2016 YALE HEALTHCARE CASE COMPETITION

Evaluating Infectious Disease Diagnostics Business Opportunities in a Next Generation Sequencing Era

Presented by: The Jackson Laboratory
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This document provides an overview of the Yale Healthcare Case Competition including a summary of the case, questions to consider and deliverable requirements. Please send the deliverable to He Zhu at YaleHCC@gmail.com by February 26th. Please contact He Zhu for questions regarding the case.

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Introduction

Daniel Brown, CEO of NextGENomics was sitting in his chair and checking emails on a usual Friday morning. As a former Yale doctoral student, he maintained the habit of reading subscriptions from academic journals. Scanning this week’s headlines, one study caught his eyes. It was a review on human infectious disease diagnostics, which made Brown ponder NextGENomics’ growth opportunities in the coming years. Diagnostic microbiology had recently drawn much attention from both basic biomedical research and clinical application communities. Moreover, the development of Next Generation Sequencing (NGS) technologies seemed to promise advances in microbe-induced infectious disease diagnostics. NextGENomics’ skillset and knowledge base made it possible for the company to begin investigations in this area. Brown wondered however, given NextGENomics’ current position, what was the best way to venture into this field.

NextGENomics is a nonprofit biomedical research institution founded by Brown and his peers twelve years ago. Its core mission is to contribute to the future of better healthcare through the unique potential of genomic research. In addition to its grant-funded cutting edge research, NextGENomics currently has a successful commercial operation selling materials and services. Through this component, NextGENomics has a strong network and access to partner organizations in the field of biomedical genomics.
Over the past decade, Brown along with a team of accomplished scientists built NextGENomics into a well-respected research institution. The nonprofit status has also aided tremendously in the growth of the organization. Brown sometimes wondered however, that in order to sustain growth in the years to come, whether the nonprofit status was the best way to position the company moving forward. While sticking to NextGENomics’ core nonprofit mission, Brown is considering the launch of a pediatric infectious disease diagnostic service based on next generation sequencing technology.

**Infectious Diseases**

Infectious diseases are caused by pathogenic microorganisms including bacteria, viruses, parasites, and fungi. The diseases are subsequently spread directly or indirectly, from one person to another. Signs and symptoms vary depending on the organism causing the infection, but often include fever and fatigue. Mild infections may respond to rest and home remedies, while some life-threatening infections may require hospitalization.

Take pneumonia as an example. Pneumonia is commonly caused by infection from viruses or bacteria. It is an inflammatory condition of the lung affecting primarily the microscopic air sacs known as the alveoli. The air sacs may fill with fluid or pus (purulent material), causing cough with phlegm or pus, fever, chills, and difficulty breathing. It is most serious for infants and young children, people older than age 65, and people with health problems or weakened immune systems. Diagnostic tools include x-rays and culture of the sputum. Vaccines to prevent certain types of pneumonia are available and treatment varies depending on the underlying cause.

Infectious diseases disproportionately harm people with weak immune system, such as infants and young children. Therefore, pediatric respiratory infection has become a major global health issue. About one-quarter of primary care consultations among children relate to respiratory complaints. The Gates Foundation has specifically called out childhood pneumonia as one of their target areas for global health. In a US survey in 2002, the neonatal mortality rate was 6.9 per 1000 babies born at 35–36 weeks, 18.5% in babies born at 30–34 weeks, and 28.5% among
babies born at < 30 weeks. In a recent follow-up of 100 infants born at 23 weeks, 60 died prior to hospital discharge, most from respiratory failure.

**Traditional Clinical Diagnostics on Infectious Diseases**

Starting from shared symptoms, such as coughing and difficulties in breathing, it is very difficult to determine the cause of the symptoms without powerful assay methods. Currently, there are two main types of pathogen detection assays provided in either hospital or independent labs: culture-based methods and PCR-based methods.

Culture-based methods take a sample of tissue or fluid from the patient and culture it in the laboratory for the detection and identification of the infections, as well as determination of the sensitivity to antibiotics. Cultures are obtained to assist the provider in determining the type of infection and in directing the antibiotic choice. However, these methods are normally slow with high false positive rates (2% -6%) and often fail to detect the cause.

After collection of patient tissue or fluid sample, PCR-based methods identify the cause of the infection by pinpointing genes that belong to specific pathogens. PCR is used to aid the detection of the tiny amount of the common pathogen genes by extensively amplifying a wide range of pathogen specific genes. Although PCR-based methods are faster compared to the culture-based methods, only pathogen-specific genes with relatively large quantities can be efficiently amplified and thus these methods are very limited in detection range.

Clinically, delayed or inaccurate pathogen identification can worsen disease severity and drive up costs. Additional repeated rounds of testing may be required, further contributing to the increased diagnostics costs and lengthened hospital stays. In fact, additional costs associated with unnecessary antibiotic use as a result of false positives or false negatives can be upwards of $1,000 per patient.
NGS-based Diagnostics on Infectious Diseases

Brown believes NGS-based methods enables metagenomic detection and can potentially be a more powerful method of diagnostics in addition to providing some unique advantages. In NGS-based methods, total DNA extraction and sequencing will be performed for the patient samples. Comparing the sequencing results with known pathogen genome and microbiome databases enables the detection and identification of the pathogen. Although NGS-based methods generate large amount of data (and thus are computational intensive and dependent on accuracy of the existing databases), they provide rapid detection methods with high accuracy and reliability as well as a broad dynamic detection range of pathogens. Therefore, NGS-based methods are potentially more efficient and effective with reduced/eliminated costs of repeat testing, incorrect empiric treatment, and extended hospital stays. In addition, NGS-based methods provide analysis of drug-resistant strains in real time, and are equally applicable to bacteria, viruses, fungi or other microbes.

NGS-based Diagnostics Customer Use Cases

The metagenomic results, generated by NGS-based diagnostic methods, have demonstrated equivalent ability to detect pathogens with improved sensitivity. Here is an example of NGS-based diagnostic methods in the detection of bacterial pathogens.

In a study at a Midwestern pediatric clinic:

- Metagenomic results agreed with standard methods in all cases
- Metagenomic analysis also detected second pathogen in 18 cases (bacteria and viruses).

Another example of NGS-based diagnostic methods in the detection of viral pathogens and others:

At a Midwestern pediatric clinic:

- 73 febrile children were compared to 103 afebrile controls via testing of nasopharyngeal and plasma specimens
- Metagenomics was able to detect excess virus in febrile patients
- Demonstrated ability to detect fungi
Notably, when there is failure to detect a pathogen, the febrile patient (child) is given an antibiotic anyway; if it is a viral infection, however, this is unnecessary and exposes the patient (child) to a treatment with potential side effects and unwanted downstream issues, such as selection for antibiotic resistant bacteria. Therefore, the additional sensitivity, NGS-based diagnostic methods provided, is highly appreciated.

Target Market Overview (pneumonia as an example)

Community-acquired pneumonia:
74-92 per 1000 children under 2 years’ old
35-52 per 1000 children 3-6 years’ old

Product Description

The product offered by NextGENomics is a hospital-based platform and will be based on sequencing of all DNA found in the patient specimen: human, viral, bacterial, fungal, etc. These analyses will not only identify what infectious species are present, but also identify genetic changes that provide clues to effective treatment.

Challenges of the IP Landscape: Barriers to Patent Protection

Unfortunately for Brown, getting patent protection on biological diagnostic tests has become increasingly difficult in the last few years. The issues stem from a trio of Supreme Court rulings: Association for Molecular Pathology v. Myriad Genetics, Mayo v. Prometheus, and Alice Corp. v. CLS Bank International. These rulings placed restrictions on what inventions are considered patent eligible. In the aftermath of these controversial decisions, the US Patent and Trademark Office issued a Guidance and further examples directed to the very patent eligibility of inventions in biotechnology and information management. More changes to patent law may be imminent, as the courts have not finalized opinions on another case, Ariosa Diagnostics v. Sequenom., a case which relates directly to diagnostics. The District and Federal Circuits found Sequenom’s diagnostic for detecting fetal abnormalities from a maternal blood sample (i.e. a vastly improved
methodology to existing amniotic fluid tests) unpatentable. The courts ruled that the cell-free fetal DNA upon which the test is based was essentially a “natural phenomenon”, which is not patent eligible. Everyone is now waiting to learn whether the Supreme Court will take up this case and determine whether such diagnostic tests, though groundbreaking, are patent eligible. Therefore, based on the Sequenom ruling, getting a patent for a device that utilizes an existing method to measure changes in the human body and diagnose disease will be challenging. For NextGENomics, the difficulty lies in demonstrating that this new use of the NextGENomics platform goes beyond an abstract idea or something found in nature – which is not patentable – and constitutes something more inventive.

Please consider all the information available when compiling your analysis. Teams are encouraged to conduct their own research on the topic and are welcome to challenge numbers and trends given in the case.

Questions to Consider

- Do you think NextGENomics should invest in a new NGS-based pediatric infectious disease diagnostics business, why?
- If you are going to launch the NGS-based diagnostics, how would you select the particular area of pediatric infectious disease diagnostics market, design the entity of the business, and allocate investment for the business?
- Why do you think the business you choose is a good fit for NextGENomics’ nonprofit entity?
- What will be the key success factors in entering and achieving a leadership position in the market you selected?
- Which elements of the current and near-term market landscape are most important for NextGENomics to watch during and immediately following their launch period? What elements will be the most important in the long run?
Deliverables:
- Annotated PPT presentation (10-15 minutes), including:
  - Market analysis of the particular area of pediatric infectious disease diagnostics you select
    (for example: pulmonary infection, bacteremia, etc)
  - Financial projections of the new business that you are going to launch
  - Commercialization strategy
  - Detailed notes for each section should be included in the “notes” section under each slide.
  - Additional exhibits for backup reference should be included in the appendices slides.
- Two-page executive summary (Word document)
Appendices:

Exhibit 1: Introduction to NGS-based diagnostic approach

Sample (blood, sputum, stool)

Total DNA extraction (blood, sputum, stool)

16S rRNA gene sequencing

Abundance of bacterial species

Shotgun sequencing

Abundance of bacterial species, viruses, fungi, antibiotic resistance genes

Exhibit 2: Comparison of current diagnostic methods

<table>
<thead>
<tr>
<th></th>
<th>Culture-based methods</th>
<th>PCR-based methods</th>
<th>NGS-based metagenomic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td>• End up with pure culture of the organism so it can be studied further (eg. to test</td>
<td>• Faster than culture-based methods</td>
<td>• Rapid and accurate</td>
</tr>
<tr>
<td></td>
<td>antibiotic resistances)</td>
<td></td>
<td>• Broad dynamic detection range of pathogens</td>
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<td></td>
<td></td>
<td></td>
<td>• Eliminate contamination</td>
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<td></td>
<td></td>
<td></td>
<td>• Reduce false positives</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>• Slow</td>
<td>• Limited in detection range</td>
<td>• computationally intensive</td>
</tr>
<tr>
<td></td>
<td>• Often fail to detect the cause</td>
<td></td>
<td>• dependent on accuracy of databases</td>
</tr>
<tr>
<td></td>
<td>• Contaminated in 2-6% of cases</td>
<td></td>
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</tbody>
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Culture

PCR

NGS
Exhibit 3: Competition with traditional diagnostic methods

<table>
<thead>
<tr>
<th>ASSAY TYPE</th>
<th>PROVIDERS</th>
<th>Metagenomics Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>• Hospital labs</td>
<td>• Comprehensive pathogen coverage</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

Exhibit 4: Metagenomic vs PCR Pathogen Detection

Exhibit 5: Some financial projection assumptions for reference (taking pneumonia as an example)
- Birth rate: ~4MM births in US/year
- Relevant pediatric incidences: community-acquired pneumonia 497,000/year
- These are underestimates based on recorded reason for hospitalization and not co-morbidities
- All data provided can be challenged or replaced with more applicable sources

Exhibit 6: Some components to be considered for financial projections (you are welcome to develop your own methodology)
- The non-profit entity of NextGENomics has already got the CLIA
- Market size and market share
- Fixed and variable costs of each service:
- Illumina machine at $300k, 100 samples per run, each run costs 12 hours, runs are unsupervised and can go overnight, machine can run non-stop as samples come at random times;
- Research associates/technicians run the operation at $80k compensation each, the technicians work one shift per day only, the two personnel can run up to 3 machines, then purchase a new one; Overhead of 75% per NIH grant requirements; $100 cost per sample; standard medical shipping for samples from hospitals)

- Pricing strategy and revenue

Exhibit 7: Some useful resources for your preparation
- IBISWorld
- BCC Research
- Wikipedia