DEVELOPING DRUGS IN THE NEW ERA OF PERSONALIZED MEDICINES

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PROPOSED AGENDA

- What is precision medicine?
- The rise & impact of precision medicine
- Impact on drug development
- Impact on clinical development
- Impact on clinical trials
- The role of genomics in development
- Case studies
- Emerging trends
- Summary and conclusion
- Q&A
WHAT ARE PRECISION OR PERSONALIZED MEDICINES

Leverage biomarkers, often genetic, to determine who is most likely to benefit from a treatment, who is at higher risk of a side effect, or who needs a different dose.

Without personalized medicine
Some benefit, some do not

With personalized medicine
Each patient receives the right medicine for them

RISE AND IMPACT OF PRECISION MEDICINES

Nearly 1 in 4 of the new drugs approved by the U.S. Food and Drug Administration between 2014-16 were precision medicines.

Currently the FDA lists almost 200 approved medicines with pharmacogenomic biomarker information in their labeling.

132 of these are considered precision medicines leveraging a biomarker to direct treatment decisions.

Over the next five years, the proportion of personalized medicines in clinical development is expected to increase to nearly 70%.

http://www.personalizedmedicinecoalition.org/Resources/Personalized_Medicine_at_FDA. Accessed 04 May 2017

Tufts Center for the Study of Drug Development Impact Report, Volume 17, No 3, May/June 2015
• Precision medicines are impacting across a wide range of therapeutic areas including Psychiatry, Infectious and Cardiovascular Diseases

• In the three therapeutic areas having a more robust base for analysis, Oncology followed by Immunology and Neurology showed the greatest penetration in the three areas accounting for a majority of the Genomic budget – Bioinformatics, Target Validation and Pharmacogenomics.

*Percentages reported for Pharmacogenomics and Data Analytics represent the mean of means for individual activities within these service areas. Detailed information for individual capabilities available in appendix.

Base: Oncology=38, CNS/Neurology=17, Immunology=17
Q. Considering the therapeutic area(s) your company works in, which of the following genomic medicine activities do you typically utilize for each? Please select all that apply for each therapeutic area.
When asked to report on the proportion of studies including some aspect of Genomic Medicine, utilization was found to be greatest in the earlier phases of development and then declines in later phases, as expected.

### Genomic Medicine Use by Study Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Count</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>50</td>
<td>63%</td>
</tr>
<tr>
<td>Phase II</td>
<td>55</td>
<td>57%</td>
</tr>
<tr>
<td>Phase III</td>
<td>45</td>
<td>49%</td>
</tr>
<tr>
<td>Phase IV</td>
<td>33</td>
<td>30%</td>
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</tbody>
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Q. Considering the following stages of clinical development, approximately what proportion of studies your company does in each stage includes some aspect of *genomic medicine*?
IMPACT ON CLINICAL TRIALS

TRIAL DESIGNS
• Basket trials
• Umbrella trials
• Master trials
• Co-development of test

PATIENT SELECTION
• Targeted selection or stratification using genetic/biomarker
• Dose selection
• Smaller numbers of patients

EXPLAIN VARIABLE RESPONSE TO TREATMENT
• Sub-populations/disease sub-types
• Ethnic variation
• Safety/adverse events
Application of genomics in developing precision medicines
THE “RIGHT” REASONS TO INCLUDE GENOMICS IN DRUG DEVELOPMENT…

THE RIGHT PATIENT
- Companion diagnostics
- Patient enrichment
- Novel clinical trial design

THE RIGHT DRUG
- Drug target of specificity
- Targeted pathway
- Drug repurposing

THE RIGHT DOSE
- PK Variability/ADME
- Genetic risk factors
- Drug combinations

THE RIGHT TIME
- Drug resistance
- Disease progression
- Non-invasive biomarker
APPLICATION OF CUTTING-EDGE METHODOLOGIES THAT INTEGRATE GENOMICS DATA CAN REVEAL NEW SCIENTIFIC INSIGHTS

• The human immune response system is highly complex with cross-talk between multiple immune-mediated pathways.

• Many currently available medicines that target the immune system affect multiple pathways – some desired, others not.

• Using cutting-edge methodologies (e.g., causal reasoning, advanced network analysis) to integrate, analyze, and interpret multi-omics experimental data led to discovery of novel drug targets that may have selectivity for IL23 pathways.

EBI Immunogenomics Conference 2015
WHAT IS PHARMOCOGENOMICS?

- Pharmacogenomics is the study of DNA and RNA characteristics as they relate to drug response
- Provides insights into drug exposure, efficacy, and safety

Pharmacogenomics helps us understand why people who receive the same drug respond differently

PHARMACOGENETICS EXPLAINS EXPOSURE DIFFERENCES

- In a Phase I drug-drug interaction study, a subset of healthy volunteers had elevated levels of Drug X when administered with the client’s medicine.

- Drug X is primarily metabolized by a CYP450 enzyme. Genetic variation in the CYP450 gene was evaluated to determine if genetic variants that lead to reduced enzyme activity might explain increased exposure of Drug X.

- The poor metabolizer CYP450 genotype was associated with elevated exposure of Drug X.

- The client’s medicine likely did not impact Drug X exposure.

Drug X plasma concentrations over time by CYP450 genotype

- IM intermediate metabolizer
- PM poor metabolizer
- WT wild-type metabolizer
DRUG REPURPOSING CAN ACCELERATE MEDICINE DEVELOPMENT

A comprehensive clinical transcriptomics analysis across multiple dermatologic conditions identified additional dermatology indications for this medicine, discovered mechanistic connections between skin diseases and generated new hypotheses to accelerate medicine development.
EMERGING TRENDS IMPACTING PRECISION MEDICINES

- Big Data Analytics
- New ‘OMES e.g. microbiome
- Co-Development Partners
- Electronic Health Records
- New Technology (cfDNA, CTC)
- Patient Partnerships
- Smart Phones/Wearables
- Data Sharing
Clinical trials for Precision Medicines may look very different from traditional drug trials.

Hard to have breadth of expertise needed to capitalize on turning

GENES > TARGETS > PRECISION MEDICINES

- Complex trial designs including co-development of companion test
- Regulatory requirements are emerging in global markets
- Reimbursement considerations for drug and test
- Ethics and local laws pose challenges for sampling and testing
- Storage and computational resources for big data
- Ensuring accuracy of results from evolving technologies such as NGS
- Integrating and analyzing multi-omics data
- Making big data accessible and understandable to drug development scientists
- Creating and communicating reproducible workflows for complex analyses

A JOURNEY WITH GREAT PROMISE…. AND CHALLENGES TOO
THANK YOU