Expanding Treatment Options with Genomics-Enabled Immuno-Oncology

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Dr. Weigman works for Q² Solutions | EA Genomics, who develops genomic assays across the indication spectrum for enhancing clinical trial enrollment. Dr. Weigman has also received honorariums for speaking engagements by Illumina and Life Technologies.
Motivation

• Evolving from broad-use cytotoxic therapies to targeted agents based on mutation status has proven effective
• As the information of [DRUG] → [GENE] interaction grows more abundant, comprehensive molecular profiling helps match patients to drugs
• Since most genomic profiling (currently) occurs in late-stage patients, most single-agent therapies show only partial response
• Immune therapies have shown remarkable response rates for those small populations that are receptive
• Genomics is poised to provide extensive molecular characterization of the mutational and immunogenic landscape of tumors and their environments
• New arms of clinical trial research are needed to better characterize effectiveness of these new assay classes
Targeted Therapies Abound

Need to match the patients to them

Personalized/ Precision Approach

Prescreened Population

Predictive Biomarker Testing

Responders

Adverse Event Patients

Non-responders

Source: http://www.personalgenome.com/translating-cancer-genome-analyses

Of the 189 oncology therapies currently under development in the period of 2012-2015, 56% have an associated biomarker.
Increasing the Adoption of Genomic Pre-Profiling

Good for the patient, good for Pharma

• Higher actionability increases patient and physician interest
  – General oncology test can identify many pan-cancer biomarkers (~2-3wks)
  – Increases chance for rare positive biomarkers to be found for various trials

• Enhanced Trial enrollment
  – Large sample study shows that 11% (of 2000) went onto genotype-matched trials\(^1\)
  – Many Groups facilitate this matching
    • Molecular Match
    • Caris
    • IBM (Watson)

• Personalized arms using genomic biomarkers had increased OS / RFS survival
  over standard protein over-expression assays\(^2\)

• New Protocols are leveraging this power!
  – TAPUR (ASCO) M-PACT (NCI)
  – Lung-MAP (NCI) IMPACT-2 (MD Anderson)
  – FOCUS-4 (UK)

• Future Longitudinal data will show how these matched therapies have performed

**The Opportunity:**

Immuno-oncology as the future of cancer treatment

- Over 45 immuno-oncology drugs approved (US)*
- 57 immuno-oncology drugs in development*
- Over 250 studies registered/ongoing*
- Increasing number of relevant publications annually**

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*UBS Immuno-oncology Monthly Handbook (Jan 2015)

**PubMed; keywords ‘cancer immunotherapy’

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Immune-oncology Biomarker Options are Numerous and may be Targeted Biological Analysis or Broad Population Profiling

Tumor – Immune Biology
- Target protein expression – IHC
- Serum proteins – ELISA
- Circulating cell populations – Flow
- RNA expression – Multiplex PCR

Patient – Tumor Profile
- Transcriptome – RNA-Seq
- Serum proteins – proteomics
- Genomics – NGS
- RNA transcriptome – RNA-Seq
Immuno-oncology is Genomics Solutions Oriented

Molecular methods provide an advantage for complex biomarker analysis

- Shift toward genomics away from other methodologies due to limitations of subjectivity, quantitative ability, low capacity for multiplex, sensitivity, etc.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Genomics Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic Mutation Analysis</td>
<td>DNA deep Sequencing, Breakpoint analysis and Fusion Detection</td>
</tr>
<tr>
<td>Gene Expression Profiling</td>
<td>RNA-Seq, Arrays, RNA panels</td>
</tr>
<tr>
<td>Germ Line Variant Analysis</td>
<td>CNV, Structural and Small Variant Detection</td>
</tr>
<tr>
<td>HLA Characterization</td>
<td>HLA Calling (DNA, RNA, Arrays)</td>
</tr>
<tr>
<td>Antigen-Specific Immune Response</td>
<td>B/T Cell Repertoire (DNA/RNA), VDJ mutation (RNA)</td>
</tr>
</tbody>
</table>
You already have material to begin
Existing clinical trial sample collection procedures leave you with these amounts already

<table>
<thead>
<tr>
<th>Assay Input Needs</th>
<th>Blood</th>
<th>FFPE</th>
<th>Solid Tissue</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctDNA Allele Calling</td>
<td><img src="10" alt="Standard Input (ng)" /> <img src="500" alt="FFPE Input (ng)" /></td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
<tr>
<td>qPCR Expression</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
<tr>
<td>PCR-enriched (NGS)</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
<tr>
<td>Whole Exome (NGS)</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
<tr>
<td>Targeted (NGS) Panel</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
<tr>
<td>IGVH Testing</td>
<td><img src="500" alt="Standard Input (ng)" /></td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
<tr>
<td>Genotyping of Risk Alleles</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
<tr>
<td>HLA Allele Calling</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
<tr>
<td>RNA-Seq</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
<td>![?]</td>
</tr>
</tbody>
</table>

- Standard Input (ng) vs FFPE Input (ng)
**Immunity Status -> Expression of Immune Checkpoints**

*B-cell gene signature* more significantly associates with improved Overall Survival than *classical clinical variables*.

**Supplementary Table 1**

<table>
<thead>
<tr>
<th>Signature (vs. Luminal A)</th>
<th>IGG_Cluster p Value</th>
<th>TNBC_B-Cell p Value</th>
<th>B_Cell p Value</th>
<th>B_Cell_cluster p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal B</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Basal-like</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Claudin-low</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Proliferation</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Node Status</td>
<td>3.21E-03</td>
<td>4.03E-03</td>
<td>2.54E-03</td>
<td>4.02E-03</td>
</tr>
<tr>
<td>Age</td>
<td>1.95E-02</td>
<td>3.05E-02</td>
<td>4.06E-02</td>
<td>1.70E-02</td>
</tr>
<tr>
<td>ER (clinical)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PR (clinical)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HER2 (clinical)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Iglesia et. al. (2014) Clinical Cancer Research 20(14):3818*
Immune Repertoire has Prognostic Value

- IGVH typing confers relative health of cellular receptors
- Patients effectively respond to Ibrutinib when IGVH type = “unmutated”

- TCRs are obviously affected in response to disease and provide potential targets for therapies (CAR-T)
- Luo et al also shows improved Erbitux response for patients with appropriate TCR repertoire

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**Table: IGVH Typing and Prognostic Value**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>ORR%</th>
<th>CR%</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed/Refractory [23]</td>
<td>85</td>
<td>71</td>
<td>4</td>
<td>75% at 26 months</td>
</tr>
<tr>
<td>Treatment Naive [3]</td>
<td>31</td>
<td>74</td>
<td>10</td>
<td>96% at 15 months</td>
</tr>
<tr>
<td>High Risk [1]</td>
<td>24</td>
<td>50</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>High Risk [1]</td>
<td>29</td>
<td>53</td>
<td>NR</td>
<td>85% at 20 months</td>
</tr>
</tbody>
</table>

**Combinations:**

- Ibrutinib + Ofatumumab [5]
- Ibrutinib + FCR [7]
- Ibrutinib + Rituximab [9]
- Ibrutinib + BR [8]

- Number of patients, CLL: Chronic lymphocytic leukemia, ORR: Overall response rate, CR: Complete response, PFS: Progression free survival, BR: Bendamustine and rituximab, NR: Not reported


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**Graph: TCR Repertoire in Healthy Donors and Sézary Patients**

Novel antigen determination can kick-start immunity

In most cases, somatic mutation calling from Exomes provides early evidence of malformed antigens.

Coupling with RNA-Seq is essential to confer expression of that variant allele.

Clinical group groups by mutation burden within antigens.

Creating custom antibodies to restore recognition has increased survivability.
Current Landscape in Oncology
Turning a fatal disease into a chronic treatable disorder

Over 800 cancer drugs in clinical trials - almost all are targeted at particular gene products

Some Fundamental Problems in Cancer Treatment

- Cancer is rarely detected early
- Cancer develops resistance rapidly to targeted therapies and chemotherapies due to the development/expansion of resistance mutations.
- Many patients do not respond to immunotherapies. Immunotherapies are changing the approach to treating cancer by treating the immune system rather than the cancer but not all patients respond.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response Rate</th>
<th>Toxicity</th>
<th>Long term Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy / Radiation</td>
<td>Low</td>
<td>High</td>
<td>Poor</td>
</tr>
<tr>
<td>Targeted Therapy</td>
<td>High</td>
<td>Lower</td>
<td>Moderate</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Mid</td>
<td>Lower</td>
<td>Good</td>
</tr>
</tbody>
</table>

Source: Sharma, Allison: Cell, April 2015
**Potential Roadmap of Mixed Genomic Testing**

Multiple parallel and synergistic pathways maximizing immediate lab opportunities as well as long term clinical differentiation

Prioritized Biomarker Activities

1. Develop next-gen IHC tests
2. RNA-Seq – gene expression analysis
3. Immunoassay serum protein proteomics
4. Flow cytometry immune cell population profiling
5. Genomic profiling for DNA repair defects/mutation load and microbiome profile

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Non-biomarker research & bioinformatics

Preclinical & Clinical Research

Patient Samples & Clinical Data

RNA-Seq

Flow cellular profiling

Genomic profiling

Microbiome

IHC Test

Serum proteomics

TIL Analysis

IHC Test

Serum proteomics

TIL Analysis

Patient Monitoring

Clinical Trial Assays and Diagnostics

CRO & Dx Manufacturer Partnerships

NGS IO CDx

Immunoscore

Multiplex IHC Test

Response Signature

Immuoassay Test

Nanostring Test

Patient Monitoring

Novel Drug Comb.'s

Opportunities for synergies
## Practice Safe Tests!

*HLA alleles have proven associations with toxicity*

### Situation

- Targeted therapy has been selected for patient.
- After treatment, certain patients develop hepatotoxicity to treatment, causing Drug Induced Liver Injury (DILI) and potential post marketing withdrawal of drug.

### Solution

- Human Leukocyte Antigen (HLA) allele calling showcases toxicogenomics and identifies type that is associated to adverse reaction in affected population
- ~30% of patients develop Colitis
- HLA gene association analysis will identify risk alleles

### Result

- Patients in trial with the risk allele can be more closely monitored / have treatment amended
- Pharmacogenomics (PGx) data also generated for all trial participants
Conclusions

Improved response from patients is coming

- Genomic panels provide mechanisms to give patient therapies based on individualized mutation status

- Targeted Therapies have improved response, but still have high level of individuals that need benefit

- Immunotherapies can give very strong response but pairing them to the patient is complex
  - Multiple assay types
  - Multiple mechanisms to profile

- Genomic Assays provide avenue to being clinical trial research on efficacy of new Immuno-oncology assays and benefit

- Most companies already have the clinical trial samples to take advantage of these technologies
Q² Solutions EA Genomics
A comprehensive suite of genomic services supports your clinical trial and research needs

Our Key Differentiators
• Key Opinion Leader with history of innovation, FDA collaborations, operational excellence and Bioinformatic Expertise
• Technical Expertise across broad technological platforms offering a comprehensive genomic service solution in clinical trials and research
• Best in class infrastructure with robust and proven quality system and the first microarray facility in industry to implement GLP compliant procedures
• Consultative and solutions based, leading to longstanding relationships with top pharma and biotech companies
• CLIA certification in 2010

Genomic Know-How® for your drug development needs
Questions

https://www.linkedin.com/company/q2-solutions
Appendix
**Precision Medicine**

Partner of choice for CDx development from biomarker ID to CDx launch

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1. Biomarker R&D services and CDx strategic consulting
2. Assay development expertise and Dx partnerships
3. Assay optimization/Bridging study/CLIA laboratory testing
4. Global study execution for pivotal CDx trials
5. Regulatory support, including BIMO/FDA inspection support
6. Commercial, diagnostic and late-phase expertise

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Genomics Laboratory

Services across the drug development lifecycle

**Rx/Dx (Pre-clinical)**

**Phase I**

**Phase II**

**Phase III**

**Regulatory Submission**

**Dx**

### Hypothesis Driven Biomarker Identification

Sequencing and array based whole genome “wide net” screening; targeted analysis.

- RNA-Seq
- Array-based Expression Profiling and Genotyping
- Exome Sequencing
- **Bioinformatics**
  - Targeted Expression Profiling and Genotyping (PCR)
  - Targeted DNA Sequencing

### Analytical/Clinical Validation

Scientific expertise to develop and validate of custom targeted expression profiling and genotyping assays as diagnostic biomarkers

**Q² Solutions Comprehensive Cancer Panel**

- A 223 gene panel specifically enhanced for drugability targets to facilitate Therapeutic decisions and clinical trial enrollment

**Complex Mutational Analysis**

- HLA allele typing for drug development
- IGVH typing for CLL patients

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*A comprehensive suite of genomic services in support of discovery, clinical trials, and CDx development*
Genomics Services
Clinical trial support across the drug development lifecycle

• Retrospective genomic testing of clinical trial samples:
  • Aid in target identification (genetic variants associated with disease)
  • Understand differences in clinical response
  • Provide visibility into safety or efficacy signaling present for a cohort of patients.

• Implementing effective biomarker strategies in discovery and clinical phases can be leveraged to reduce drug development costs and timelines:
  • Increase statistical power and stratification of trial populations
  • Reduce risk of adverse events
  • Improve efficacy and efficiency in later phase trials
  • Implement targeted therapy:
    • Identification of responders vs. non-responders.
    • Effective dosing schedules

Provides molecular testing of both predictive and pharmacogenomic biomarkers using microarray, genotyping and next generation sequencing
Q² Solutions Genomics Capabilities for IO
Developing gene and microbiome signatures

**Gene Expression**
- Commercial panels for inflammatory or other immune-related gene expression
  - Nanostring PanCancer Immune
  - HTG EdgeSeq Immuno-Oncology Panel*
- RNAseq: complete transcriptome analysis
- Custom gene expression panels (e.g. TaqMan, digital)

**Microbiome Analysis**
- 16S ribosome sequencing
  - Illumina 16S Metagenomics protocol
    - Quick
    - Cost-effective
    - High specificity for species tested

*In development; planned for 1H 2016
**Genomics Capabilities for IO, cont.**

Analyzing the tumor: immune system interface

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**Mutation Analysis**

- Whole-exome deep sequencing to quantify mutational burden
- Identification of ‘neo-antigens’
  - Coupled with RNAseq to confirm tumor antigen expression
- BFx and predictive algorithms to generate ‘immunogenicity score’
- DNA damage and mismatch repair:
  - MSI instability (PCR and IHC)
  - BRCA1 mutation analysis

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**HLA and KIR Genotyping**

- HLA allele calling from:
  - Microarray
  - RNAseq
  - Targeted DNA sequencing
- KIR genotyping and expression (from PAXgene) using commercial kit (Miltenyi)

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**Immune Repertoire**

- TCR (α/β, γ/δ) and BCR receptor sequencing to assess clonal diversity*
- IgVH mutation analysis (RNA-based)

*In development; planned for Q1/Q2 2016

Source: Draper et al, Clinical Cancer Research. October 1, 2015