Title: Technology Transfer at the Berkeley Lab

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Abstract

The Berkeley Lab is located in the hills above the University of California's Berkeley campus and is the oldest of the U.S. Department of Energy's National Laboratories. The lab is managed by the University of California.
The Berkeley cholesterol test is a relatively new comprehensive test that has helped make state of the art cholesterol risk testing publicly available [1]. The test, made available by Ernest Orlando Lawrence Berkeley National Laboratory in agreement with the private company Berkeley Heart Lab, is designed to help many detect heart disease earlier than normal [2].
Cardiovascular disease, which accounts for 35 to 40 percent of all deaths in the United States, is the leading cause of death in the country [3]. The Berkeley cholesterol test is designed to identify and detect a number of new traits and abnormalities that are known to be associated with high-risk of heart disease. The objective is to identify risk factors at an earlier stage and assist physicians to better decide which therapy is best suited for individual patients [3].
The basic cholesterol tests (blood lipoprotein analysis) which most people receive consists of total cholesterol, low-density lipoprotein cholesterol (LDL or bad cholesterol), high-density lipoprotein cholesterol (HDL or good cholesterol), and triglycerides levels. The Berkeley test consists of these basics plus a number of additional tests to give a greater overall picture of an individual's cholesterol levels. Among the additional tests included with Berkeley are LDL particle size, HDL sub classification, Apo lipoprotein A-1, Apo lipoprotein E, and Apo lipoprotein B-100 [4]. Berkeley lab researchers hope over the long term to also build a comprehensive database of families and individuals with shared traits which may then be used to define genetic markers of heart disease risk.

Berkeley lab has a list of technologies that already licensed and some technologies seeking for commercialization. 80% of the individuals suffering from Coronary Artery Disease (CAD) have normal cholesterol levels, 50% of the 1.5 Million heart attacks in the US each year strike people without symptoms who also have normal levels of cholesterol. Berkeley Laboratories have discovered a new method to identify individuals who may not have any idea they are at risk [5], [6].
The mechanisms for technology transfer, as identified in this section, are to facilitate the support of measuring in minutes all classes and subclasses of cholesterol-transporting lipoprotein simultaneously. The purpose of the proposed mechanisms is to develop meaningful and effective actions to enhance the implementation of technology transfer in this research by increasing the transfer of and access to environmentally sound technologies.

In Basic terms there are five main types of lipoproteins: HDL, LDL, IDL, VLDL, and Chylomicrons [7]. The bloodstream is water based, therefore cholesterol is a way of transporting lipids and triglycerides or fats to the organs. These lipids include enzymes, vitamins, etc. Lipids are needed for chemical reactions; provide fuel and energy-storage to the cells. Lipids are needed for all living organisms in order to promote life itself. High Density Lipoprotein (HDL) better known as good cholesterol. These particles are able to remove cholesterol from within artery Atheroma and transport it back to the liver

for re-utilization. Individuals with [8] higher levels of HDL have fewer problems with cardiovascular disease. In healthy individuals about 30%of blood cholesterol is carried by HDL. While higher HDL levels correlate to cardiovascular health, no incremental HDL increase has proven to increase health [8].

Low Density Lipoprotein (LDL) better known as bad cholesterol because studies have shown higher levels of LDL particles promote health problems and cardiovascular disease. LDL is essential in muscle building. LDL produces Vitamin D in conjunction with sun exposure and LDL is essential in conducting nervous impulses [9].

Intermediate Density Lipoprotein (IDL) are formed when LDL is degraded. Like LDL can promote the growth of atheroma, which is an accumulation and swelling of arteries walls, caused by lipids, calcium, and fibrous connective tissue [9]. Very Low Density Lipoprotein (VLDL) it's a lipoprotein made by the liver. Chylomicrons are "large" lipoproteins particles which transport dietary lipids from the intestines to other locations in the body [10].

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INTRODUCTION

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Measuring Cholesterol (Background Research)

There are two main ways of measuring Cholesterol levels: Direct and Indirect. Indirect Cholesterol measurements involved calculations of LDL. First total cholesterol is measured, then HDL and triglycerides are subtracted, from that calculation LDL levels are estimated [10]. This process is not very accurate and is relatively inexpensive.

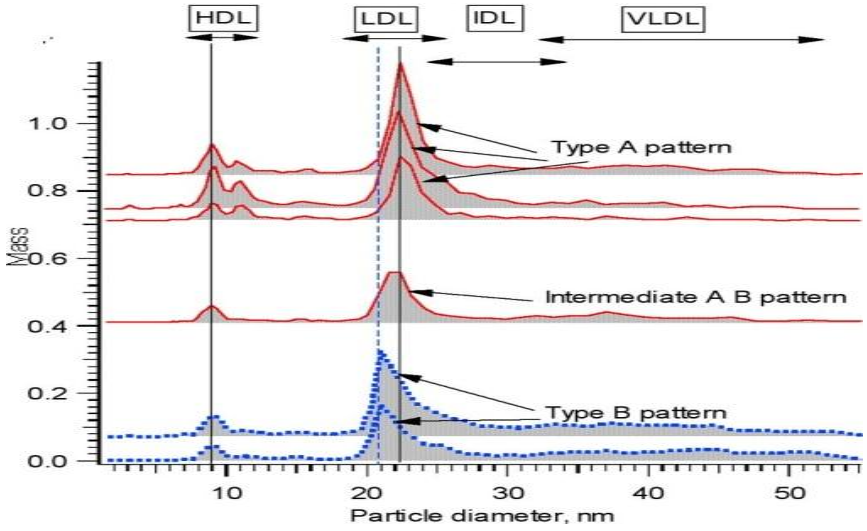
Direct Cholesterol measurement involves an Electrophoretic method where blood is passed through an electric field and particles are separated by its physical size/charge [11]. This process is time consuming and accurate but very expensive, costing around 5K/person

New Method for Measuring Cholesterol Levels Developed at Berkeley Labs:

Berkeley Lab Researchers Henry Benner, Ron Krauss and Patricia Blanche developed a rapid direct method of lipoprotein assessment. Aerodynamic Electrical Mobility Measurements: Ion Mobility Analysis The procedure can measure in minutes all classes and subclasses of cholesterol-transporting lipoprotein simultaneously.

The technology is based on measuring drift of charged particles as they are dragged through air by the force of an electric field, and then determining particle size from drift velocity. The method is the first technology capable of measuring all size distributions and counts of individual particles in all lipoproteins Berkeley Lab's goal is to conduct the cutting-edge research that will allow the U. S. to continue to be a world leader in providing transformational solutions for research and technology transfer.

Results of Classical vs. Ion Mobility Analysis:



Lipoprotein heterogeneity has been recognized as a clinically important cardiometabolic issue for over 50 years. A growing body of published, peer-reviewed data indicates that the presence of predominantly small dense LDL subclass particles identifies a group of individuals, frequently genetically determined, with significantly increased risk for CVD and CVD events. This important risk metric is often independent of standard cardiovascular risk factors such as total cholesterol, LDL-C, HDL-C and TG [14], [15].

Berkeley's R & D Group continues to evaluate and advance technological improvements in the proprietary S-GGE platform to improve resolution, improve manufacturing processes and make the technology more scalable [15]. Very important advances have been made. Specific improvements include developing and customizing a segmented gradient gel casting process, converting to a more stoichiometric fluorescent lipophilic staining methodology, and building a proprietary next-generation gel analysis software [15].

Berkeley's research has amplified the gel process and addressed the challenges of manufacturing highly reproducible custom segmented gradient gels. In collaboration with chemical engineers, mechanical engineers, and fluidics experts, the gel casting process has evolved by re-engineering casting chambers, pumping systems, catalytic mixing chambers, and non-reactive tubing [15]. Additional GMP-like quality control and assurance systems have been incorporated to ensure a consistent product [16]. Lab manufacturing presently produces ~750 LDL and HDL segmented gradient gels per week with significant capacity for further expansion. The process has also been stabilized to allow effective and safe remote delivery of the gels, while maintaining consistent quality [16].

Analyzing the Technology Transfer Process used by LBNL

Many studies have been performed to measure the effectiveness of technology transfer process and infer which methodology is best suited for each technology area. According to Austin Spivey[20], Coordinating the Technology Transfer and Transition of Information Technology, there are seven main steps or stages in the transfer of technology. 1. Disclosing the Technology; 2. Linking the technology with needs; 3. Assessing the Technology; 4.Matching the technology with functional needs; 5.Refining the technology for

specific needs, 6. Preparing to launch into the user's world, and 7. Managing the technology over its life cycle.

After analyzing the process used by the researchers at Lawrence Berkeley National Labs, they indeed follow a similar path. They found a need in the medical community, worked on a solution, disclosed the technology, patented it for protection purposes, showed the technology to potential customers, signed agreements, helped in the technology transfer process from lab to industry, and provide technical support to the customers. At the end, they continued to provide support on technology issues found during the implementation period, assuring a successful product into the market place.

To increase the value of the relationship, and of the technology itself, LBNL researchers continuously work on product improvements and manufacturing yields improvements as well. LBNL provide their customers with competitive and up to date products in order to give them a market advantage over the competition.

We will use the Austin Spivey methodology to describe the stages LBNL researchers used to bring to market the successful invention of a new technology for accurately measuring LDL and HDL cholesterol levels.

1. Disclosing the Technology

Berkeley Laboratory researchers discovered a novel and vastly superior way of measuring cholesterol to better determine coronary risks of individuals. The classical way of measuring cholesterol in the blood was a time consuming and expensive medical procedure. These accurate tests were performed by very select labs in the country and the cost was around five thousand per test. To make matters worse, the test took days to complete and there was a long wait list of samples waiting to be processed. There were less expensive methods but they did not have the precision or quality needed to correctly identify people at risk of coronary disease. These methods typically were based on estimates of LDL, better known as bad cholesterol, and did not provide an accurate measurement of LDL's pervasiveness. To make things worse, there are many sub-levels of LDL's and each of them is associated with coronary heart disease, these estimates could not account for sub-types of LDL cholesterol, and the error margin was large.

The new methodology developed by the Lawrence Berkeley National Laboratory researchers was able to use technology which produced accurate and complete results in minutes. At the same time, the results obtained from the new technique matched the results of the older, more time consuming, and more expensive technology. The researchers quickly understood the value of this new technology to people with coronary disease. It could save lives, and at the same time, lower the costs of existing blood tests.

These new techniques were disclosed to some select group of medical laboratories and two of them showed great interest Berkeley HeartLab and Quest Diagnostics. LBNL worked closely with these two potential partners in order to assure a good understanding of the value of the technology. At the same time, show the competitive market advantage of using this new technology, over existing technology, which could provide a good financial reward as well.

The usage of the new technique developed to measure cholesterol levels could indeed provide financial rewards as well as a competitive advantage over existing technologies. These factors made the new technology very appealing to all potential customers.

2. Linking the Technology with needs

Dr. Ronald Krauss began researching cholesterol fractions and cardiovascular risks in 1978. From the very beginning he was aware of the multiple sub-classes of LDL's cholesterol, and the difficulty in providing an accurate, rapid, and inexpensive test in order to quantify the amount of these substances in the bloodstream. Dr. Krauss realized that developing a rapid and accurate solution would be a "lifesaving" enterprise. He also realized the value of the solution to more than 1.5 million Americans who are susceptible to coronary disease and are not aware of those risks because they do not show any symptoms.

Common cholesterol tests, which measure total cholesterol and then subtract HDL from the total, can only estimate the amount of LDL cholesterol in the bloodstream. To make matters worse, there are many sub-types of LDL cholesterol. Therefore being able to correctly characterize the amounts of cholesterol in an individual is an urgent medical need. It would be a very valuable tool for doctors and patients who are fighting coronary heart disease.

Besides the medical need of a test to save lives, the laboratory who can make those tests readily available to the public could get a large revenue stream, because the medical community would be more inclined to test all its patients and if the test was accurate, rapid, and inexpensive it would be very desirable indeed.

This new invention could create a whole new technology enterprise between hospitals, patients, and laboratories. Each group would gain financial rewards and a potential competitive advantage. This new development would benefit mankind in general and improve the health of all individual, and would lower medical expenses for individuals, insurance companies, and hospitals.

Everyone involved in the medical field would gain from this new invention. Doctors would be more inclined to send their patients to be tested, because of the speed and accuracy; Insurance companies would demand these tests, because it could easily prevent many expensive procedures after a heart attack occurs, and hospitals would could reduce the number of patients, because many preventive measures could be implemented, if enough early signs are discovered before the patient showed serious health problems.

3. Assessing the Technology,

Dr. Ronald Krauss began his work on a new cholesterol test in 1978, together with Henry Benner; and Patricia Blanch began the laborious task of developing a new methodology to accurately and rapidly measure cholesterol levels in the bloodstream.

The main challenges facing researchers and existing technology were the different subtypes of cholesterol.

It was very difficult to separate and label the subtypes, because they fell into a spectrum of densities and varied from individual to individuals. A given cholesterol levels for individual A could be harmless, however when individual B had the same cholesterol value it was harmful. The nature of these discrepancies were not very well understood.

There were multiple false starts, and perseverance paid off. In 1999, twenty one years later, Dr. Krauss was issued a patent for his work on cholesterol sub-classes. He developed LDL-S3GGE and HDL-S3GGE tests, which provided an accurate, rapid, and inexpensive test to measure LDL and HDL cholesterol levels in the bloodstream of an individual. These tests were able to discriminate and map all types and sub-types of cholesterol. The results matched the best results obtained by a more time consuming more expensive test available in the market

After obtaining the Patent, Dr. Krauss contacted multiple medical laboratories to assess the willingness of those laboratories to bring to market the new invention. Two laboratories were especially interested HeartLab and Quest diagnostics.

Dr. Krauss and his medical team, work closely with these two enterprises to facilitate access to the new technology. The potential partners ran independent studies to verify and validate the potential advantages of this new technique, and its potential financial rewards. The LBNL team continued to work with these two institutions on all the technical aspects of the transfer to make sure the technology could be used in a commercial setting, and bring to market a successful product.

4. Matching the Technology with functional needs

There are 1.5 million heart attacks in the US each year and 50% of those individual strike people without symptoms. These individuals also have normal cholesterol levels.[21]

The medical community needs to find a better test to discriminate those individual with high risk of heart attack, and those with lower risk, The costs to perform a heart attack surgery are very large, both in terms of financial costs to the patient, the insurance companies, or the hospital. At the same time, the patient, after receiving a heart operation, oftentimes suffers a lower quality of life. The individual must take time off, from normal activities, and often time it takes a long time, for the patient to regain its normal functionality.

Therefore, there is a need for a better more accurate test which could simplify testing for coronary risk on individuals. A better test would Increase life expectancy, quality of life for individuals and loved ones. And as an added bonus it could provide financial rewards to the enterprises using them. Perhaps lower medical premiums to the individuals, lower medical costs to the insurance companies, and more profit margins for the labs conducting the tests.

All the participants in this new technology discovery would obtain a distinct competitive advantage by lowering costs and increasing profit margins. With these factors in mind, it was indeed realized there was a large need for this technology in the market place, and bringing it to market rapidly would increase its competitive value. Therefore it was in the best interest of all actors to work closely and rapidly to bring to market this disrupting technology.

5. Refining the technology for specific needs,

Lawrence Berkeley Laboratories demonstrated proof of concept to medical laboratory needs; they showed the benefits of using this new technology, and the potential competitive advantage over existing products. LBNL researchers showed ways of implementing the technology with custom setting in order to allow for product differentiation and gain a foothold in the competitive market place. The technology transfer could be done in such a way, as to allow individual licensors to implement their unique solutions and provide to the market custom products and unique solutions.

The Berkeley labs provides technical support to the labs interested in the technology as well as licensing rights to use the technology. LBNL works closely with its customers and potential customer to assure proper usage of the technology, and helps in transitioning the product from the lab environment to a commercial setting. It also helps the potential customer with manufacturing support in order to improve yields and increase efficiency and profit margin.

Berkeley labs continuously work on improving its products, and are currently working a improving the efficiency output of their product, and at the same time are working on the next generation technique to improve the sensitiveness of the test. The current customers get to notch technology and support, and get early access to the next generation technology in the pipeline. They also provide for a feedback mechanism in order to take customer feedback and improve its current products as well as future products.

LBNL has taking the technology transfer process to the next level accelerating time to market and improving the competitive advantage of its customers. It provides insights into upcoming technology and its benefits as well as technical support to successfully commercialize the product.

6. Preparing to launch into the user's world,

Berkeley Laboratories signed with two independent medical laboratories. These two agreements focused on implementing profitable relationships. Berkeley labs would allow use of its patents and techniques and know how, and the companies would pay royalties back to Berkeley labs.

The two partners that signed with LBNL were Quest Diagnostics Inc., and Berkeley HeartLab Inc. These two enterprises worked closely with LBNL and obtained all the necessary technical support to successfully bring to market the new Cholesterol Diagnostic Lipoprotein Analysis Test. [23]

LBNL provided guidance and support when issues were encountered. They send representatives to make sure a smooth transition happened during the transfer of technology from the lab environment to the large scale commercial manufacturing. They also helped its customers with manufacturing yields and set-up issues and provided guidance on the assessment of quality control.

To highlight the successful technology transfer model, Quest Diagnostics introduced its first product based on Berkeley's Labs Ion Mobility Lipoprotein assessment in 2008. It has been received very well by the medical community.

7. Managing the technology over its life cycle.

Berkeley Laboratories provides technical support during the lifecycle of its products. LBNL creates a symbiotic environment where customers can interact in a closely managed manner. Guidance and support is provided from the early stages of the technology transfer. An early assessment is made by LBNL to make sure all the necessary technical issues are understood by the customer before any transfer takes place. Once the technology transfer agreements are signed, and there is a legal framework in place, the technology sharing process is taken to the next level, and LBNL personnel helps establish the technical groundwork to guarantee a smooth transitions.

When issues are found, LBNL personnel works closely with their partners and solves the technical issue in a timely manner. If technical issues persist, LBNL personnel try to replicate the issues in house in order to resolve the problem as fast as possible.

To assure success of its clients, LBNL is already working on the next generation products as well as improving its current products to be easier to manufacture in high volumes. Lowering the prices as well as increasing availability of the product to its customers.

LBNL works during all stages of the technology transfer process, from the early stages where basic knowledge is shared, to later stages, where agreements are in place, which guarantee complete sharing of knowledge. Support is provided at all stages, and when issues are found LBNL works closely with its technology partners to resolve those issues in a timely and efficient manner.

Milestones accomplished by LBNL labs

LBNL is working on the next generation of gels, to increase the quality and availability of its product.
LBNL has secured funding, primary fund from the US department of Health and services
LBNL already is improving it manufacturing process to increase its yield and quality of its products in the pipeline.

CONCLUSION

Lawrence Berkeley National Laboratories completed the successful transfer of its Direct Cholesterol Assessment Test to the medical community. This new technique started in LBNL labs in 1978; it was pioneer by Dr. Ron Krauss and his medical colleagues Henry Benner and Patricia Blanche. After twenty one years of medical experimentation and multiple false starts, the technique was patented in 1999.

LBNL worked closely with private institutions, negotiated agreements, to bring to market this new revolutionary technique. And most of all, helped improve the lives of many people whose coronary risks health problems were unforeseen by existing medical techniques.

The new technology brought to the marked vast improvements compared to existing tests. It made them more readily available to the average user provided a superior product in terms of quality, cost, and availability. At the same time, it helped multiple companies take advantage of the new technology and helped increase the financial rewards of these companies bottom line.

The technology transfer process accomplished by this team did not end with the licensing agreements to commercialize the new technique. LBNL continues to work on process improvements as well as volume manufacturing improvements, and constantly improves its current products in the pipeline. LBNL works closely with its partners when issues are found and helps them resolve those issues in a timely manner.

LBNL has allow these companies to develop unique solutions and provided them with all the basic knowledge to continuously improve the process and its products. This allows these companies to remain competitive and be at the fore front of the competitive market. It also allows these companies to be first to market and increase its profit margins by making the top of the line solutions for their respective fields.

LBNL has formed a partnership with the Licensing laboratories to assure success of its licensees as they bring the new products to the market. They have forged a strong partnership between lab and Industry. LBNL is constantly monitoring the relationships as well as the successes of its partners to make sure there is a mutual need for both enterprises to work closely in a cohesive fashion.

LNBL showed in this example of technology transfer, all the necessary steps in order to promote a positive trusted relationship. LBNL showed the seven steps discussed in Austin Spivey research. From the Disclosing of Technology, Linking technology with needs, Assessing the Technology, Matching the technology with functional needs, Refining the technology for specific needs, Preparing to launch into the user's world, and Managing the technology over its life cycle.

I personally like this technology transfer example because it showed that proper planning and execution can bring positive rewards to enterprises in the form of financial rewards and positive press reviews. At the same time provide answers and solutions to problems which affect human kind.

Technology used properly can solve problems and the results benefit all suffering those ailments and the results are enjoyed by all of us.

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