DIFFUSION OF CLONOSEQ INTO THE CLINIC

6/5/13

Consulting Project for MGMT 522

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Diffusion of ClonoSEQ into the Clinic

CONSULTING PROJECT FOR MGMT 522

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EXECUTIVE SUMMARY

Our objective for this project was to provide guidance on how to get Adaptive's ClonoSEQ diagnostic test into the clinic for minimal residual disease (MRD) detection of Acute Lymphoblastic Leukemia patients. We gathered data from Dr. Kirsch, secondary research, and interviews with doctors and scientists. From our data, we have identified customer segment classes, discovered the process of diffusion to each customer segment, and developed several recommendations to address potential customer concerns.

Customer Segments

We used Moore's technology adoption curve as a framework to describe the potential customers. In addition to a description of each customer segment and their concerns, we provide recommendations on how to encourage each segment to adopt ClonoSEQ. Here are the three main segments:

- Lab researcher scientists – innovators that will help develop your technology
- Cooperative group keep opinion leaders – early adopters and visionaries
- Doctors, clinics, and hospitals – the majority and final target customer

Technology diffusion course

We also describe the course to navigate, so ClonoSEQ can eventually become standard-of-care in the clinic:

1. Publications proving increase sensitivity and specificity
2. Retroactive clinical trials with a large medical center
3. Prospective, phase 3 clinical trials
4. Publish strong clinical correlation
5. Convince each hospital and institution to adopt
6. Insurance reimbursement

Customer concerns and recommends

Finally, we use Roger's five factors as a framework to present customer concerns and our recommendation to improve diffusion. The following is a selection from this section:

- Price must be between $500-700 to be competitive
- Result turnaround must be within 3-4 days
- ClonoSEQ does not provide strong advantage on day 1, so include other prognostic genetic testing along with ClonoSEQ
- Result interpretation must be straight forward
- Give trial offers to scientists and hospitals to encourage adoption
- Target researcher scientists and doctors involved with national cooperative groups

INDUSTRY ANALYSIS

Each year, 350,000 people worldwide are diagnosed with leukemia, the mortality rate of which is over 70% [1a]; within the United States, there are approximately 47,000 new cases annually [1b]. There are four main types of leukemia: Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Chronic Myeloid Leukemia (CML), and Chronic Lymphocytic Leukemia (CLL). When patients present with leukemia symptoms on day 1, physicians extract bone marrow and send it for testing. These patients then undergo appropriate treatment for their cancer, and on day 29 of treatment, physicians conduct another bone marrow extraction for the purpose of minimal residual disease (MRD) detection. The results of the MRD testing influence the remaining course of treatment. The methods for testing MRD are as follows:

Flow Cytometry[2]

Within the United States, Flow Cytometry is commonly used to conduct MRD tests. It is used for diagnosis, and is becoming more standard for pediatric MRD tests for ALL. In these cases, enough studies have been completed to show a correlation with disease prognosis. For most other cancer types, however, Flow Cytometry is not the standard of care and is unlikely to become standardized due to the difficulty of interpreting results (Greisman). Flow cytomery typically costs between $300-500.

Pros:

- Results in 3-4 hours; doctors want results in 24-48 hours ***(Fromm)***
- Tests for multiple parameters such as abnormalities in cells ***(Fromm)***
- Does not require PCR reaction ***(Greisman)***

Cons:

- Dependent on immunophenotype of the patient
- Differences in immunophenotypes make testing more difficult for some patients
- 3-5% of cases require second or third opinions and subjective calls ***(Fromm)***
- Requires intact, viable cells ***(Greisman)***

PCR-Based Tests

PCR-based testing is more commonly used in Europe. These tests analyze specific genetic mutations that are known to cause different types of leukemia.

Pros:

- Direct analysis of the DNA
- High sensitivity to MRD

Cons:

- Can only detect known genetic causes
- Does not analyze an entire DNA sequence

Next-Generation Sequencing

Next-generation sequencing (NGS) technology is a high-throughput method for sequencing all DNA for a specific segment of the genome. Its use for MRD detection of leukemia is an emerging field. Adaptive uses this technology for ClonoSEQ to identify an individual's immune system profile, and other companies such as Sequenta are developing similar methods using NGS to test for MRD. Sequenta did not respond to our requests for an interview.

Pros:

- High sensitivity to MRD
- Improved accuracy
- Ability to analyze full DNA sequence

Cons:

- Reliance on PCR
- Time consuming
- More expensive
- Unproven

Market Conclusion

Although it is unproven, NGS technology may find a place in the MRD market due to its increased accuracy. ClonoSEQ will be primarily displacing Flow Cytometry in the US market; as a result, ClonoSEQ needs to cost approximately $500-700 and return results within three to four days.

CUSTOMER SEGMENTS

Moore's Technology Adoption Curve

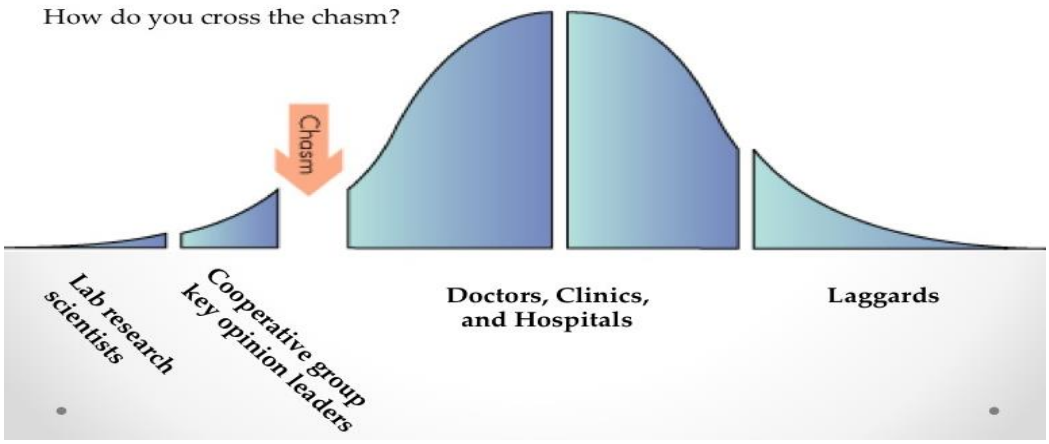

Fig 1

Research Lab Scientists: Innovators

The research lab scientists are the technology enthusiasts that will help hone and debug ClonoSEQ as a new test, and are considered the innovators. This group requires the smallest burden of proof, and is the most likely to help run additional tests, publish papers, and present at conferences. At this stage, the most important consideration is the ability to build momentum in order to catch the eye of national oncology clinical trial groups. These innovators will be a voice of support when approaching clinical trials. Traditionally the faculty in each lab decides as a group whether to adopt the new technology *(Sabath)*.

This group anticipates that both Flow Cytometry and NGS will be used in the future, and that such technologies only rarely replace the current standards. Instead, new tests like ClonoSEQ may be added on as a part of standard-of-care. In time, there may be enough pressure to pick one or the other. However, if the insurance companies will cover both, then physicians are likely to order both *(Fromm)*.

Encouraging Adoption:

- Provide preliminary data showing the technology's effectiveness
- Discuss the technology with researchers in person
- Offer free testing for research studies

Key Players:

- Brent Wood
- David Wu

Cooperative Groups: Early Adopters

Key opinion leaders within cooperative groups are the most likely to be the visionaries and early adopters. They will have many demands and high expectations, and will want to work very closely with Adaptive as ClonoSEQ emerges. Once they are familiar with ClonoSEQ and convinced of the test's effectiveness, cooperative groups will provide access to tissue repositories and implement the technology in clinical trials.

Implementation Process:

STEP ONE: RETROSPECTIVE STUDY: Gain access to sample repositories and perform retrospective analysis. If these studies show a good medical correlation, then biology chairs can advocate for Adaptive within the national cooperative group committees. Access to the Children's Oncology Group's tissue repository can be requested through the biology chairs for the respective cancers: Dr. Mignon Loh, University of California, San Francisco.

STEP TWO: PROSPECTIVE STUDY: Convince clinical trial committees to implement the new technology in phase three clinical trials, either through national cooperative groups or on the institution level with organizations like the Seattle Cancer Care Alliance (SCCA) or MD Anderson. Local groups like the Seattle Children's Hospital, Fred Hutch, and the SCCA may offer an advantage in terms of communication and personal relationships. However, access to a high volume of patients in a single

institution makes MD Anderson and similar organizations the recommended choice for initial trials at this level. Implementing the diagnostic in a research study at such institutions would help to avoid some red tape, build data on human trials, and increase awareness of the test in the leukemia treatment community.

Encouraging Adoption:

- Provide extensive evidence of improved sensitivity and specificity
- Show clinical correlation
- Learn the burden of proof required by the biology chair for each clinical trial
- Work with researchers who are members of cooperative groups

Key Players:

- Dr. Mignon Loh at UCSF – Pediatric ALL clinical trials
- Dr. Soheil Meshinchi at UW – Pediatric AML clinical trials
- Dr. Jerry Radich at SCCA – Adult clinical trials with SWOG
- Dr. Phoenix Ho at FHRCRC
- MD Anderson, Memorial Sloan Kettering, MCI, Johns Hopkins, Stanford

Clinics and Hospitals: Early and Late Majorities

Clinics and hospitals will be considered the majority of customers; cancer care centers are one of the primary targets. They are the institutions most often treating and testing leukemia patients, and as such they would derive the most value from Adaptive's new diagnostic tool. Hospitals and cooperative groups like the SCCA have large pathology departments that perform most of the testing, like Flow Cytometry, in-house.

Implementation Process:

This group requires an extensive amount of evidence from publications, experiments, and clinical trials that demonstrate the technology's sensitivity, specificity, and clinical correlation. Some clinics and hospitals will adopt the new technology faster than others: the physicians at each hospital will examine the results of clinical trials to decide if they want to incorporate ClonoSEQ into their standards of care. The senior and ranking faculty members who are also involved with clinical trials will have the greatest influence, and are a critical factor in determining when an organization will implement changes.

Encouraging Adoption:

- Complete phase three trials
- Publish results in journals like Journal of Pediatric Hematology and Oncology
- Present at conferences like American Society of Hematology
- Establish pricing from $500-700
- Return results within three to four days
- Make results easily interpretable
- Demonstrate that results may change treatment options
- Hire or convert product evangelists for both hospitals and insurance companies

Key Players:

- http://cancercenters.cancer.gov/cancer_centers/index.html

VALUE PROPOSITION

One of the biggest advantages that ClonoSEQ offers over the current standard of care is vastly increased test sensitivity. In comparison to Flow Cytometry, Adaptive's technology can detect resurgence of cancer growth up to months in advance. The extra-sensitive disease detection gives doctors a chance to provide preventative care to patients whose leukemia types allow for it.

When treating leukemias, knowing how a patient is responding to the initial chemotherapy is critical for deciding follow-up treatment, and ClonoSEQ offers the possibility of a less invasive test using blood samples instead of bone marrow. This change would allow doctors to run tests with greater frequency when necessary, and could also cut down on costs by reducing the number of hospital staff that would otherwise be involved in a bone marrow extraction. Blood testing also carries the advantage of eliminating the pain that accompanies marrow extraction, which can be a considerable advantage from the patient's perspective.

ClonoSEQ also offers greater accuracy than Flow Cytometry; at present, fifteen percent of leukemia cases are misdiagnosed [5a], leading to delays in treatment that can negatively impact patient outcomes. Finally, the increased accuracy of ClonoSEQ is compounded by its flexibility. A given sample can be analyzed at different levels of granularity, and it may be possible to look for other genetic markers to increase the breadth of Adaptive's testing. The ability to conduct multiple genetic tests could simplify a hospital's workflow by consolidating services.

KEY PARTNERS AND OPINION LEADERS

- David Wu at Brent Wood's lab
- Dr. Mignon Loh at UCSF – Pediatric ALL clinical trials
- Dr. Soheil Meshinchi at UW – Pediatric AML clinical trials
- Dr. Jerry Radich at SCCA – Adult clinical trials with SWOG
- ECOG cooperative group
- Leukemia Society and similar foundations
- Dako and Genomic Health: companies that successfully launched commercial tests which became standard care

INSURANCE COVERAGE

Generally once Medicaid starts to cover something, the private insurers will follow suit and begin to cover it as well. Research and efficacy are very important to the insurers' determination of coverage. Experts at the Washington State Health Care Authority conveyed their main message as follows: "Show the evidence of the treatment's effectiveness and safety, and cost."

Two programs are recommended to deal with the process of assessing health technology; these serve as a resource for state and federal agencies purchasing healthcare.

Health Technology Assessment Program (HTA), WA State Health Care Authority [6a]

This program convenes an expert panel and reviews health technologies with contracts for scientific reports about whether certain medical devices, procedures, and tests are safe and work as promoted, and "an independent clinical committee of healthcare practitioners then uses the reports to determine if programs should pay for" them. Medical agencies that would look at the HTA's decisions include the Health Care Authority, the Department of Social and Health Services (Medicaid), Labor and Industries, the Department of Corrections, the Department of Veterans' Affairs, and so forth.

Assessment Criteria:

- Safety
- Efficacy
- Cost-Effectiveness

The HTA investigates eight new technologies yearly, with no present plans to increase capacity. New requests are lined up until 2014, and it takes about six to eight months to complete the process for a new technology from key questions to a final decision by the committee. The program is designed to be public, transparent, and open to outside commentary. It is possible for a technology to be approved for insurance coverage before it is proven through clinical trials; the HTA will perform appropriate due diligence to ensure reliability. Later they may review the technology based on the efficacy shown by clinical trials.

Process:

Selection → Key Questions → Evidence Report → Coverage Decision and Meeting

U.S. Preventive Services Task Force (USPSTF) [6b]

"The USPSTF is an independent panel of non-federal experts in prevention… medicine" that "conducts scientific evidence reviews of a broad range of clinical preventive healthcare services such as screening, counseling, and preventive medications, and develops recommendations for primary care clinicians and

health systems." Under the Affordable Care Act, their recommendations must be implemented by all health plans [6c].

Assessment Criteria:

- Effectiveness, based on benefit to harm ratio
- Cost-effectiveness of preventive services is NOT evaluated

"Development of a Recommendation Statement' from a newly nominated topic takes approximately two to three years. In past years, the USPSTF has generally selected one or two new topics per year for evaluation in order to develop a recommendation."

RECOMMENDATION TO IMPROVE DIFFUSION

(Based on the framework of Rogers' Five Factors of Diffusion)

Relative Advantage

- Must demonstrate relative advantage through publications, clinical trials, and medical correlation
- MRD detection from a blood sample provides a great advantage
- Cost needs to be $500-700
- Return results within three to four days

Compatibility

- Doctors, researchers, and labs already have workflows for sending out samples for testing
- Additional bone marrow will not need to be extracted
- Include other prognostic genetic testing along with Adaptive results. If the NGS capture can include known prognostic genetic markers at little additional cost, then customers can save money by ordering a single test.

Complexity

- Convincing doctors of the relative advantage
- Data analysis and results interpretation need to be straightforward

Trialability

- Provide initial testing to research labs for free
- Pay for clinical trials testing, as neither the patients or insurance companies will pay until the test has been sufficiently trialed
- Offer deals to hospitals to gain customers with little risk to them. For example, first fifty samples are free or reduced
- Research grants could make this more affordable

Observability

- Advertise through conferences, presentations, publications, and clinical trials
- Quickly win over key opinion leaders within national cooperative groups
- Provide access to the database of immune-profiles

IMPLEMENTATION RISKS AND PITFALLS

- Which aspects of the technology require FDA or other approval?
- Will clinicians and technicians need to be trained to interpret results?
- Cancers with relatively high survival rates, like ALL, may not be a priority moving forward for researchers constrained by the sequester [3a].
- Clinical trials are a slow process; Sequenta has already performed more than ten clinical trials [4a].
- The cost must be comparable to Flow Cytometry.
- Clinicians are not likely to stop using Flow Cytometry for the initial diagnosis of cancer, because doctors want results in less than 24 hours. In order for ClonoSEQ to be useful for MRD on day 29 and beyond, clinicians will need to order it on day 1 in addition to Flow Cytometry.

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APPENDIX:

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Interview Summaries

A. Dr. Brandon Hadland

Pediatric Oncologist, FHCRC

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Summary:

In order for a technology to make it into the clinic it must:

1. **Be developed and tested in a lab and have publications.** Papers need to show the effectiveness of the diagnostic tool. It needs to build up enough momentum to catch the attention of the National Oncology clinical trial groups.

2. **Be accepted to the large National Oncology Groups that design and run clinical trials.** These groups tend to meet once a year to discuss the scientific progress and decide which technologies they will incorporate into the clinical trial designs. The group members come from institutions across the country (or world) and are leaders in the field. This is the best way to get broad exposure and further testing. This organization is a HUGE keep opinion leader for all the individual institutions.

3. **Perform well in clinical trials and be adopted by the National Oncology Group(s) as best practice and current standard-of-care.** The clinical trials are setup so that patients randomly get assigned to receive the current "standard-of-care" treatments and tests or they receive the new treatments and test. The current "standard-of-care" is determined by the group and is based on previous trials they have done as well as trials that are done by other groups (sometime in other countries). As a new treatment or test is proven in clinical trials, it is adopted as standard practice.

4. **Be accepted by each institution's Oncology groups (e.g. Seattle Children's).** The members of the National Groups also are physicians and researchers at institutions. Each institution is in charge of determining their own "standard-of-care". Each month all the oncologist in the institution meet to discuss the recent advances and decide what changes they want to make to their current roadmap or "standard-of-care". Once they come to a consensus, they all follow the stay roadmap and it is very unlikely that any physician will deviate from this plan. This group isn't as concerned about pricing, because most insurance companies will pick up the tab after it has been proven in a clinical trial and is accepted at common practice. Within each institution, the key opinion leaders are the senior oncologists that are affiliated with the National Oncology Group.

There is one major National children's oncology group because child cancers are far less common than adult cancers. Additionally, child cancer care is a much smaller market, but it is much more centralized at major hospitals across the country. Adult cancer treatment is done at many small and large clinics and there is several adult oncology clinical trial groups.

The NGS MRD diagnostic tool will not be used for initial diagnostic of whether a patient has Leukemia or not. Nor will it be used to distinguish between ALL and AML. These test results are needed quickly and

are often done within a day so treatment can begin immediately. However, NGS MRD tools can be used to investigate the cancer profile, and maybe investigate specific genomic polymorphisms or alterations. If NGS could also target the known prognostic genetic markers while provided the immune profile, it will be able to do a current test while provided additional benefits. This may be able to provide enough incentive to get these groups to switch or at least try it out. 50% of ALL/AML patients have known disease profiles that they test for in house using probes, stains, and PCR. The NGS MRD could do all of these, then it would be of increased value. Additionally, if the new technology can provide better resolution on these profiles or identify new profiles, then it will have a strong advantage.

Part of the NGS MRD diagnostic tool's value proposition is in detecting lower levels of MRD than Flow Cytometry. Currently, flow can detect residual cancer cells at 0.01%, and doctors generally feel like that is sufficient. They feel that patients below 0.01% have such a low chance that the cancer will return, that they group them all together. However, they isn't enough data to prove that segmenting the >0.01% group can't provide further resolution. If you can show that there is a segmentation of this group with respect to disease risk, then you will have a strong argument to make this standard-of-care.

As for the length of time for return of results, 4-7 days is adequate.

B. Jonathan Fromm

Brent Wood's UW clinical lab

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What is the current use of flow for MRD in your lab?

45 flow cases a day

Amount of MRD testing has expanded and diagnostic tests (presentation testing) have decreased because of economics and medical students can do the diagnostics. However, Brent is expert so samples from all over the country.

Day 29 look at AML for MRD. Normal morphological pattern of cells.

What other tests are done?

Hematologics is a clinical commercial lab in the area and Michael Lokken.

You can do immonuhistochemistry… for diagnosing

Does the pattern of maturation differ enough from normal and if you know what it looks like at presentation = MRD technique. Doing this up front helps at day 29 detection.

Even when in remission patients who are into long term follow-up and get tested about once a year. Hemotologists are the ones that order future test. In general the returning profiles match very closely. B-ALL does seem to change when treated with prednisone.

David Wu – there is a paper that David Wu was the first author on and is spending more of his time looking at molecular MRD testing.

Drawbacks with flow – it is sensitive but it is dependent on immonophenotype of the patient. You can detect readily 1 cell in 100,000 and they collect 1 million cells and want to see a cluster of 10 cells. Problem is that cetein immonu phenotypes are not that different than normal. Most are different, but not all are. To get around this you can look for new informative markers. Phenotypes are not all stable. If there is a change is it the same disease? New disease? There are some changes that are associated with therapy.

Everyday there are 3-5% of cases that are really hard and you need to get a second or third opinion.

PCR based testing is very common in AML to stratify patients by prognosis.

There is currently an orderable test for solid tumors: oncoplex. Takes 8 weeks to be recorded. A test you can order on a patient today looking at about 100 genes. David does the onco plex routinely. Colin Pritchard (UW) does this as well. Problem with oncoplex is that it has included oncogenes that do

not have literature support: what do you do with it? They quite often have to do individual literature searchers.

What additional information do you get from flow?

Flow can be used for diagnosis. The tubes they use for flow on MRD is different than presentation tubes. If don't have targets in the tube for NGS you will miss any changes. There is much more general information with flow. Example: Flow has CD45 one looks at the antigen and the side light scatter and look where they fall out in the plot and they can see where the different cell types fall out in this plot. If you notice that in the blast region the cluster is too big but isn't expressing markers expected for that region.

NGS is not competitive now compared to flow. Basic flow assay is between $300-500 and NGS $1000-1500. Another huge issue for NGS is time. At day 29, Doctors will want to know in 24-36 hours to know who to repeat. 4 days is still too long.

Cells are incredible aneuploidy and as a result will be unpredictable. He anticipates that both flow and NGS will be used. Technologies are added on and not replace. There may be enough pressure to pick one or the other. If the insurance companies will cover both then physicians will order both, no doubt.

They will run 3 flow tubes at once because each tube will have 10 antigen. Due to overlap, 22 different antigens across the three tubes. AML is probably about $500.

C. Harvey Greisman

Brent Wood's UW clinical lab

e-mail: greisman@uw.edu

What are you concerns about sending samples to Adaptive for MRD testing?

Would be willing to send to Adaptive for testing if it is affordable and time efficient. Concern that it will not be optimal and need years of work and may be suboptimal for specific needs.

Information on flow, both good and bad

Flow is most useful in hemaplastic cells

Agwus and add antibodies that will detect cell linages. Then shine

Advantage is the number of cells that you can put through the machine(max of a million or a few million cells)

Sample bone marrow and blood

Requires intact viable cells.

Flow doesn't require PCR amplification

Flow is not standard everywhere. It is slowly getting out into the rest of the world.

Most places will not use flow for MRD at a low level. They will use it for diagnosis, but not MRD.

Flow is can be done in less than 24 hours.

Has Flow become standard of care? Why or why not?

One type of cancers where it is becoming standard is pediatric Acute lymphoblastic lucemia (ALL) because it will affect prognosis.

For most other cancers it is not standard of care. Not enough studies done yet. AML (mioloid) is more challenging because it is not straight forward and requires a experts and even then they have to check each other.

Standards flow are not there yet to be standardize and probably won't be make standardization.

How can NGS become standardized?

- Standardization:
- Ease of adoption: turnaround time, cost, and utility and would have to meet criteria for your test and answering the question. Fear of having to buy equipment. Need follow-up time to validate. Probably not an issue for amount of samples. The lab would have to prove that their product works. Would FDA get involved and regulate it? Who is going to regulate it?
- Turn around time: Clinical trial will change treatment based on tests. Minimum turnaround would need to be 1-2 week for MRD, maybe. 1 week clinical trials, and ASAP for doctors
- Cost: $500. Insurance pays for it. NGS will need to get down to $500 or so. Problem may be that the technology is geared at way too much which will require lots of samples at once to make it economically feasible.
- Clinical sensitivity and specificity: Flow has to be cells that can be circulated. NGS can ne used on almost anything. If antigen behave normally you will miss it with flow. How do you know what the spectrum looks like for each cancer? Not every cancer will have a mutation in that region. Mutation spectrum will change. Great challenge for NGS compared to flow: flow tells you more about the cell that is affected, there are residual cells and DNA after cancer is dead that will cause false positive with NGS. You have to prove that if patient does have DNA that the patient actually will have the cancer return.

What is a disadvantage of NGS for MRD?

Amplification with PCR targeted at specific mutations

D. Christine Masters

Program Specialist
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WA State Health Care Authority
Health Technology Assessment Program (HTA)

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The Washington State Health Technology Assessment (HTA) Program (http://www.hta.hca.wa.gov/) - This program convenes an expert panel and they review health technologies. The approval of the safety and efficacy of the technologies lead to insurance coverage for state insurance plans through the Health Care Authority, Medicaid, Labor and Industries, the Department of Corrections and the Department of Veterans Affairs.

Purpose
The primary purpose of HTA is to ensure medical treatments and services paid for with state health care dollars are safe and proven to work. HTA serves as a resource for state agencies purchasing health care. HTA contracts for scientific, evidence-based reports about whether certain medical devices, procedures, and tests are safe and work as promoted. An independent clinical committee of health care practitioners then uses the reports to determine if programs should pay for the medical device, procedure, or test.

HTA does 8 topics per year, no plan to increase capacity at current stage; new requests line up to 2014. The process is designed to be public (open to public comments) and transparent (how one topic is picked).

Due to the fact that the assessment of a new technology will be based on evidence in clinical studies, new technology doesn't have to be assessed before coverage.

There are multiple ways to request for review. Medical directors from agencies (Health Care Authority; Department of Social and Health Services (Medicaid); Labor and Industries; Department of Corrections etc.) would look at the utilization trends (they discuss on a regular basis), instead of the technology itself, to decide which topics to do research.
Or contact the Administrator (Director of the Health Care Authority) and request.

It takes about 6 to 8 months for one topic to complete (from the drafting of key questions to final decision/voting by the committee).

3 main criteria: safety, efficacy/efficiency, cost-effectiveness
- all parties (medical directors from agencies, 3rd party research companies (external/independent organizations), committee members, (as well as the public) would involve;
- 3rd party research companies would focus on online research medical databases(random control trials, case studies, registry or peer-review--if available/less likely), key words, dates, study has been completed
- HTA look at whether the results are than current technology; how much is being paid, how many bad effects/reoperations; for new technology that has not set a price, HTA would get some ideas/data of costs, and do the best as they can.

There are similar programs, but don't have mandates to follow as HTA does. Not all agencies would adopt HTA's decisions and offer coverage, they have leeway to decide (like Department of Veterans Affairs).

WA HTA share information or studies/cooperate with some of other similar programs (Oregon), but would still fulfill the review process before making a decision.

E. Soheil Meschinchi

Co-director of the COG Myeloid Resource Laboratory, chairman of the COG Myeloid Disease Biology Committee, Vice chair of the COG Myeloid Disease committee and the Biology chair and vice chair of the COG acute myeloid leukemia (AML) phase III trial

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How can the NGS MRD be adopted?

Demonstrate it is better

1. Sensitivity – what can it detect
2. Specificity – being able to reliable to pick up variants. Making show their isn't a technical glitch that will be picking up false things.
3. Clinical correlation – identifying the variant and showing that the presence of MRD is clinically significant. Can you do it time efficiently and cost efficiently? If you get the same data as flow, then they will go with whichever is easier.

Pros/cons?

Flow is 1/10000.

PCR is deeper

NGS how is the specificity and how reliable is the variant.

NGS can Look at multiple targets

Lets say we have a technology and we want to start testing it, what do we do next?

Next step would be two create a CLIA approved lab and test. Is it general enough to use on a phase three type trial. Need to incorporate it into a trial. Needs to have some data that there is a clinical correlation. After one course of therapy and then do NGS assay, and find the clinical implication based on the assay results.

How do you get into a phase three clinical trial?

To get into phase three. You can do this at the local level. SCCA may have a ALL trial running then you need to discuss with them showing data and offer the test to be used if there is a clinical trial at the local setting. You can approach a national organization to do that. Until you do an assay in a retrospective trial and you show clinical correlation. Then you take it to a prospective phase three clinical trial. Adaptive will

pay the bill for retrospective. It may be picked up by insurance companies for phase 3 or some other commercial sponsorship.

Who can I contact specifically?

For ALL, you need to talk to Children's Oncology group committee and say I have an assay that I want to test on your tissue samples. There is a biology chair at the COG for each disease. Send a package with statistical limits and all other evidence to support the need for retrospective clinical trial

ALL – Dr. Mignon Loh at UCSF

AML – Soheil Meshinchi

4 cooperative groups in adults

SWOG – Dr. Jerry Radich –is biology chair of AML and maybe ALL

ECOG –

MD Anderson has a huge number of samples that go through and it may be easier to do it their because it is only one institution and they have a lot patients. You can pay them.

After clinical trials, how will this new technology be adopted by the hospitals?

There is a standard of care committee that will adopt a technology and this will make it be pretty uniformly adopted across the nation. Some places will hold out, but most will change. The standard of care committee is made up of prominent leaders from major institutions from across the country.

F. Daniel Sabath

Brent Wood's UW clinical lab

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1. Other than Flow Cytometry, what other tests are performed on bone marrow samples?

Microscopic examination, immunohistochemistry if needed, molecular testing depending on the patient's disease.

2. Who takes care of sending out any samples for external (off site) assays?

We have staff responsible for send-outs.

3. Are all of these tests incorporated into the hospital information systems with shipping data included?

Results certainly are. Not sure about shipping data.

4. What burden of evidence would be required to convince you to switch from Flow Cytometry for MRD detection to a new molecular based technology (e.g. next-generation sequencing)?

Better cheaper faster.

5. Within your lab, if you were going to make a change from flow to NGS, who would be responsible for making that decision? In other words, who has the final say?

The faculty (or a subset of them) would probably decide as a group.

G. Ann Breen

Head of Patient Education at the Seattle Cancer Care Alliance

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Key Takeaways:

- The SCCA and likely the whole industry is very data driven. Questions include where was it tested, what lab, with whom, which researchers/doctors were involved, how many patients? Must have scholarly papers, peer review articles written, and be at conferences.
    - Part of the process: have a study to make ppl aware of a new process, introduce it to a leader in the leukemia world, then they have to demand it at the institution.
- Patients are not involved in the decision making process of which tests are conducted/diagnostic tools used.
- Effectiveness and usefulness of tests may vary significantly with different types of leukemia.
- SCCA does its own testing, it has a huge pathology department, which conducts its own Flow Cytometry.
- There is very high value added by being able to test blood. Not only because of saving customers pain, but there are obviously limits to how often bone marrow aspirates can be taken (day 29,50, 80 after a transplant).
- Adaptive can get a small level of implementation by getting SCCA/clinics to implement it as a research study (apparently Adaptive would pay for this, but this would help gain momentum and prestige/confirmation depending on who they can get involved).
- Current state of minimal residual disease detection:
    - When you look at someone's peripheral blood, already took at immature cells, look at left shift, if there's a left shift, there's already a worry than leukemia is coming back.
    - Can already see immature cells in peripheral blood.
- Reimbursement: Insurance coverage is extremely important (obviously)
    - "all insurance takes longer than you think", depends on how efficient they are with billing.
    - Have to show the efficacy of the test to show that it's better and actually helps. Just to say you found a disease a month earlier, would have to have data you helped ppl.
    - Insurance needs to see that it's approved (shown to be effective) and standard practice, insist on seeing data or else they don't cover it. Need data of clinical trials that show effectiveness.
- Potential customers: http://cancercenters.cancer.gov/cancer_centers/cancer-centers-list.html
- People to talk to:
    - Can try Howard Shulman – retired pathologist from SCCA
    - People from the College of American Pathologists (CAP)
    - Pathologists/lab people, can look up individuals on SCCA site

H. Mr. James

I only had 5 minute discussion with Mr. James at Seattle Children hospital [which is part of The Children's Oncology Group].

He told me that various research is going on Next Generation Sequencing and not only for Leukemia but in many different field. He told me that, the early detection of the Leukemia would be very useful for doctors to start therapy early on the patient. He asked that how are we going to prove significance of this technology through the clinical trials. As, I have describe the 2 month early detection example he said, this technology could really pick up if you have enough evidence support with the clinical trials. Also, quantity matters so you would be needing more than thousands of human subjects to test your result. Also, this takes time minimum of year or more. Usually during the clinical trials they try to cover every possibility of the condition in patients and with sometimes random healthy patients. Accuracy is very important; he did ask me about what is the chance of failure in early detection of leukemia. According to current usage, Flow Cytometry is very able method and is being used by so many years and doesn't have any critical pitfalls also it is faster than NGS. He believes that faster we get is the better but 4 days may be acceptable in most of the cases. But if they can reduce the time, it would be one of the positive benefits.

Details for the Flow Cytometry with reference links

I have attached two document one have all the details about the Flow Cytometry, specimen requirements, average time of result is approx. 24 hrs to 2 days.

Ref#1 University of Florida http://pathlabs.ufl.edu/tests/flow-cytometry-on-aspirate-with-or-without-bone-marrow-biopsy

Ref#2 University of Arkansas for Medical Science http://www.uams.edu/clinlab/flow.htm

This link includes timings of several tests performed on the Bone Marrow, details and average time, also specimen rejection criteria, and details related different type of diagnostic of different type of Leukemia.

I. Dr. Roopa De Chowdhury

M.D.

Maryland Oncology Hematology

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Key Takeaways:

- Flow Cytometry is pretty standard
- It is useful for a lot of things aside from detecting Leukemia. Does the NGS MRD technology cover those as well?
- To be worthy (or be accepted by the insurance companies), following need to be shown:
    - Study and publications in Journals like JPO – *compare* the two technologies.
    - Lab Tests (**LabCorps**) and research – getting/ building consensus from key people in universities, prominent researchers, etc.
    - Certifications and Approvals – FDA, CLIA, NIH, etc.
    - Blind randomized clinical trials in large numbers - Use the Phase 3 tests to generate a database for validity.
    - Just the organization's word that the technology is effective and useful won't be of any value.
- Flow Cytometry also does stuff with Bone Marrow and Blood. Companies with NGS MRD need to specify very explicitly what exactly is it that they are able to detect by blood alone which Flow Cytometry can't do with the same accuracy.
- Neither the people nor the insurance companies are going to pay till the the NGS MRD gains traction in terms of it being a significant tool and providing a value that Flow Cytometry doesn't.
- Also, need to consider this : Flow Cytometry is like a big canvass painting from which you intend to remove a small piece and replace that piece by the NGS based one. The question is how well will the NGS MRD fit in with the rest of the picture. This is because Flow does a lot of other stuff as well and will still exist even if NGS MRD comes into the market as the latter will only provide a subset of the functionality that Flow Cytometry provides.
- The advantage of NGS in terms of *early detection* is of **no value** if this is to be used on the patients for the first time – i.e. when the patient hasn't been diagnosed and treated before. These tests are expensive and are normally not ordered based on 'suspicion'. There needs to be something clinical (symptoms) and lab related (abnormal results) for the doctor to order these type of tests.
  In a nutshell, this technology is of *additional* value *only* under the condition of checking the resurgence of leukemia after the treatment.

J. Dr. Hitomi Momose

MD MBA

Pathologist, VP at Mission Pathology Med Assoc, Inc

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This was a telephonic interview which we conducted in the later phase of our project.

Key Takeaways:

- NGS MRD technology is based on detecting molecular changes. The problem with early detection could be that even if the disease is there, it will still be too premature to start a treatment. (Drugs and other standardized treatments are administered when the disease reaches a certain level.)

- He Treatment isn't administered unless the disease is sufficiently manifested. NGS MRD shows molecular mutation, but the patient may not be 'sick' yet and doesn't show the symptoms. (Most of the drugs are targeted to remove the symptoms – depends upon the age of the patient whether the goal is to reduce the symptoms or directly attack the disease)

- Should talk to pharmaceutical companies and find those drugs that exist to slow down the cancer at molecular level. Focusing on those types of cancer and doing NGS MRD would be more useful because there is something significant that can be done after that.

- Here are some of the specific questions that were asked in the interview:

- **What is the process for a new diagnostic tool to go from a research lab to become standard of care in a hospital?**
  FDA approval- show clinical claims, lab tests of early detection – lots of data, money and time required > NCCN (guidelines)>

- **Is the process "Research lab development -> convince clinical trial organization that it is useful -> run a clinical trial -> show great results -> the physicians are each hospital look at the clinical trial results and decide if they want it to be standard practice"?**
- Yes

- **Who has the greatest influencing on the decision to start using a new test? How do they make this decision?**
  Regulatory people-CMS, FDA- doctors can't do much- their job is to utilize things that are already there and proven.

- **Do you know anyone who is involved with clinical trials?**
  Yes, research coordinator, few physicians in Institutional Review Board (IRB).

- Dako, Genomic Health- successfully launched diagnostic commercial test to standard care.
- Chief investigator within clinical trial, MD, Professors at University ,or/and board of directors/ shareholders/stockholders of the company (big companies- who want to bring new technologies to the market). If there is any chance of killing people, the investors say no and the money is gone.
- Leukemia society, Foundations interested in diagnosis and treatment (go hand in hand). They are passionate about such causes
-
- **What pitfalls do you see with the transition to molecular base MRD detection, particularly using Next-generation sequencing?**
- Cost, and lack of properly trained technicians, absence of specific treatment, drug companies have to come up with a drug to treat cancer in very early stages of resurgence.

- **What are the drawbacks of using flow cytometery?** None.

- **Note:** Adults - need insurance approval
  Kids – more compassionate, MediCal or somebody else will pay. Will help in building PR as well if started with pediatrics or given adequate focus in their beginning period.

K. Amelia Vader

2nd year MPA student at the Evans School of Public Affairs, UW

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She claims that under the Affordable Care Act, USPSTF recommendations must be implemented by all health plans. She pointed us to:

"The Patient Protection and Affordable Care Act (PPACA) is aimed at expanding access to health care and lowering cost barriers to seeking and receiving care, particularly high-value preventive care. The legislation requires Medicare and all qualified commercial health plans (except grandfathered individual and employer-sponsored plans) to cover routine preventive services graded A and B by the U.S. Preventive Services Task Force (USPSTF) at no cost to the consumer, along with recommended immunizations and additional preventive care and screenings for women (*1*). "

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6039a3.htm

L. Lean Canvas Model

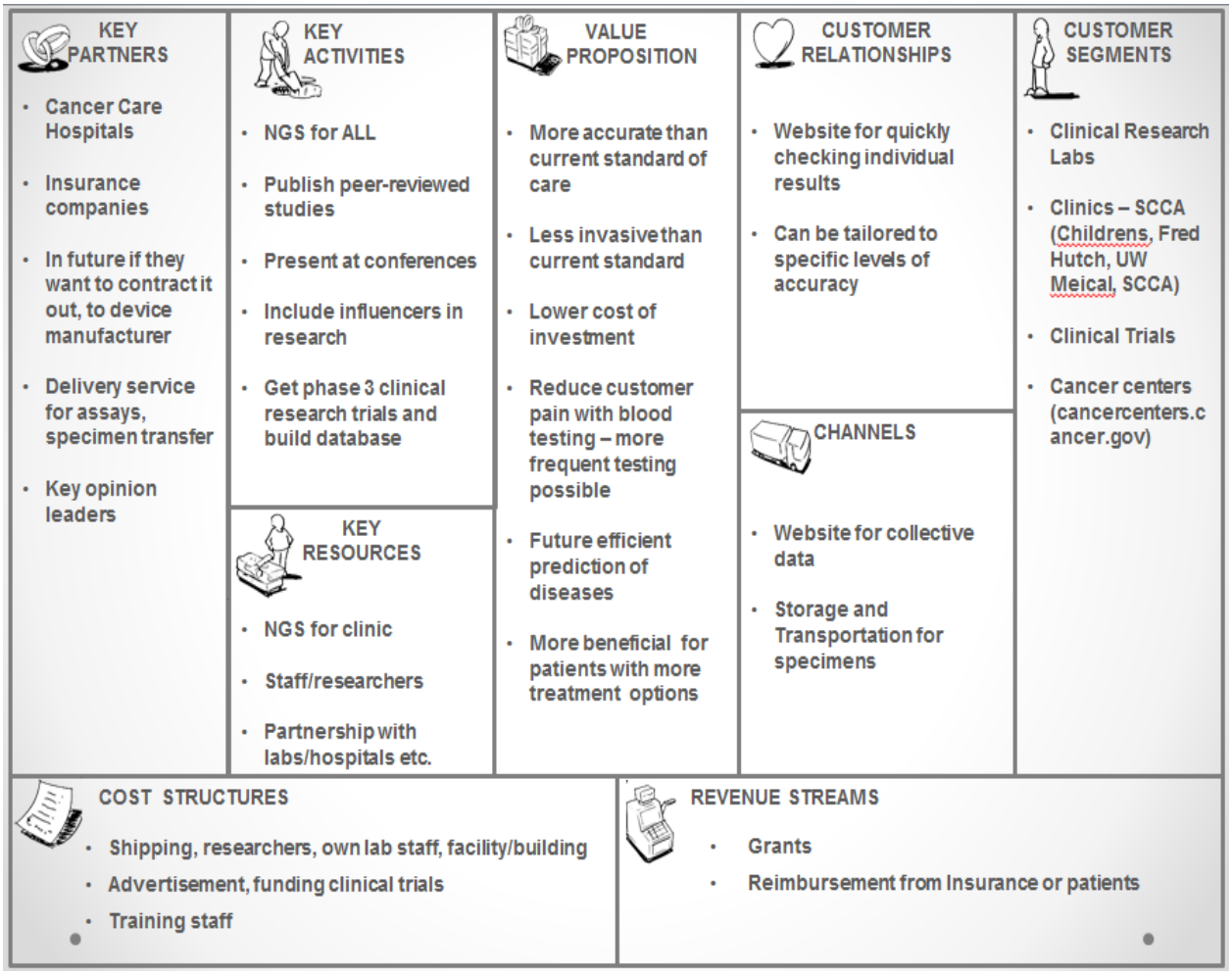

Fig 2