr>
<tr>
<td>Invitae Melanoma Panel</td>
<td>5,635</td>
<td>4.67</td>
<td>3.04</td>
</tr>
<tr>
<td>Invitae Lynch Syndrome Panel</td>
<td>4,793</td>
<td>11.25</td>
<td>19.11</td>
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</table>