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Economic Impact of ATP's Contributions to DNA Diagnostics Technologies

Alan O'Connor, Brent Rowe, Michael Gallaher
Joel Sevinsky, and Dallas Wood

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- On the Internet: www.atp.nist.gov/eao/eao_main.htm
- By e-mail: atp-eao@nist.gov
- By phone: 301-975-8978, Stephanie Shipp, Director, Economic Assessment Office, Advanced Technology Program
- By writing: Economic Assessment Office, Advanced Technology Program, National Institute of Standards and Technology, 100 Bureau Drive, Stop 4710, Gaithersburg, MD 20899-4710

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National Institute of Standards and Technology
Gaithersburg, MD 20899-4710

By
Alan O'Connor
Brent Rowe
Michael Gallaher
Joel Sevinsky
Dallas Wood

RTI International
Research Triangle Park, NC
oconnor@rti.org

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U.S. DEPARTMENT OF COMMERCE
Carlos M. Gutierrez, Secretary
TECHNOLOGY ADMINISTRATION
Robert C. Cresanti, Under Secretary of Commerce for Technology
NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY
William A. Jeffrey, Director
ADVANCED TECHNOLOGY PROGRAM
Marc G. Stanley, Director

Abstract

Since 1993, the Advanced Technology Program (ATP) has provided technical and financial support for 42 Tools for DNA Diagnostics projects, most of which were competitively funded under a focused program established to drive innovation in the biotechnology sector.

When the focused program was launched, the scientific and medical community's understanding of molecular biology and genomics was increasing rapidly, as was the accumulation of genetic data. But tools had yet to be developed to efficiently acquire that information or make efficient use of the enormous potential it held for medical science. Advances in molecular diagnostics technologies would permit scientists to conduct more robust tests and analyses for disease susceptibility in humans, plants, and animals; forensics testing; disease identification; and drug effects studies, among other biotechnology applications.

ATP contracted with RTI International to perform an independent assessment of its Tools for DNA Diagnostics projects. This report reviews eight such projects, three of which are presented in two in-depth case studies.

The first case study is the Affymetrix-Molecular Dynamics MIND Development project—the largest in ATP's history—which led to advances in DNA microarray technologies and the development of the first high-throughput capillary array DNA sequencer. The case study chronicles how ATP-sponsored research accelerated the scientific community's adoption of microarray technologies, the Human Genome Project, and innovations in DNA sequencing.

The second case study reviews two projects at Molecular Tool (later known as Orchid Cellmark) and their contributions to rapid genetic analysis testing. Qualitative analyses of the remaining five projects

contribute to a broader understanding of the market, scientific, and public health impacts of the Tools for DNA Diagnostics project portfolio.

The analysis covers the period from the first project start date in 1993 through the last project end date in 2006. Resources and time were not available to investigate all 42 projects; therefore, the benefits quantified in the two case studies were compared with the costs of all 42 projects to provide a set of conservative, lower-bound performance measures. The following measures reflect realized benefits that accrued through 2005:

- net present value of net public benefits, using a 7% discount rate (1995 base year and real 2005 dollars): $119.7 million
- internal rate of return: 28%
- benefit-to-cost ratio: 1.90

Disclaimer

Certain trade names, company names, products, and services are mentioned in the text to contextualize the ATP projects and their innovations and to adequately specify the technical procedures and equipment used. In no case does such identification imply recommendation or endorsement by the National Institute of Standards and Technology (NIST), ATP, or RTI, nor does it imply that the products and services are necessarily the best currently available for the purpose.

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Acronyms and Abbreviations

ABI	Applied Biosystems, Inc.
APB	Amersham Pharmacia Biotech
ASO	Allele-specific oligonucleotides
ASPE	Allele-specific primer extension
ASR	Analyte-specific reagent
ATP	Advanced Technology Program
BCR	Benefit-to-cost ratio
BLS	U.S. Bureau of Labor Statistics
bp	Base pair
CAE	Capillary array electrophoresis
CDD	Cleavase Direction Detection
CEO	Chief Executive Officer
CFLP	Cleavase Fragment Length Polymorphism
DARPA	Defense Advanced Research Projects Agency
DNA	Deoxyribonucleic acid
FBI	Federal Bureau of Investigation
FDA	Food and Drug Administration
FTP	Federal Technology Partnership Program
GBA	Genetic bit analysis
HGP	Human Genome Project
IPO	Initial public offering
IRR	Internal rate of return

IT	Information technology
JV	Joint venture
MIND	Miniature Integrated Nucleic Acid Diagnostic
mRNA	Messenger ribonucleic acid
MT	Molecular Tool
MTAP	Microarray Technology Access Program
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NSF	National Science Foundation
NPV	Net present value
OMB	Office of Management and Budget
OMRF	Oklahoma Medical Research Foundation
PCR	Polymerase chain reaction
R&D	Research and development
RFLP	Restriction fragment length polymorphism
RNA	Ribonucleic acid
RTI	RTI International
SAGE	Serial analysis for gene expression
SARS	Severe Acute Respiratory Syndrome
SBIR	Small business innovation research
SBPE	Single base primer extension
SDK	Software developer's kit
SEC	Securities and Exchange Commission
SNP	Single nucleotide polymorphism
STI	Soane Technologies, Inc. (later known as Aclara)
STR	Single tandem repeats
UK	United Kingdom

Executive Summary

Since 1993, the Advanced Technology Program (ATP) has provided technical and financial support for 42 Tools for DNA Diagnostics projects, most of which were competitively funded under a focused program established to drive innovation in the biotechnology sector. The projects are within the realm of molecular diagnostics—the acquisition and use of genetic information to diagnose and treat diseases and discover new medical therapies and drugs.

When the focused program was launched, the scientific and medical community's understanding of molecular biology and genomics was increasing rapidly, as was the accumulation of genetic data. But tools had yet to be developed to efficiently acquire that information or make efficient use of the enormous potential it holds for medical science. Advances in molecular diagnostics technologies would permit scientists to conduct more robust analyses for testing for disease susceptibility in humans, plants, and animals; conducting forensics testing; identifying diseases; and testing drug effects.

ATP, a program of the Department of Commerce's National Institute of Standards and Technology (NIST), contracted with RTI International to perform an independent assessment of its Tools for DNA Diagnostics projects. The purpose of this assessment is to inform policy makers and the public of ATP's performance in meeting its mandate: creating public–private partnerships to accelerate the development of high-risk, innovative technologies that promise significant benefits to the nation.

RTI evaluated 8 projects—3 quantitatively and 5 qualitatively—to estimate lower-bound performance measures for all 42 projects (see Table ES-1). Conducting an in-depth case study of each project was not

Table ES-1. ATP Projects Profiled in this Report

Company(-ies)	Project Name	Period of Performance	ATP Cost Share (million)	Industry Cost Share (million)
Affymetrix, Inc. and Molecular Dynamics, Inc.	Miniature Integrated Nucleic Acid Diagnostic (MIND) Development	1995–2000	$31.5	$31.5
CuraGen Corporation	Integrated Microfabricated DNA Analysis Device for Diagnosis of Complex Genetic Disorders	1995–1998	2.3	2.9
Nanogen, Inc.	A Portable Genetic Analysis System	1997–1999	2.0	1.9
Nanogen, Inc.	An Integrated Microelectronic DNA Diagnostic System	1995–1997	2.0	1.5
Orchid Cellmark, Inc. (formerly Molecular Tool, Inc.)	Integrated Microfabricated Devices for DNA Typing	1995–1998	2.0	0.5
Orchid Cellmark, Inc.	Polymerase Signaling Assay for DNA Variation Detection on Universal Processor Arrays	1999–2001	2.0	1.0
Third Wave Technologies, Inc.	Development of a Generic Technology for the Targeted Detection and Cleavage of DNA and RNA	1995–1996	2.0	0.8
Third Wave Technologies, Inc.	Simple, Generic, and Low-Cost Genetic-Based Tools for Disease Detection, Monitoring, and Intervention	1997–1999	2.0	2.1

Source: ATP.

possible, given time and resource constraints. However, the realized economic benefits from the two quantitative case studies can be used to calculate a lower-bound estimate of the return on ATP's entire molecular diagnostics portfolio.

RTI quantified economic benefits relative to the technologies that each ATP-cofunded technology superseded, estimated the likely achievement of the same accomplishments with the less-effective and less-efficient defender technology, and then calculated the savings.

Performance measures reflect realized benefits that accrued through 2005. That this report quantifies realized benefits was a coincidence; cash flows were not purposefully stopped in 2005. The projects have ongoing economic benefits; however, they could not be quantified.

Data to inform the technical and economic impact metrics were collected from primary and secondary data sources. Primary data sources included current and former representatives from the funded firms, end users of their products that contain ATP-cofunded technology, and individuals with significant domain expertise in and historical knowledge

of the technologies and the events surrounding their development. Secondary sources included published articles in scholarly journals and trade publications as well as reports prepared by government agencies.

To the extent possible, RTI reconstructed historical events to model the projects' technology outcomes as accurately as possible in the market and scientific context in which the innovations were generated. Where experts, company representatives, and end users provided conflicting reports and data, RTI worked to develop a consensus view.

ES.1 MIND DEVELOPMENT PROJECT

The first case study was a collaborative effort between Affymetrix, a DNA microarray manufacturer, and Molecular Dynamics, a molecular biology instrument manufacturer. This project, originally budgeted at $63 million, remains the largest award in ATP's history.

The project's goal was to combine Affymetrix's expertise in DNA microarrays and Molecular Dynamics' expertise in instrumentation to develop a handheld Miniature Integrated Nucleic Acid Diagnostic (MIND) device. This device would enable doctors to rapidly analyze patients' blood samples in the office and output the data from a handheld unit to a desktop reader that would determine a clinical diagnosis.

The MIND Development project, as it was called, was envisioned as an ambitious, broad-ranging effort to overcome technical and market barriers to point-of-care diagnostics.

In the mid-1990s, biotechnology companies saw point-of-care diagnostics—the use of miniaturized devices and processes in a medical office setting to provide medical diagnoses—as the next major market opportunity. Though many technical concepts had been proposed, the actual technologies required to make practical diagnostic tools possible did not exist. The companies' proposal set an overall goal of developing the full suite of instrumentation, assays, protocols, and data analysis and management systems necessary to make the device a reality.

Yet over the course of the 5-year period of performance, challenges in developing molecular diagnostics for the point-of-care market shifted the market opportunity toward research applications and clinical diagnostics, particularly as the pending completion of the Human Genome Project refocused the scientific community's interest on gene expression, genotyping, and sequencing.

Each firm consequently commercialized its individual technology outcomes. As a consequence, the joint project accelerated the introduction and use of microarray technologies and significantly advanced the quantity and quality of genomic data available for research and analysis.

ES.1.1 Affymetrix Technology Outcomes

Affymetrix's ATP-cofunded research led to advancements in microarray design and manufacture, sample labeling, and assay protocols as well as in the software used to analyze data output. The project accelerated the development of process technologies that made microarray production more efficient and increased the analytic capability of the chips fourfold while simultaneously increasing their quality. The whole of the microarray technology experience was improved, which had the effect of accelerating the acceptance of this new technology platform.

Although project outcomes from Affymetrix's work have ongoing value for the organization and society, in terms of quantifiable benefits, this analysis was able to quantify a 1- to 2-year acceleration in the adoption of improved Affymetrix microarrays.

The ATP award helped Affymetrix reduce each microarray's feature size from 50 microns to 25 microns, which increased each microarray's analytic capability fourfold. The indirect value of what researchers were and still are able to learn from analyzing the data output is unquantifiable. However, it is possible to value this development by estimating the reduction in the number of microarrays, the amount of consumables, and the labor hours needed to generate a comparable volume of data with microarrays with 50-micron feature sizes from 1999 through mid-2000.

RTI estimates that during the acceleration period, approximately 25% of the incremental value delivered to end users by purchasing the new microarrays can be attributed to ATP funding. These benefits were approximately $54.4 million in 1999 and $47.5 million in 2000.

ES.1.2 Molecular Dynamics Technology Outcomes

Molecular Dynamics' research led to the first high-throughput DNA sequencer, induced innovation at its main competitor, Applied Biosystems, and accelerated the Human Genome Project (HGP), and other high-throughput genomics projects.

The need for improved DNA sequencing technologies was apparent during the earliest years of the Human Genome Project. For researchers to achieve their goal of understanding the link between human disease and certain genes, they first needed to decipher the sequence of the approximately 3 billion DNA base pairs contained in a human's 23 pairs of chromosomes. Determining genetic sequences was costly and time consuming; even the most well-equipped laboratories, operating state-of-the-art instrumentation, were only able to determine one genetic sequence every few days (Regis, 1995).

ATP cofunding enabled Molecular Dynamics to develop the first high-throughput, capillary array DNA sequencer, the MegaBACE 1000, which also included concepts and technologies developed by and licensed from its subcontractor, Richard Mathies of the University of California, Berkeley.

With the introduction of the MegaBACE, and the accelerated introduction of competitor Applied Biosystems' Prism 3700 sequencer, sequencing moved from a cumbersome process to a highly automated process that produces several times more data with near-perfect accuracy (see Table ES-2). Once the human genome was mapped, there was an enormous improvement in gene expression and other applications. Improved data quality and production also had significant downstream impacts on data analysis, outcomes, and research.

Experts agree that the introduction of high-throughput capillary array electrophoresis (CAE) sequencing was a watershed event that accelerated the HGP, scientific discovery, and downstream medical innovations that the completed sequence of the human genome and other scientifically-important genomes enabled (International Human Genome Consortium, 2001).

High-throughput sequencers moved the HGP's target completion date for a finished draft forward from 2006 to 2003 (Hodgson, 2000). The project was supposed to be completed in 2006, but a first draft of 90% of the genome was completed in June 2000.

RTI calculated the total economic benefits laboratories reaped from using new capillary array sequencers instead of the slab gel electrophoresis systems they replaced. These benefits included labor, equipment, and consumables savings. Total public benefits generated by Molecular Dynamics' project work, net of technology adoption costs,

Table ES-2. Productivity Comparison of Slab Gel and High-Throughput Capillary Sequencers

	Slab Gel Electrophoresis (ABI Prism 377)	Capillary Array Electrophoresis (MegaBACE 1000)
Instrument run time	6.5 hours	2.5 hours
Combined instrument run time and manual intervention time	6.83 hours	2.75 hours
Number of lanes	96 lanes	96 lanes
Average readlength	400 bps	650 bps
Pass rate	85%	98%
Consumables cost per sample (2005 $)	$0.50	$1.25

Source: RTI estimates.

were estimated to be $280.2 million, more than half of which accrued during 2000.

ES.1.3 Project Performance Measures

Public economic benefits from the MIND Development project totaled $394.5 million. When adjusted for inflation, ATP's contribution was $34.7 million. The net present value (NPV) of net public benefits for the entire project was $215.6 million. The project had an internal rate of return of 84% and a benefit-cost ratio of 8.7 (see Table ES-3). For every $1 ATP invested, the public realized $8.70 in benefits.

ES.2 MOLECULAR TOOL/ORCHID CELLMARK PROJECTS

The second case study analyzed the impact of two projects at Molecular Tool (MT) and the company that acquired it, Orchid Cellmark (Orchid). The two projects, one which sought to devise rapid DNA testing technologies that study genetic differences and a second for the development of a complete DNA analysis system, were combined into one case study because the technology that was commercialized embodied outcomes from both projects.

In the mid-1990s MT recognized the need for an automated system that could conduct parallel genetic analysis procedures in a miniaturized format, allowing more cost-effective and faster analyses. MT hoped to reduce the processing time for a DNA test from 30 minutes to 5 minutes.

Table ES-3. Public Performance Measures—MIND Development Project

Public benefits (2005 $ millions)	394.5
Public costs (2005 $ millions)	–34.7
Net public benefits (2005 $ millions)	359.8
NPV of net public benefits (2005 $ millions) [a]	215.6
Benefit-to-cost ratio	8.7
Internal rate of return	84%

[a]To compute NPV, net public benefits were discounted to 1995 using a 7% annual discount rate.

Source: RTI estimates.

Reducing the processing time would yield substantial labor and materials savings as well as greatly improved throughput capacity.

The first project improved the state-of-the-art technology by developing analysis techniques for analyzing single nucleotide polymorphisms (SNP). SNPs are one-nucleotide variations in the order of nucleotides that compose DNA. The second project incorporated that advance and yielded an entire miniaturized analysis system complete with digital imaging capabilities and pattern-matching software.

These technologies, collectively called SNP-IT, enabled an increase in the accuracy of hereditary DNA analysis from one in a million to one in several billion and a cost reduction of approximately $1 per genotype, or half that of common polymerase chain reaction (PCR) and sequencing techniques used at the time.

In 1999, Orchid Cellmark released one of the first commercially available instruments able to conduct high-throughput SNP analysis. Orchid also built a facility, called the MegaSNPatron, to offer contract-based SNP analysis services using SNPStream products. This facility has conducted millions of SNP analyses since it first opened in 1999.

Today, the SNP-IT technology forms the backbone of Orchid's DNA analysis services business. Beckman Coulter acquired the rights to use SNP-IT in its products shortly after Orchid discontinued the SNPStream product line. In addition, Orchid licensed SNP-IT technology to ABI, Quest Diagnostics, GE Healthcare (formerly Amersham Biosciences), Affymetrix, Hitachi MiraiBio, Invitrogen, Luminex, PerkinElmer, Quest Diagnostics, Thermo Biostar, and Asper Biotech.

Three separate measures of the projects' performance are provided in Table ES-4. Realized public benefits totaled approximately $7.8 million in

Table ES-4. Public Performance Measures—Molecular Tool/Orchid Projects

Public benefits (2005 $ millions)	7.8
Public costs (2005 $ millions)	–4.6
Net public benefits (2005 $ millions)	3.2
NPV of net public benefits (2005 $ millions) [a]	1.4
Benefit-to-cost ratio	1.4
Internal rate of return	19%

[a]To compute NPV, net public benefits were discounted to 1995 using a 7% annual discount rate.

Source: RTI estimates.

2005 dollars. After deducting public investment costs of $4.6 million, the realized net public benefits were $3.2 million.

Using 1995 as the base year and a 7% discount rate, the NPV of realized net public benefits was $1.4 million. The public benefit-to-cost ratio was 1.4, implying that for every $1 ATP invested, the public realized $1.40 in benefits. The public internal rate of return was 19%.

ES.3 TECHNOLOGY OUTCOMES AND MARKET IMPACTS

ATP funding invigorated market interest in a growing sector and contributed to the emergence of an industry. The R&D that ATP supported enabled awardees to bring technologies to market sooner than they otherwise would have. In some instances, the technologies would not have been developed at all, and their contributions to science might not have occurred.

In addition to the two main case studies, five additional projects were reviewed qualitatively:

- **CuraGen** sought to develop a device that would be similar to the MIND device, but foresaw that microfluidics would be a challenge, and instead developed a microarray-based drug discovery platform.
- **Nanogen** (two projects) developed the first microarray platform for the clinical diagnostics market during a period when its competitors were intent upon research applications.
- **Third Wave Technologies** (two projects) invented easy-to-use genetic analysis test kits that could quickly identify the presence of genetic markers for several inherited and infectious diseases. Third Wave, which may not have survived without ATP funding, developed inexpensive, easy-to-use diagnostic tests that were used to complete 25% of the International HapMap project.

Representatives from Affymetrix and the former Molecular Dynamics believe that the success of the JV and ATP's support was "a shining light" that encouraged other firms "to go for it" and develop and market technologies for what was becoming the pharmacogenomics and genomics marketplace.

When ATP's Tools for DNA Diagnostics focused program was launched in 1994, the biotechnology sector was still in its infancy. Up to that point, the industry had been dominated by large laboratory instrumentation and medical device manufacturers. Small start-up companies often relied on angel financing, partnerships with large pharmaceutical companies, or personal financing to get their ambitious technologies off the ground. As one participant noted, even if a biotech company had external financing, an additional $1 or $2 million provides researchers with greater freedom to pursue scientific discovery.

The founders and principal investigators at MT, Orchid, CuraGen, Nanogen, and Third Wave all expressed the importance of the ATP funding in supporting very small companies in a new industry. The challenge for innovators is that venture capitalists often require that firms have already met their first few technology milestones, yet many innovators deplete their funds before they achieve such milestones. Furthermore, venture capitalists bring focus but at the expense of scientific discovery.

One industry expert believes that the technologies that will revolutionize health care between 2009 and 2020 were pioneered in the 1990s. Incubation time—the period between conceptualization and adoption—is long for biotechnologies. ATP's support of core research and technology development helped provide a foundation for accelerating technologies that can have incubation times of 15 years or more.

The projects profiled in this report moved medical science closer to the era of personalized medicine in which patients will have medical therapies recommended to them based on their genetic makeup. Doctors' ability to identify the genetic basis of many diseases and pharmaceutical companies' ability to develop new drugs have been greatly advanced.

Ultimately, the principal beneficiaries of these technologies are the patients who one day will receive more timely, better quality, and more effective health care because doctors, clinicians, and researchers have more powerful DNA diagnostic tools. The information generated—a

sequenced genome, an expression profile of a diseased tissue sample, or an early warning of a gene that may make a patient more likely to contract an illness—have social impacts that are invaluable.

ES.4 PERFORMANCE MEASURES

The public benefits realized from Affymetrix's, Molecular Dynamics', and MT/Orchid's ATP projects were compared with ATP's total investment in all 42 Tools for DNA Diagnostics projects to calculate lower-bound measures of economic performance.

Table ES-5 presents the time series of public benefits quantified in the two case studies. These public benefits were summed and reduced by ATP's inflation-adjusted annual spending on all 42 projects to derive a lower bound of net public benefits. In all, RTI calculated $402.3 million in public benefits, of which approximately 98% were contributed by ATP's investment in the MIND Development project.

ATP's investment was $164.2 million, which yielded lower-bound net public benefits of $238.2 million. Thus, although only three projects were

Table ES-5. Time Series of Public Benefits, Costs, and Lower-Bound Net Benefits—All Tools for DNA Diagnostics Projects (2005$)

Year	Public Benefits: MT/Orchid Cellmark Case Study	Public Benefits: Affymetrix and Molecular Dynamics Case Study	Lower Bound Public Benefits	Public Costs for All 42 Projects	Lower-Bound Net Public Benefits
1995				–$1,994,000	–$1,994,000
1996				–47,849,000	–47,849,000
1997				–58,616,000	–58,616,000
1998		–$3,501,000	–$3,501,000	–18,937,000	–22,438,000
1999	$2,106,000	751,000	2,857,000		2,857,000
2000	1,638,000	201,620,000	203,258,000	–21,926,000	181,332,000
2001	1,638,000	53,983,000	55,621,000	–4,831,000	50,790,000
2002	1,229,000	53,983,000	55,212,000		55,212,000
2003	819,000	51,479,000	52,298,000	–2,120,000	50,178,000
2004	410,000	30,331,000	30,740,000	–6,136,000	24,604,000
2005		5,844,000	5,844,000	–1,762,000	4,081,000
Total	7,839,000	394,490,000	402,329,000	–164,171,000	238,158,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding.

reviewed quantitatively, those projects alone had benefits sufficient to yield positive net benefits for all 42 ATP Tools for DNA Diagnostics projects.

Using the retrospective, realized net benefits data presented in Table ES-5, RTI calculated lower-bound performance measures for ATP's entire portfolio of molecular diagnostics projects. A discount rate of 7% was applied to the time series of net cash flows to calculate a lower-bound NPV of $119.7 million. The lower-bound public rate of return was 28%, and the benefit-to-cost ratio was 1.9 (see Table ES-6).

Table ES-6. Lower-Bound Public Performance Measures—All Tools for DNA Diagnostics Projects

Public benefits (2005 $ millions)	402.3
Public costs (2005 $ millions)	–164.2
Net public benefits (2005 $ millions)	238.2
NPV of net public benefits (2005 $ millions) [a]	119.7
Benefit-to-cost ratio	1.9
Internal rate of return	28%

[a]To compute NPV, net public benefits were discounted to 1995 using a 7% annual discount rate.

Source: RTI estimates.

1 Introduction

Since 1993, the Advanced Technology Program (ATP) has provided technical and financial support for 42 Tools for DNA Diagnostics projects, most of which were competitively funded under a focused program established to drive innovation in the biotechnology sector. The projects are within the realm of molecular diagnostics—the acquisition and use of genetic information to diagnose and treat diseases and discover new medical therapies and drugs.

When the focused program was launched, the scientific and medical community's understanding of molecular biology and genomics was increasing rapidly, as was the accumulation of genetic data. But tools had yet to be developed to efficiently acquire that information or make efficient use of the enormous potential it holds for medical science. Advances in molecular diagnostics technologies would permit scientists to conduct more robust tests and analyses for disease susceptibility in humans, plants, and animals; forensics testing; disease identification; and drug effects studies.

ATP supported core scientific research at mostly start-up, small, and medium-sized enterprises that otherwise would not have occurred. The availability of $137.5 million in ATP matching funds induced $119.4 million in additional investment from the fledgling biotechnology sector, bringing the aggregate public–private investment in the 42 projects to $256.9 million.

A program of the Department of Commerce's National Institute of Standards and Technology (NIST), ATP contracted with RTI International to perform an independent assessment of its Tools for DNA Diagnostics projects. The purpose of this assessment is to inform policy makers and

the public of ATP's performance in meeting its mandate: creating public–private partnerships to accelerate the development of high-risk, innovative technologies that promise significant benefits to the nation.

RTI reviewed 8 projects—3 quantitatively and 5 qualitatively—to estimate lower-bound performance measures for all 42. The three quantitative reviews were in the context of two comprehensive case studies: one of a joint project between Affymetrix and Molecular Dynamics and another of two projects at Molecular Tool (MT), which was acquired by Orchid Cellmark.

This report presents the assessment's methodology and analysis results for each case study individually, as well as all 42 projects as a portfolio. Because this study quantified the benefits of three projects and compared their combined economic benefits with the costs of 42, the performance measures presented at the end of this report are lower-bound estimates.

1.1 OPPORTUNITIES FOR DNA DIAGNOSTICS TECHNOLOGIES IN PUBLIC HEALTH

In 1908, the British physician Archibald E. Garrod published a paper claiming that there was a genetic basis for the disease alkaptonuria, a rare and harmless disorder that causes urine to turn dark when exposed to air. Alkaptonuria was not widespread among the general population, but it was common among children from marriages of first cousins. Garrod argued that his patients inherited an enzyme deficiency that impeded protein breakdown. Garrod's work was the first to suggest that there was a link between disease and genetic defects.

In the century since Garrod's early hypotheses, science has progressed rapidly to the point where today researchers are bringing medical technologies to market that exploit science's recent accumulation of vast quantities of genetic information.

The genetic basis for many diseases and conditions moved from conjecture to accepted science. Research and discovery into the structure and composition of DNA, and the tools to reveal them, formed the foundation for the study of genomics.

DNA is a nucleic acid that contains the genetic instructions for life. It was first identified in the 19th century, and intensive research over the

decades that followed revealed its location and composition in human cells.

After the discovery of the structure of DNA in 1953, it became clear to scientists that if they had a detailed blueprint of an organism's genetic make-up, they could decipher its entire DNA sequence. With that DNA sequence, they would gain tremendous insights into an organism's structure, function, and evolution. In the case of human beings, this information would be an invaluable tool with which to understand how diseases affect the body, which in turn would aid in the search for new drugs and therapies. The sequenced human genome would be a platform from which to study genetic differences among people and determine their individual responses to diseases and medications.

Beginning in the 1980s, large research projects to acquire many organisms' genetic blueprints were launched. The most notable of these was the Human Genome Project in 1990 that was projected to take at least 15 years and cost approximately $3 billion.

But tools had yet to be developed to efficiently acquire the genetic information or make efficient use of the enormous potential that information holds for medical science. As these projects progressed, the need for a new generation of diagnostic procedures, scientific instruments, and analytic tools became ever more pressing.

Technical advances would permit scientists to conduct more robust analyses for testing humans' and animals' parentage, conducting forensics testing, identifying diseases, and testing drug effects. Although a complete map of human genetic code would amplify the capabilities of such analyses, researchers working on this map were eager for new technologies that would enable better DNA analysis in all research and commercial environments.

The potential benefits DNA diagnostics hold for society are great, both in terms of an overall improvement in public health and cost savings from more efficient and effective treatment of disease. Pharmaceuticals are currently not tailored to a patient's genotype; DNA diagnostics technology will enable that tailoring and may help avoid adverse reactions and the cost of ineffective therapies (Karet and Boguslavsky, 1999).

1.2 GOVERNMENT'S ROLE IN SUPPORTING TECHNOLOGY RESEARCH AND DEVELOPMENT

Private-sector research and development (R&D) is often aimed at producing or improving private goods and services to capture economic benefits through higher prices, unit sales, or margins. In contrast, the goal of most basic and applied research is to create or contribute to the body of scientific and technological knowledge.

In the latter case, it is often difficult for innovators to capture the major portion of the benefits from their inventions. This is particularly true in biotechnology, which is characterized by technologies requiring substantial investments in time, money, and energy to develop and sustain concepts through long incubation times. An innovator's inability to capture benefits dampens the desire to innovate, which will yield a suboptimal level of these goods, leading to a lower than desirable level of technical progress.

To correct for this potential market failure, ATP was created in 1990 to foster the development of high-risk, high-reward public technologies where market failures or externalities are likely to lead to underinvestment by private firms. ATP funds, on a cost-sharing basis, precommercial R&D into new technologies and process improvements where substantial spillovers are expected and where technical and investment recovery risks are high.

ATP's Tools for DNA Diagnostics focused program was the first federal effort to invest in advanced biotechnologies for molecular diagnostics, and it was the only one that did so broadly, without mandating specific applications. Awarding projects without mandating specific applications enabled innovators to develop technologies according to market conditions. ATP funded these projects through a focused program and through open and general competitions. ATP awarded matching funds to firms' projects based on their scientific merit, potential benefit for the nation, and risk profile. ATP funded the best proposals and supported multiple platforms and competing organizations.

The Tools for DNA Diagnostics projects all aimed to develop inexpensive and easy-to-use tools for generating diagnoses through rapid DNA analysis. Before personalized DNA diagnostics and therapeutics are possible, medicine must first have a variety of tools available with which

to compare patient blood or tissue samples to science's expanding catalog of genetic information. When the program was launched, science concentrated on acquiring the information. It was only after ATP began to support projects in DNA diagnostic tools and promising technologies began to emerge that the market opportunities for such tools became more apparent to the private sector.

1.3 EVALUATING THE EFFECTIVENESS OF ATP PROJECTS

Since its inception, ATP's Economic Assessment Office (EAO) has taken an active role in supporting the evaluation of funded projects and shares external assessments like this report with the public. These assessments have measured the impact of the ATP on U.S. firms, industrial sectors, and the overall economy. These assessments include the following:

- real-time evaluations of project progress, using ATP's project management teams and analysis of the data reported by the companies through the business reporting system;
- surveys of the participating companies to assess ATP's effect on the companies' decisions and success;
- project case studies that assess the costs and benefits of ATP's investments in specific technologies or technology areas;
- general studies of how ATP funding leads to spillover benefits to beneficiaries other than the ATP award recipients; and
- models that link large-scale macroeconomic models with microeconomic project analyses.

Case studies are an important part of ATP's economic analysis strategy. They provide an in-depth view of how ATP-cofunded technologies lead to economic benefits for the awardees, other companies, and consumers. Case studies also provide qualitative details about how ATP funding affects the investment decisions of companies and the success of the projects. Ideally, case studies provide credible quantitative estimates of the economic performance of ATP's investments in these technologies.

1.4 ATP PROJECTS ANALYZED IN THIS REPORT

The eight ATP projects this report analyzes are listed in Table 1-1. (Information on all 42 projects can be found in Appendix A.) For reasons discussed in the chapter devoted to the project's conceptual approach

Table 1-1. ATP Projects Analyzed in this Report

Company(-ies)	Project Name	Period of Performance	ATP Cost Share (millions)	Industry Cost Share (millions)
Affymetrix, Inc. and Molecular Dynamics, Inc.	Miniature Integrated Nucleic Acid Diagnostic (MIND) Development	1995–2000	$31.5	$31.5
CuraGen Corporation	Integrated Microfabricated DNA Analysis Device for Diagnosis of Complex Genetic Disorders	1995–1998	2.3	2.9
Nanogen, Inc.	A Portable Genetic Analysis System	1997–1999	2.0	1.9
Nanogen, Inc.	An Integrated Microelectronic DNA Diagnostic System	1995–1997	2.0	1.5
Orchid Cellmark, Inc. (formerly Molecular Tool, Inc.)	Integrated Microfabricated Devices for DNA Typing	1995–1998	2.0	0.5
Orchid Cellmark, Inc.	Polymerase Signaling Assay for DNA Variation Detection on Universal Processor Arrays	1999–2001	2.0	1.0
Third Wave Technologies, Inc.	Development of a Generic Technology for the Targeted Detection and Cleavage of DNA and RNA	1995–1996	2.0	0.8
Third Wave Technologies, Inc.	Simple, Generic, and Low-Cost Genetic-Based Tools for Disease Detection, Monitoring, and Intervention	1997–1999	2.0	2.1

Source: ATP.

and methodology, Chapter 3, three projects were selected for in-depth case studies.

This assessment also relies on many concepts and events to contextualize and estimate the economic benefits of ATP-cofunded technologies. Chapter 2 provides an introduction to molecular biology, a description of key events and global research projects, and the rationale for ATP becoming involved in this technical field. Readers may also find particularly useful the section that compares the technology platforms and applications presented in Chapters 3 through 7.

The first case study, MIND Development: The Affymetrix-Molecular Dynamics Joint Venture Project, is presented in Chapter 4. This case study analyzes the collaboration between two California biotechnology companies to develop the first handheld DNA diagnostic device, the

change in their project's strategic direction, and the microarray and DNA sequencing technologies they developed.

Chapter 5 is a case study of two independent projects: a first project at MT to reduce the amount of time required to complete genetic analyses and a second project at the firm that later acquired MT, Orchid Cellmark, to develop tools for rapid identification of genetic variations.[1]

Chapter 6 presents three qualitative reviews of additional projects at CuraGen, Nanogen, and Third Wave Technologies. Chapter 7 presents quantitative performance measures for all 42 Tools for DNA Diagnostics projects using the benefits from only the two case studies to calculate lower-bound measures of return.

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[1] ATP does not fund follow-on research, nor does it bar firms from pursuing multiple awards. In some instances, commercialized products and services contain technologies from two independent projects at one company.

2 ATP's Role in DNA Diagnostics

Science is approaching an era in which medicine will not be conducted through the diagnosis of symptoms, but by managing patients' health according to their individual genetic make-up, or genotype. This is commonly referred to as "personalized medicine." Molecular diagnostics tools capture and analyze information from organisms' cells that can be used in medical research and health management, or in determining clinical diagnoses. It will likely be a decade or more until medical care reaches the point of personalization, but ATP's Tools for DNA Diagnostics projects helped lay the technology foundation that brought that point forward in time.

The public health benefits of personalized medicine are best understood in terms of accuracy, efficacy, safety, and speed. It is not possible to overstate the impact advanced molecular diagnostics technologies may have on disease management and prevention, quality of life, and health care spending. The ultimate benefit of these technologies is a healthier, more productive population and an increase in our understanding of life.

If doctors had access to patients' genetic libraries and a means of rapidly interpreting and understanding them, they would be able to prescribe medical therapies that they know would be efficacious. Doctors would avoid the trial and error process of finding the most effective prescription based on a patient's symptoms. The patient might avoid some or all adverse reactions, side effects, and ingestion of medicines that would have no therapeutic effect. Treatment would be faster, safer, and more effective. Better still, people could manage their health and mitigate their known risks for developing certain conditions.

In the 1990s, major initiatives were underway to catalog genetic data, but low-cost, rapid, and generic technologies did not exist to make practical use of those data. The technologies that were available were too cumbersome, slow, expensive, and/or ineffective for practical applications at clinical laboratories (point-of-diagnosis locations) or doctors' offices (point-of-care locations). ATP sought to bridge the technology gap with the focused program and projects.

This chapter contextualizes ATP's DNA Diagnostics projects and presents, in layman's terms, technical background information on DNA, genomics and major initiatives in the molecular diagnostics field. The purpose is to facilitate an understanding of the ATP awards profiled in this report, the awards' impacts, and how ATP's involvement accelerated molecular diagnostics technology development.

2.1 OVERVIEW OF MOLECULAR DIAGNOSTICS

This section introduces molecular biology, genetic analysis techniques, and several projects that employ those techniques to contextualize the ATP awards.

2.1.1 Molecular Biology

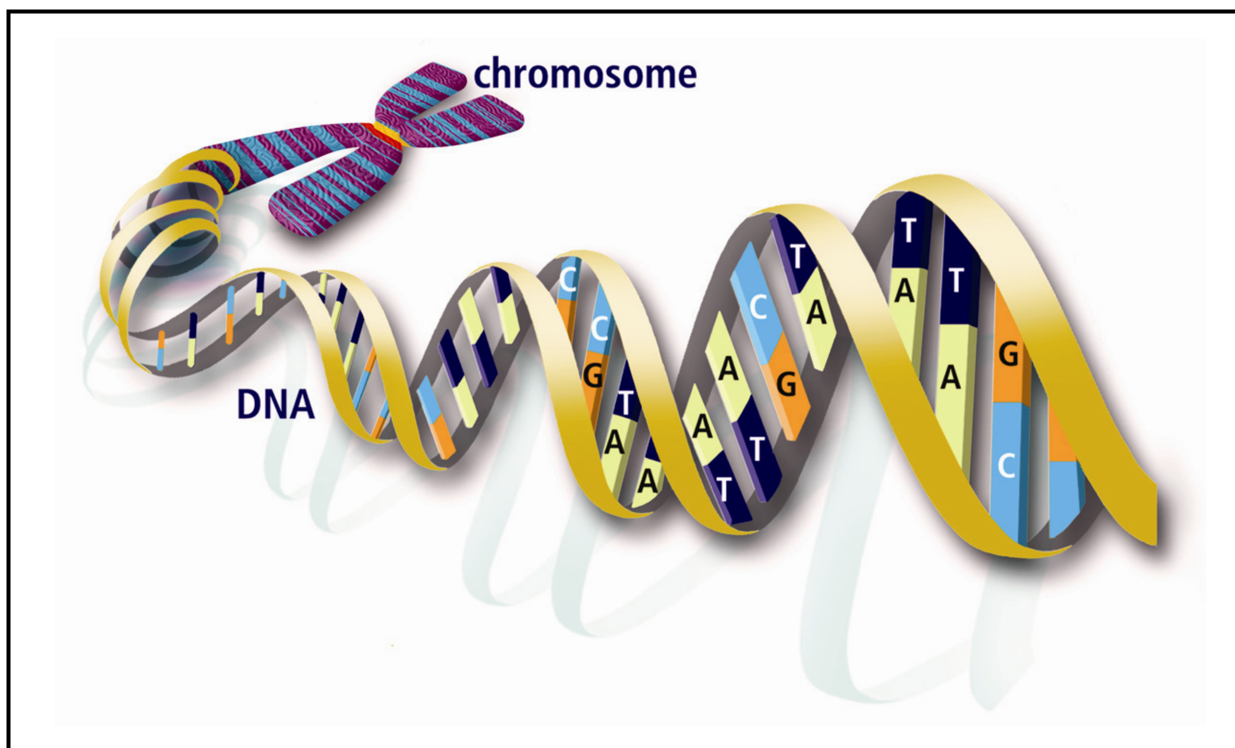
ATP's projects in molecular diagnostics fall into a field known as molecular biology. Molecular biology is not an independent field of study; rather, the discipline encompasses theories and techniques from traditional biology and chemistry, biochemistry, genetics, and engineering. It is the study of how cells' systems interact and function, including the relationships between DNA, RNA, and proteins.

2.1.1.1 Deoxyribonucleic Acid (DNA)

The instructions for every life form are contained in its DNA. DNA molecules are made up of two strands of nucleotides held together along their lengths by the hydrophobic effect, pi stacking, and hydrogen bonds. As Figure 2-1 illustrates, DNA has a twisting, double helix structure and resides in the nucleus of a cell.

DNA in all living things is composed of four nucleotides—adenine (A), thymine (T), guanine (G), and cytosine (C). Each strand of an organism's DNA will have these nucleotides in a specific order, and the strands are complementary, where A on one strand bonds with T on the other, and C on one strand bonds with G on the other.

Figure 2-1. The Double Helix Structure of DNA



Source: Courtesy of U.S. Department of Energy Human Genome Program.

Nucleotides are commonly referred to as bases, and each rung in the double helix ladder of a DNA molecule, which consists of complementary binding nucleotides, is commonly referred to as a base pair (bp). The length of a DNA molecule is described in terms of how many base pairs (bps) are in the molecule. A specific region of DNA, normally thousands of bps in length, that encodes the information for one protein sequence is commonly referred to as a gene.

The specific order or sequence of nucleotides in a DNA strand determines the order of amino acids in a protein. Proteins are important to the function and structure of an organism. Each unique gene will produce a unique protein. Change the sequence of nucleotides in the gene and one potentially changes the sequence of amino acids in a protein.

When the same gene in two different individuals differs in its nucleotide sequence, and hence are two different versions of the same gene, the two individuals are said to have different "alleles" or variations of the same gene. Allelic variation is the genetic source of variation between individuals.

DNA resides in the nucleus of the cell, but protein creation occurs outside the nucleus. In order for the protein-coding information contained in DNA to direct protein synthesis outside the nucleus, a copy of the DNA must be made and brought to the site of protein synthesis. This copy is known as messenger ribonucleic acid (mRNA).

Quite often, the number of mRNA copies of a gene (DNA) that are made can be used as a measure of how active a gene is. If no mRNA for gene A is detected, then gene A can be considered "off." If many copies of mRNA for gene A are detected, then gene A can be considered very active or "on."

2.1.1.2 Genomics and Genetics

The term "genomics" refers to the study of an organism's genome—its entire hereditary set of genetic information or DNA—and how all of an organism's genes function and interact to make the organism what it is. Genomics should not be confused with genetics, which is the study of how traits are passed from one generation of organisms to the next.

Genes and genomes are two distinct, but commonly misunderstood, terms. Whereas a gene is the small section of DNA that encodes the information for a protein, a genome is the full DNA sequence of an organism organized into subsets called chromosomes.

An organism's genome comprises a specific number of chromosomes. Some very simple organisms, such as bacteria, have only one chromosome. Others have a large number. Dogs, for example, have 78 chromosomes. Each chromosome contains hundreds, if not thousands, of genes.

The human genome consists of 24 distinct chromosomes: 22 autosomal chromosomes (1–22) and 2 sex chromosomes (X and Y). Most human cells contain 23 pairs of chromosomes, a genetic state known as "diploid." Diploid cells contain two of each autosomal chromosome (one from each parent) and have either two X chromosomes (a maternal X and a paternal X) or one X (maternal) chromosome and one Y (paternal) chromosome, giving each diploid cell a total of 46 chromosomes.

2.1.1.3 Single Nucleotide Polymorphisms (SNPs)

Single nucleotide polymorphisms (SNPs) are one-nucleotide variations in the sequence of DNA and are the most basic and common unit of

genetic variation. They are a subset of variations that help determine the allelic variation as discussed earlier.

For example, if most people have an "A" in a certain location, one person might have a "G," and this would be called an "A" to "G" SNP, which could distinguish two different alleles of the same gene.

If the DNA for 400 people were being compared, researchers might find a SNP if, in a given location in a gene, 25 people have a "G" instead of an "A." Because bases are complementary, their rung in the ladder of DNA would be "G-C" instead of "A-T." Thus, there is a single-base pair difference, or SNP, in the DNA of those 25 people (see Figure 2-2).

This change can be important, because a change in the DNA sequence of a gene can create a change in the amino acid sequence of a protein and possibly the protein's function. When a protein's function changes, this can create a different cellular state and sometimes a disease state.

It is commonly estimated that there are between 3 and 10 million SNPs in the human genome, representing much less than 0.1% of the billions of base pairs that make up the total human genome (Phillips and Boyce-Jacino, 2001).

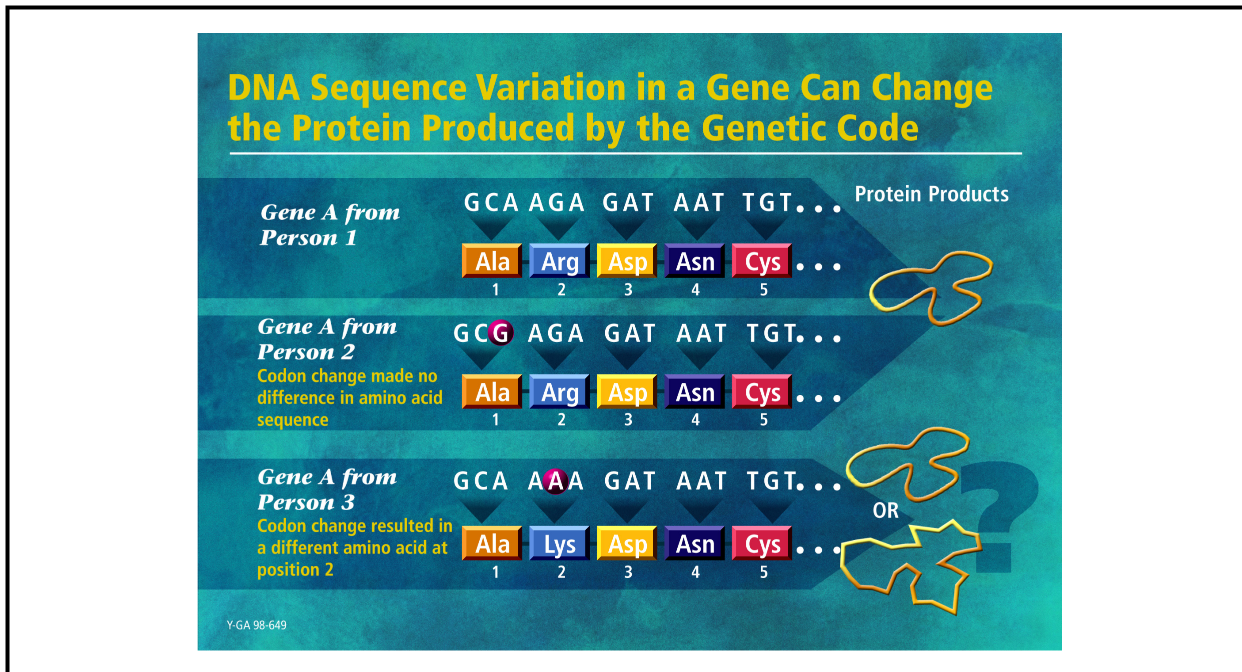
SNPs are useful for analyzing complex multifactorial diseases, such as diabetes, cardiovascular diseases, and psychiatric disorders, which, as a group, are much more prevalent than single gene, or monogenic, disorders. Understanding a person's SNPs can help researchers or physicians

- determine the likelihood that the person will develop a particular disease,
- understand how the person would respond to that disease, and
- develop therapies tailored to the person's specific genetic makeup.

2.1.2 Genomic Analysis Techniques

There are many analysis techniques in molecular biology. This report makes repeated reference to several of them, such as PCR, DNA sequencing, and expression analysis, that are explained in this section.

Figure 2-2. Effect of Single Nucleotide Polymorphisms



Source: Courtesy of U.S. Department of Energy Human Genome Program.

2.1.2.1 Polymerase Chain Reaction (PCR)

DNA replication is a process of making two identical copies of DNA from one copy. This process involves a complex series of steps in which large macromolecular complexes separate the two strands of DNA, and by "reading" the sequence of nucleotides on each single strand, they synthesize a new complementary strand of DNA for each, resulting in two identical DNA double helix molecules.

DNA replication is a naturally occurring process in cells; however, researchers can recreate this process in a laboratory through a process called PCR.

When researchers wish to examine a region of DNA in the laboratory, they often require many identical copies of this DNA region for their experiments. Through PCR, DNA can be synthetically replicated in a test tube from a single molecule to billions of molecules within a few hours, enabling researchers to study the molecule. In molecular biology, researchers also refer to this process as amplification, or amplifying the DNA.

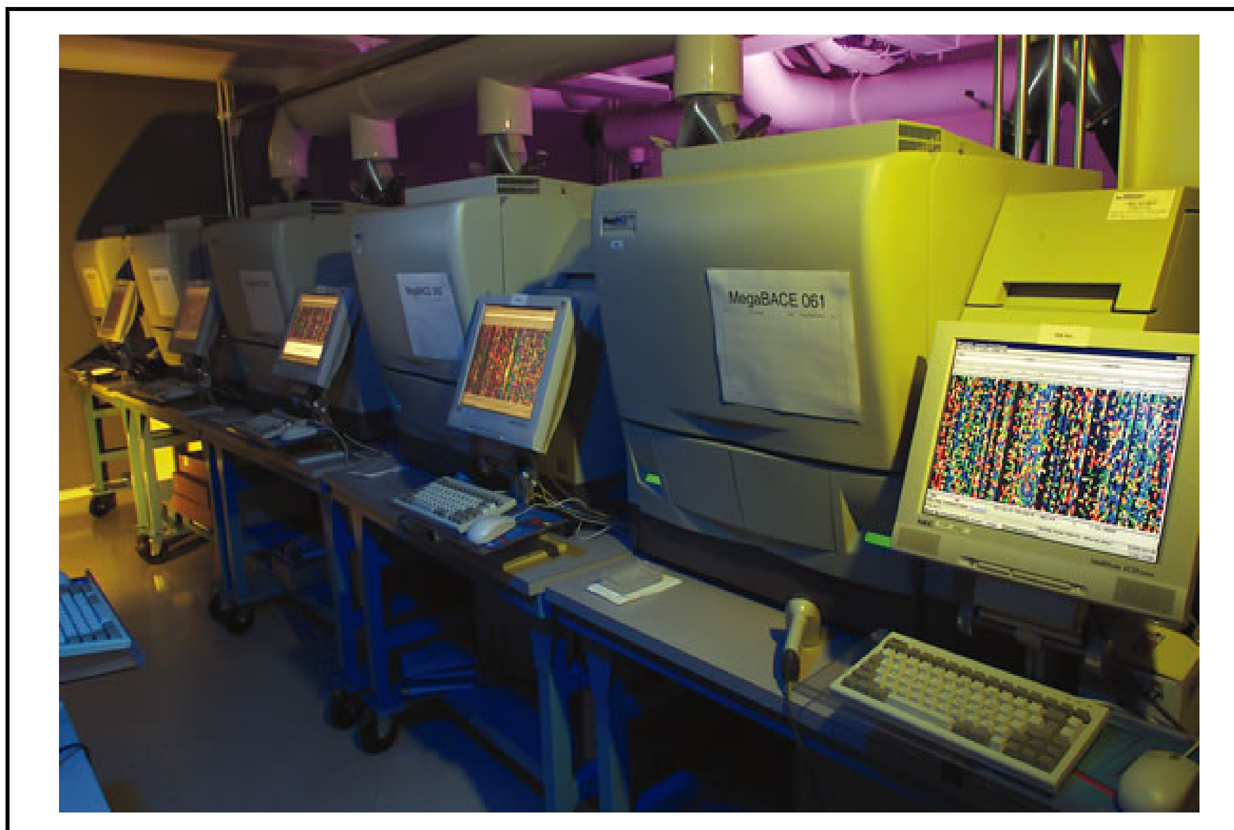
2.1.2.2 DNA Sequencing

DNA sequencing is the process of determining the order of nucleotides, or bases, that make up an organism's DNA. Many genetic analysis techniques take advantage of sequenced DNA. Indeed, because DNA contains the instructions for life, sequenced DNA, especially entire genomes, are among the most valuable tools in the life sciences.

DNA sequencing involves looking at short segments of DNA, typically less than 1,000 bps, and fluorescently tagging the nucleotide molecules in these segments such that they can be visualized, or "read," by fluorescent scanners. This process is performed by automated instruments called DNA sequencers (see Figure 2-3). This report discusses DNA sequencing at greater length in the analyses for Molecular Dynamics' and CuraGen's ATP awards.

Traditional genome sequencing involved a process called chromosome walking, where the genome is broken up into small pieces of greater than

Figure 2-3. DNA Sequencing Operation



Source: Courtesy of U.S. Department of Energy Human Genome Program.

100,000 bps in length. The location within the genome of each of these fragments is mapped. Each of these fragments is then sequenced much the same way we read a book, by starting at the beginning and reading one sentence after another (each sentence less than 1,000 bps). The reading of each sentence depends on reading the sentence before it; hence this process is time consuming, especially for the 3 billion bps human genome.

A new method of genome sequencing, called whole genome shotgun sequencing, emerged in the late 1990s. This process involves breaking the genome into random size fragments, anywhere from 2,000 bps to 150,000 bps, and sequencing only the ends of each of these fragments. When this process is performed repeatedly (millions of times), one will have sequenced the entire genome many times over, and all the sequences will be in sets of two 500 to 1,000 bps reads. Sophisticated computer algorithms are used to piece these segments together based on their overlapping sequences and recreate the entire genome sequence in a relatively short period of time.

DNA sequencing efforts are categorized into two distinct types, each of which has implications for the sequencing approach and analysis requirements:

- *De novo sequencing* is sequencing DNA for the first time where there is no prior knowledge of the sequence. The Human Genome Project was a *de novo* sequencing project.
- *Resequencing* is sequencing DNA when a reference sequence is available from a previous *de novo* effort. Researchers have a reference sequence available and compare a DNA sample with that reference sequence. An example would be comparing a new virus strain with an old one to identify mutations between the two.

2.1.2.3 Gene Expression Analysis and Profiling

Gene expression analysis and profiling provide a complex picture of a cellular state by determining whether genes are turned off or on in a cell, or their expression level, for tens of thousands of genes at a specific time for a specific biological sample.

Expression analysis can be performed on blood, tumors, normal tissue, and many other types of samples. One example of gene expression analysis is comparing the gene expression levels between normal and cancerous tissue to identify genes that are differentially expressed only in the disease state. Not only could this information be used as a

potential molecular diagnostic, but it could also direct new research to enlighten our basic understanding of these disease states.

Expression analysis is predominately performed on DNA or RNA microarrays. Microarrays are small glass or silicon surfaces that are divided up into tens of thousands of "features," where each feature is a small area that contains DNA or RNA sequences that are complementary to a specific gene sequence. These features are also known as "probes."

In a microarray experiment, mRNA is isolated from a cell, amplified, labeled for detection, and bound to the surface of the microarray. The labeled RNA molecules will only bind to the specific features or probes that are complementary to their sequence. The sequence and location of every feature are known; hence, by determining the amount of mRNA for a specific gene that is bound to a specific feature, a quantitative measure of gene activity can be made.

Microarrays are discussed at greater length in the analyses for Affymetrix and Nanogen; both companies used ATP cofunding to significantly enhance DNA microarray technologies.

2.1.2.4 Genotyping

An individual's genotype is the combination of alleles that makes up that individual's specific DNA sequence. In other words, it is the actual genetic code the organism inherited from its parents. Genotyping is the process of determining an organism's specific genetic code. Genotyping may involve genetic fingerprinting, forensic testing, or searching for SNPs by using techniques such as DNA sequencing, diagnostics tests, or DNA microarrays.

When genotyping, researchers are looking for common markers or mutations in the DNA that will allow them to determine the individual's lineage or determine whether the individual has certain markers associated with resistance or susceptibility to a certain disease. Affymetrix, Nanogen, Orchid Cellmark, and Third Wave Technologies all developed technologies with their ATP awards that are commonly employed in genotyping.

Many other types of genetic analysis exist; however, the majority of the technologies discussed in this report are best suited for DNA sequencing, gene expression, and genotyping.

2.1.3 Large-Scale Human DNA Sequencing Projects

The Human Genome Project (HGP) was the single largest and most important DNA sequencing milestone. Other notable projects in human medical science that enlisted the efforts of major sequencing centers around the world include the HapMap project and the Cancer Genome Atlas. Large-scale sequencing efforts, which were originally defined as those seeking to acquire more than 1 million high-quality bps per year, are not limited to humans.

Though this report most frequently refers to human genome sequencing projects, many major mammalian, bacterial, plant, and viral genomes have been or are in the process of being sequenced, especially as costs have fallen significantly and sequencing technologies have improved. Completed maps of scientifically and commercially important genomes include wheat, rice, and soy as well as chicken, dog, rat, cat, and cow.

2.1.3.1 The Human Genome Project

Launched in 1990 by the U.S. Department of Energy and the National Institutes for Health (NIH), the HGP was an international, collaborative research program to map and sequence the entire human genome. The completion of the project in 2003 was a milestone event in science and revolutionized the medical sciences.

The human genome is extraordinarily complex: it comprises 23 pairs of chromosomes, each of which contains several hundred to several thousand genes. In total, the genome consists of 3 billion bps.

Throughout the 1990s, the majority of DNA sequencing was focused on the HGP effort to map the entire human genome. In practice, the process of DNA sequencing involves analyzing specific segments of DNA to determine the order of the bases therein. However, the process of sequencing and analyzing the human genome's 3 billion bps was a significant impediment to the HGP (see Figure 2-4 on pages 2-12 and 2-13).

When the HGP began it was originally expected to be completed in 2005. At the project's outset, the process of determining the DNA sequence of even very small subsets of the genome was painstakingly slow. Technologies had yet to be developed that could sufficiently automate the process, but the project was launched with full anticipation that new technologies and organizational strategies would emerge over time to meet the estimated completion schedule (Hodgson, 2000). It was

widely recognized that a 100- to 1,000-fold improvement in throughput would be required to meet the projected HGP completion deadline (Hunkapiller et al., 1991).

Large-scale sequencing efforts ultimately benefited significantly from increased automation in sample preparation, new sequencing technologies, and advances in organizational strategies (Smith, 1993; Collins, 1999). ATP-awardee Molecular Dynamics used ATP cofunding to develop the first high-throughput DNA sequencer and spurred other sequencer manufacturers to quickly innovate to match its milestone achievement.

A draft sequence of the human genome was completed in 2000, ahead of schedule, in large part because of the introduction of new DNA sequencers that enabled scientists to sequence larger volumes of DNA more accurately and more quickly (Collins, 1999).

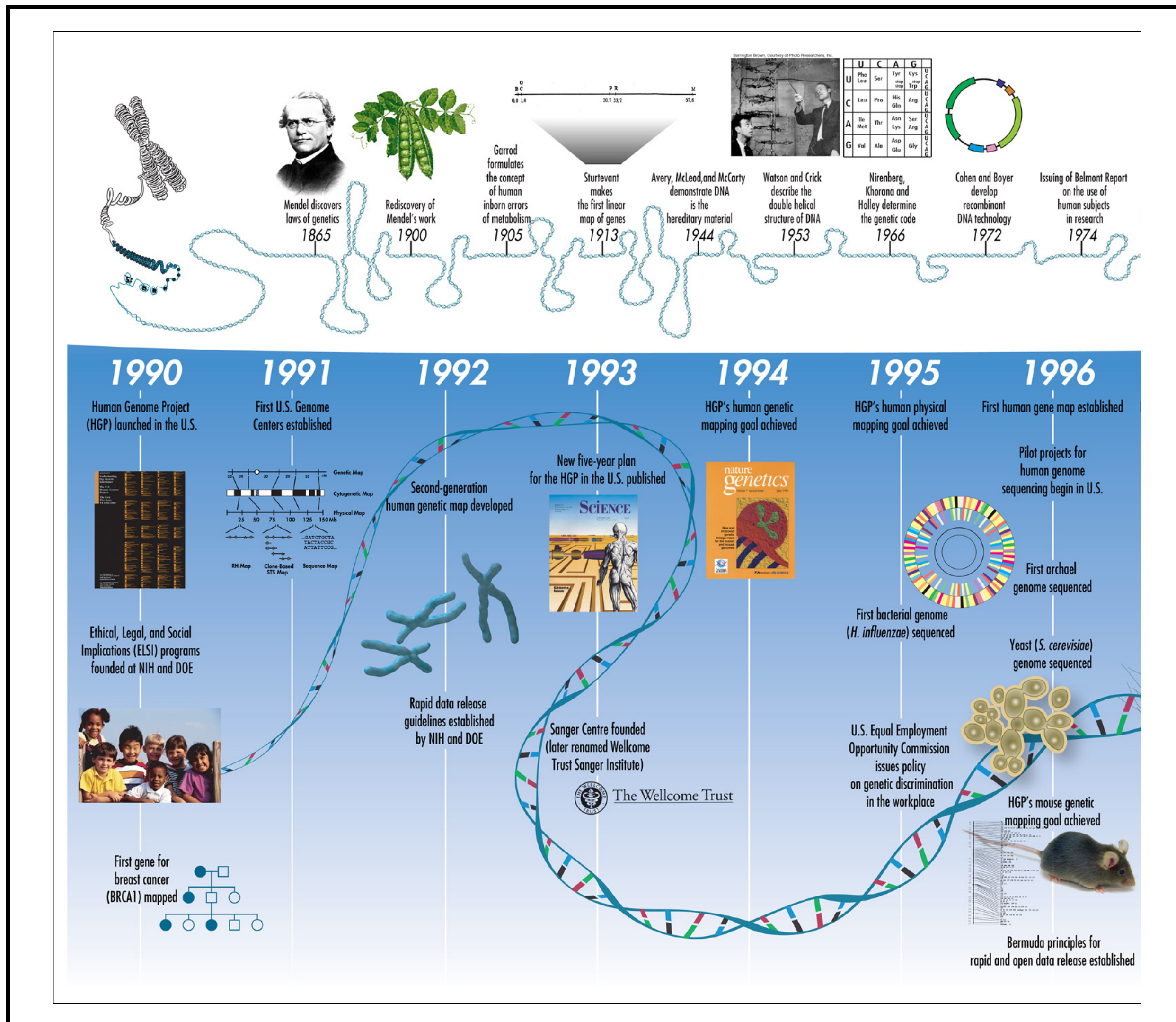
On June 26, 2000, President Bill Clinton; Francis Collins, Director of NIH's National Human Genome Research Institute; and Craig Venter of Celera Genomics announced the first working draft of the human genome. The working draft had 90% of the DNA sequence. The final draft, covering 99% of the human genome, was completed in 2003. It was anticipated that the entire budget for the project would be $3 billion in real 1991 dollars, but the project was completed at a cost to taxpayers of $2.7 billion.

2.1.3.2 The International HapMap Project

The International Haplotype Map (HapMap) Consortium was formed in 2002 by some of the world's top genetic researchers to create a map of human genetic variation (Rotman, 2003). This map would be based on the observation that when SNPs are located close to each other on the DNA molecule, they tend to be inherited together. These regions of linked variants are known as haplotypes (HapMap, 2002).

The goal of the HapMap project was to create a map of these haplotypes so that researchers could more easily identify and locate genetic variations in individuals. HapMap researchers believed this would accelerate the search for genetic causes to common diseases such as asthma, cancer, diabetes, and heart disease (Thorisson et al., 2005).

Figure 2-4. History of the Human Genome Project

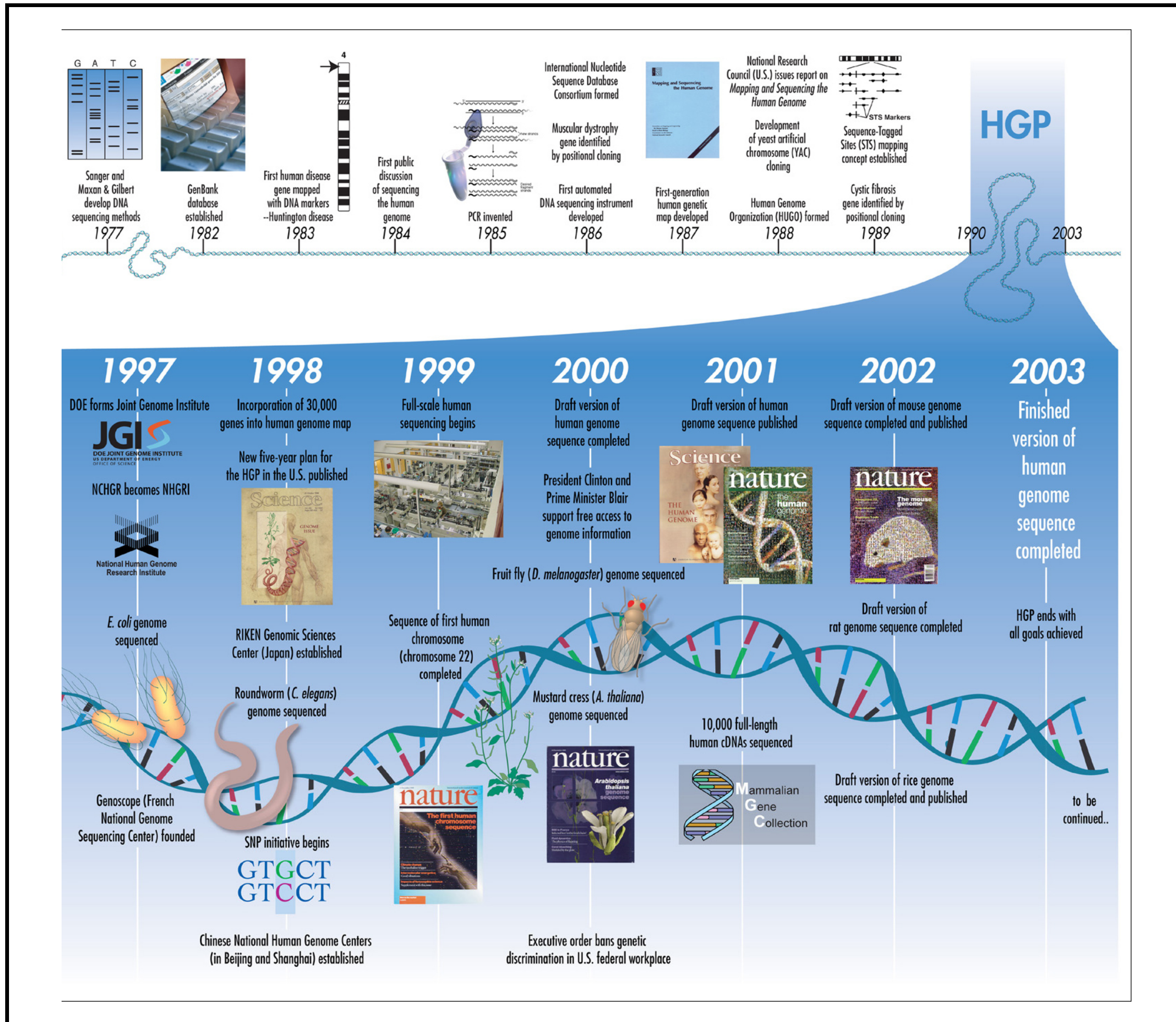


Source: National Human Genome Research Institute.

The HapMap Project research was expected to last 3 years and received $100 million in initial funding from a variety of private groups (such as the Wellcome Trust and the SNP Consortium) and public entities (such as the Chinese Ministry of Science and Technology and NIH (NHGRI, 2002).

HapMap researchers collected DNA samples from 270 individuals of three distinct ancestries—African, Asian, and European—to construct its haplotype map. These samples were divided among 10 individual research centers for genotyping. The 10 researcher centers were located in Canada, China, Japan, the United Kingdom, and the United States (NHGRI, 2006*a*).

Figure 2-4. History of the Human Genome Project (continued)



By early 2005, HapMap researchers had largely completed a first draft of the haplotype map. The project's rapid success helped researchers obtain an additional $3.3 million boost in public-private funding. This money was used to fund a more ambitious "second phase" of the project, where researchers would attempt to genotype even more SNPs in the samples they collected.

Twenty-five percent of the project was completed using Third Wave Technologies' ATP-cofunded diagnostic tests.

In October 2005, the project published an initial version of the HapMap that only included the 1.3 million SNPs genotyped during the "first phase"

of the project (Davies, 2005). The following year, HapMap released an expanded version of the HapMap that included an additional 4.6 million SNPs that were genotyped during the second phase of the project (Davies, 2006). As a result of the HapMap project, a total of 6 million SNPs were discovered and became publicly available. This represented a two-fold increase in the number of SNPs catalogued in the NIH's public SNP database at the project's inception (NHGRI, 2006a).

2.1.3.3 The Cancer Genome Atlas

The Cancer Genome Atlas is perhaps the largest and most significant genetic research endeavor since the HGP. The goal of the Cancer Genome Atlas will be to collect 12,500 tumor samples and systematically search the genetic material of each sample for common mutations. After this information is collected, it will be used to develop a comprehensive Web resource that would describe the genetic "fingerprints" of specific cancer types. This resource would be known as the "Cancer Genome Atlas" (Kaiser, 2006).

Advocates of the Cancer Genome Atlas believe that creating genetic profiles of various cancers will help accelerate advancements in cancer diagnosis, treatment, and prevention (TCGA, 2006a). Such developments could result in significant benefits for cancer patients both in terms of increased likelihood of survival (cancer currently kills 564,000 Americans each year) and avoided treatment expenditures (Weiss, 2005).

The project is expected to cost up to $1.5 billion over 10 years. To ensure that a full-scale effort is feasible, the National Cancer Institute and the National Human Genome Research Institute launched a $100 million pilot project in December 2005 (Weiss, 2005).

The pilot project will have to address a number of technical issues before the full-scale project is approved. These challenges include

- improving genome characterization and DNA sequencing technologies,
- developing standards and quality control criteria in bio-specimen handling,
- improving data analysis accuracy, and
- evaluating the utility of the data produced by genomic analyses of tumor bio-specimens (TCGA, 2006b).

2.1.3.4 Other Significant Efforts in Human Genomics

Many genomic research initiatives are being pursued around the world. These projects range widely in terms of size, subject, and intended application, making an exhaustive list unwieldy for this report.

For example, the Sanger Institute's Cancer Genome Project is devoted to identifying genes critical in the development of cancer. As part of its Cancer Gene Census initiative, the project has already catalogued nearly 400 genes that are causally implicated in cancer. Project researchers hope that their efforts will foster better cancer diagnostics and therapeutics by providing researchers with a better understanding of cancer's genetic roots.

Table 2-1 provides a description of this project and a number of other completed and ongoing human genomics projects.

2.1.3.5 Significant Sequenced Genomes

Genomic research projects have done much to increase the amount of genetic information available to researchers. This fact is evidenced by the growth of data freely available in public databases such as GenBank.

The GenBank database is an open-access, annotated collection of nucleotide sequences and their protein translations. This database was created in 1988 and is maintained at the National Center for Biotechnology Information (NCBI) as part of an international collaboration with the European Molecular Biology Laboratory Data Library from the European Bioinformatics Institute and the DNA Data Bank of Japan (NCBI, 2004).

According to the 2004 *NCBI Handbook*, the amount of information contained in GenBank doubles every 10 months (NCBI, 2004). Today, GenBank has grown to contain information on over 5,500 species. Whole genome sequence data, a small subset of the entire database, have been collected and deposited for 422 different species of plant, animal, fungi, bacteria, and protozoa. As of this writing, whole genome sequence information is available for several genomes important for medical research, including humans, lab rats, and fruit flies. Sequence information like this can be used by researchers to better understand the genetic roots of disease and potentially develop new therapeutics.

Table 2-1. Sampling of Major Human Genomics Research Initiatives

Project Name	Date Started	Country of Origin	Description
The SNP Consortium	1999	United States	The SNP Consortium was established as a collaboration of several companies and institutions to produce a public resource of SNPs in the human genome. The initial goal was to discover 300,000 SNPs in 2 years, but more than 1.4 million SNPs have been released into the public domain by the end of 2001 (Thorisson and Stein, 2002).
Cancer Genome Project	1999	United Kingdom	Launched in 1999 at the Sanger Institute, the project will use the human genome sequence and high-throughput mutation detection techniques to identify genes critical in human cancers (TCGP, 2006).
Knockout Mouse Project	2005	United States	Knockout Mouse is a NIH-funded project to build a comprehensive and publicly available resource of knockout mutations in the mouse genome. Researchers could use this resource to develop knockout mice that better model human diseases (NHGRI, 2006b).
ENCODE Project	2006	United States	Encyclopedia of DNA Elements (ENCODE) is the name of a public research consortium launched by NIH in September 2006. The purpose of this project is to identify the elements of the human genome sequence that code for proteins (called functional genes) (NHGRI, 2006c).

2.2 TECHNICAL BARRIERS TO GENERIC MOLECULAR DIAGNOSTICS TECHNOLOGIES

The techniques and projects described in Section 2.1 were made possible by the accelerated pace of our understanding of molecular biology and the sophistication of tools that gather and harness that knowledge. In the early 1990s, genomic analysis techniques were cumbersome; in fact, as the main body of this report discusses, research sponsored by ATP in the mid-1990s triggered exponential gains in the productivity of these techniques while simultaneously reducing their costs.

In addition to research applications, molecular diagnostics tools for health care were envisioned for

- *point-of-care* locations, such as doctors' offices, to offer personalized therapies (where low cost, portability, and speed are important);

- *point-of-need* locations, such as hospital emergency rooms (where speed and accuracy are important); and
- *point-of-diagnosis* locations, such as medical and public health laboratories running standardized tests (where economies of scale are important) (Harbert, 2005).

The challenge in the 1990s was that the technologies had yet to be developed for what was expected to be the future of medicine. There were many technical barriers to point-of-care diagnostics because of the difficulty in collecting and carefully handling samples, the variety of sample types, and the need for strictly controlled environments. In point-of-care settings, patients receive diagnoses shortly after providing the sample. The doctor or clinician must be able to take a patient's sample, introduce it to the device, conduct the analysis, and provide a diagnosis within a few moments.

Accordingly, the point-of-care market's usability, reliability, and accuracy requirements presented many technical hurdles, including the following (Abramowitz, 1996):

- **Miniaturization:** Several processes needed to be miniaturized, including sample preparation, chemistry, the handling of liquids, and the machining of the tool. There was little work in advance of the ATP projects to address many of these barriers.
- **Assay capabilities:** New technologies for DNA diagnostics, like miniaturized sequencers and microarrays, were discussed, but few technologies were commercially available.
- **Amplification:** The process of performing real-time PCR to amplify the sample DNA would also need to be miniaturized. As discussed later in this section, sample preparation was one of the most significant obstacles. Technologists aspired to develop new tools that would circumvent the amplification process entirely.
- **Detection:** Detection techniques would need to be extraordinarily accurate, precise, and sensitive to extract the data needed for analysis from the analyzed sample.
- **Data processing:** New information technologies for bioinformatics had yet to be developed, particularly tools for data analysis and management that would quickly analyze and produce results and diagnoses.
- **Integration:** All the mechanical, chemical, and robotic systems would need to be integrated and automated into accurate, mobile, rapid tools.

The point-of-care market's needs required that systems eliminate all these barriers at a lower cost and greater accuracy than the processes that the systems would supplant if they were to be widely adopted. Even

the most capable technologies in the early 1990s had to be performed by expert staff in a strictly controlled environment with dedicated facilities, using large volumes of equipment and processes that took several hours.

Molecular diagnostics was highly labor intensive and lacked the automation and integration of all the steps surrounding the actual analysis (McGlennen, 2001). Reducing costs, enabling portability, and meeting stringent quality requirements were critical success factors.

The market's needs included research into technologies that would integrate or eliminate the time-consuming steps in sample preparation. For diagnostic tools to be effective and for the results to be reliable, the sample must be adequately prepared, eliminating contaminants without destroying the DNA under investigation.

2.3 MARKET BARRIERS TO GENERIC MOLECULAR DIAGNOSTICS TECHNOLOGIES

During the mid-1990s, the biotechnology sector was still a fledgling industry, and the pharmaceutical industry and the investment community expected that the large suppliers of equipment to pharmaceutical companies would be the major players in the field. These included many of the largest companies in medical diagnostics, such as Abbott, Boehringer Mannheim, Miles, Baxter, Beckman, Becton Dickenson, Ciba-Geigy, Johnson & Johnson, Eastman Kodak, and Bio Rad, that were either acquiring technology by buying companies, forging alliances, or supporting in-house R&D. However, these companies did not emerge with winning technologies, scientific leadership, or strategies (Silverman, 1995).

The firms that succeeded at delivering on the promise of DNA diagnostic services and devices were small start-up biotechnology companies founded by geneticists, molecular biologists, engineers, and their colleagues (Silverman, 1995). These specialists had the combined technical savvy and application insight to develop sophisticated tools outside the limitations of large corporate R&D divisions.

Over the course of this analysis, RTI learned that many of the most notable molecular diagnostics firms in business today were unable to acquire venture capital financing. Federal technology development and application awards, of which ATP was the largest, provided the funding

that these firms needed to continue their core research, according to experts interviewed by RTI.

The HGP was raising the possibility of point-of-care diagnostic tools, but corporate R&D programs were failing to provide the scientific leadership required to make that possibility a reality (Silverman, 1995). It was not until the late 1990s that larger, entrenched companies became players in this industry, and often they became so through acquisitions of or strategic alliances with start-ups, many of which were funded by ATP.

2.4 ATP'S TOOLS FOR DNA DIAGNOSTICS PROJECTS

ATP's Tools for DNA Diagnostics focused program created public-private partnerships to hasten the development and commercial introduction of advanced technologies to enable cost-effective and efficient methods for sequencing, storing, and interpreting DNA sequences (ATP, 2004).

As huge publicly funded projects like HGP acquired massive volumes of genetic data, few generic tools had been developed that could translate that resource into easy-to-use, effective, and efficient technologies that could rapidly analyze DNA. The focused program and other ATP projects in DNA diagnostics sought to overcome the technical and market barriers to new DNA diagnostic technologies through public-private partnerships.

ATP launched its first competition under its Tools for DNA Diagnostics focused program in 1994. It would be 3 more years before investors would begin to invest heavily in the biotechnology sector.

ATP solicited participation from industry, academia, and government to help scope the technology goals of the proposed focused program. Several academics and representatives from start-up biotechnology companies submitted white papers and attended a conference where the papers were presented and the proposed program was discussed. The white papers presented the technologies and concepts that experts believed were yet to be developed but were necessary to enable practical applications of genomics.

The focused program and other projects in this field aimed to assist biotechnology, pharmaceutical, and analytic instrument manufacturers in pursuing pioneering research into new technologies, methods, and instruments that would leverage the enormous opportunity presented by advances in genomics.

The United States stood to benefit a great deal from the effect such advances would have on health care, forensics, biomedical and biological research, drug design, animal husbandry, and agriculture, among other industries (ATP, 1999).

In all, 42 Tools for DNA Diagnostics projects were awarded, either through one of the DNA diagnostics competitions or a general competition. ATP committed nearly $137.5 million from 1995 through 2006 to the projects listed in Appendix A. The private sector provided the remaining $119.4 million of the $256.9 million investment.

2.5 DIFFERENTIATION OF TECHNOLOGY PLATFORMS IN THIS REPORT

In molecular diagnostics, different technology platforms, such as DNA microarrays or DNA sequencers, can be used for the same application. In fact, many of the technologies in this report could be adapted to perform gene expression analysis, genotyping, and DNA sequencing.

The end users of the technologies, which are predominantly researchers, clinicians, and lab technicians, select the platform that will best deliver the breadth and depth of data required. The choice of platform depends on the balance between the depth of information required, the number of samples, and logistical considerations. The information requirements, such as the volume of data, number of results, and speed of analysis, present technical constraints that must be met. Operationally, researchers also consider time, ease of use, variable costs, and fixed costs, including overhead. The costs incurred will depend on the amount of information required and the expense of the platform (Abramowitz, 1996).

Although researchers could adapt many of the technologies to any of these three applications, for some platforms that process would be too inefficient and costly given the results.

ATP sought to cofund innovative, early-stage technologies that otherwise might not have emerged. The heterogeneity of platforms and technologies better suited for some projects than others is the result of ATP's practice of funding competing technologies proposed by diverse industry players. ATP funding helped move these technologies from the conceptualization stage through prototyping.

Table 2-2 characterizes the platforms through which the companies commercialized their ATP-cofunded research. Included in the table are the fixed cost, variable cost, and data output per sample for each platform, relative to one another. In addition, it presents the primary applications and markets for these technologies.

2.5.1 Applying the ATP-Cofunded Technologies in DNA Sequencing

DNA sequencing is characterized by a high fixed cost investment in an instrument and low variable consumable costs. Because of the large number of DNA fragments to be sequenced, end users accept a high fixed investment to save on ongoing costs, especially in *de novo* sequencing. Molecular Dynamics' DNA sequencer was developed with this market in mind.

Years after its project ended, CuraGen's research also helped its 454 Life Sciences subsidiary develop a DNA sequencer for the resequencing market. It does not read DNA fragments long enough to be effective in

Table 2-2. Comparison of Molecular Diagnostics Technology Platforms

Company	Technology Platform Type	Primary Application	Variable Cost	Fixed Cost	Data/ Output Sample	Throughput	Market
Affymetrix	DNA microarrays	Gene expression, genotyping	High	Medium	High	Medium	Research
CuraGen	Analytical services	Gene expression, sequencing	High	Low	High	Medium	Drug discovery
454 Life Sciences	Sequencing Instrumentation	Sequencing	Low	High	Low	High	Research
Molecular Dynamics	Sequencing instrumentation	Sequencing	Low	High	Medium	High	Research
Nanogen	DNA microarrays	Genotyping, gene expression	Medium	Medium	Medium	Low	Clinical diagnostics, research
Orchid	Diagnostic tests and services	Genotyping	Medium	Low	Low	Medium	Forensics, services
Beckman Coulter	Genotyping instrumentation	Genotyping	Low	High	Low	Medium	Research
Third Wave Technologies	Diagnostic tests	Genotyping, gene expression	Low	Low	Low	Medium	Research, clinical diagnostics

Source: RTI estimates.

Note: Cost, data output, and throughput comparisons are for quantitative comparison only. The technology platforms and thus their attributes differ by application focus. No usage recommendations are implied, nor should be inferred.

most *de novo* sequencing applications, but it generates large numbers of short sequences very quickly.

Affymetrix's or Nanogen's DNA microarrays can be used for resequencing, but researchers incur a high variable cost for the arrays and the chemicals needed for the analysis. They would not be used in a large sequencing effort, but perhaps in a resequencing effort to compare one genetic sequence with another on an ad hoc basis.

2.5.2 Applying the ATP-Cofunded Technologies in Gene Expression Analysis and Profiling

Gene expression is a large portion of the molecular diagnostics market, and many companies have developed tools for this market. At the high end of the market, DNA microarrays, such as those produced by Affymetrix, dominate. They have the highest variable cost because they are disposable but also the highest data output per sample analyzed.

These tools are especially useful in research applications with high data needs.

Third Wave is also in the gene expression market but develops test tube diagnostic tests that investigate DNA samples to quickly ascertain whether a known gene is active in the sample. These tests are fast, low-cost, and easy-to-use tools for the clinical market.

CuraGen was a player in this area shortly after their ATP project ended; however, they now apply their ATP technology in their internal biopharmaceutical R&D program.

2.5.3 Applying the ATP-Cofunded Technologies in Genotyping

As with gene expression, microarrays are most prevalent in the high-end, research portion of the market. Orchid offers genotyping services at a moderate variable cost to end users who do not wish to purchase an instrument that automates the process. The services are frequently used in paternity testing and forensics. One genotyping instrument sold by Beckman Coulter contains the technology Orchid developed during its ATP projects. Affymetrix, Third Wave, and Nanogen all developed technologies that could be used in genotyping.

2.6 ATP'S ENDURING IMPACT ON MOLECULAR DIAGNOSTICS

ATP's Tools for DNA Diagnostics projects have an enduring impact on molecular diagnostics. The eight projects profiled in this report illustrate the diversity of technology platforms that ATP supported. ATP sought to support innovative, early-stage technologies that otherwise might not have emerged. The heterogeneity of platforms and technologies better suited for some projects than others is the result of ATP's practice of funding competing technologies proposed by diverse industry players.

The breadth and depth of this support multiplied by time helped supply researchers with tools like advanced microarrays and high-throughput DNA sequencers and techniques that are now considered indispensable to modern science. Furthermore, industry insiders credit ATP with shining an early light on start-up biotechnology companies, supporting core technology R&D, and helping build a foundation on which an industry emerged.

These tools are now used in environments as diverse as pharmaceuticals, agrichemicals, biotechnology, and public health, with applications in the life, food, and plant sciences, including

- human disease research,
- genetic analysis,
- pharmaceutical drug discovery and development,
- pharmacogenomics,
- molecular diagnostics,
- plant breeding,
- food testing,
- pathogen identification, and
- consumer genetics.

The need for improved DNA sequencing technologies was apparent during the earliest years of the HGP. Determining genetic sequences was costly and time consuming; even the most well-equipped laboratories, operating state-of-the-art instrumentation, were only able to determine one genetic sequence every few days (Regis, 1995).

Experts interviewed by RTI and many published articles agree that the introduction of high-throughput CAE sequencing by ATP awardee Molecular Dynamics was a watershed event that accelerated the HGP,

scientific discovery and the downstream medical innovations that the completed sequence of the human genome enabled (International Human Genome Consortium, 2001). This was the equivalent to DNA sequencing's industrial revolution.

When the HGP began, the cost to sequence one base pair ranged from $5 to $10. All along, researchers anticipated that technical and organizational advances would enable the project to be completed on time. They also believed that the cost per sequenced base would drop from $2 to $5 per finished base pair to $0.50 or less per pair (Hodgson, 2000). Now that cost is $0.01.

Having the finished sequence of the human genome enables downstream innovations in microarrays and other technologies because they require the reference sequence that Molecular Dynamics accelerated. These data make SNP analysis, genotyping, gene expression, and resequencing possible.

ATP had an impact on the technologies used in medical research and clinical diagnostics beyond DNA sequencing. Affymetrix's and Nanogen's DNA microarrays are more effective and efficient and are supported by a more robust assay system as a consequence of ATP awards. The acceptance of microarray technologies, and the research they enabled, was accelerated by ATP support for the entire microarray research solution, including assay protocols, software, and equipment in addition to more robust microarrays.

Affymetrix leverages mapped genomes to create diagnostic tools that in turn yield invaluable information about the presence of genes, genetic mutations, and the efficacy of medical therapies for patients of varying genetic backgrounds.

Microarrays now facilitate research and discovery in cancers, cystic fibrosis, HIV, and many other chronic ailments and infectious diseases. Microarrays can also be used with whole and/or partial gene sequences for humans, mice, cats, dogs, and cows. Microarrays are also produced to study bacteria and insects (e.g., fruit flies, mosquitoes) and vegetation (i.e., rice, corn, poplar trees, and sugar cane).

CuraGen's ATP-cofunded research not only led to a drug discovery platform, but also to a next-generation DNA sequencing company that the World Economic Forum named one of 47 technology pioneers. CuraGen established a subsidiary, 454 Life Sciences, Inc., in part to

pursue technology solutions to the microfluidics problems it encountered during the ATP project.

The importance of ATP cofunding in supporting these developments was voiced by CuraGen cofounder and 454 Chairman, Dr. Jonathan Rothberg, in a 2004 interview with *Nature BioEntrepreneur*, in which he was quoted as saying that "the ATP [award] led to CuraGen's success and indirectly to a new company" (Surendran, 2004).

More broadly, ATP's support validated a new industry and moved new biotechnologies from the periphery to the spotlight. Representatives from Affymetrix and the former Molecular Dynamics believe that the success of the joint venture (JV) and ATP's support was "a shining light" that encouraged other firms "to go for it" and develop and market technologies for what was becoming the pharmacogenomics and genomics marketplace. In addition, Affymetrix's ATP-supported software research spawned an "ecosystem of companies" that serves the IT needs of an industry.

Many of the leaders in the molecular diagnostics field were ATP awardees that were afforded the opportunity to further invest in their technology because of the support they received. Some of these technologies might not have even survived at all without ATP. The founders and principal investigators at MT, Orchid, CuraGen, Nanogen, and Third Wave all expressed the importance of the ATP funding in supporting very small companies in a new industry. A good number of ATP-supported start-ups in this field were founded by former academics with ideas and technical acumen, but little access to capital.

One industry expert believes that the technologies that will revolutionize health care between 2010 and 2020 were pioneered in the 1990s. Ultimately, ATP's Tools for DNA Diagnostics projects accelerated the rate of scientific discovery. The introduction of ideas and prototypes that are next-generation concepts germinated during the projects, such as 454's sequencers, attest to the enduring impact of ATP's technology development programs.

3 Methodology

This study employed established theory in the economics of technology innovation and diffusion to estimate the benefits of technologies developed during three projects to provide a conservative, lower-bound estimate of the economic performance of all 42 Tools for DNA Diagnostics projects. Because of resource limitations, the other five projects profiled in this report were analyzed qualitatively to illustrate areas of economic and social impact outside of the case studies.

The case studies—two MT/Orchid Cellmark projects and the joint Affymetrix-Molecular Dynamics project—are completed projects for which avenues to calculate benefits were the most clear. Other factors that influenced these projects' selection were the following:

- Preliminary qualitative assessments by ATP and RTI suggested that the economic benefits were among the largest for the 42 projects.
- Products incorporating the projects' technologies have been commercially available since the mid- to late-1990s.
- End users are familiar with the technologies and the technologies' applications and advantages relative to defender technologies—the tools and processes that the ATP-cofunded innovations supplanted.

The theoretical approach outlined in this chapter reviews the valuation of economic benefits from technological innovations, including what constitute economic benefits and how those benefits are calculated. The approach involved a series of counterfactual analyses that were based on RTI's established analytical process that links hypotheses about the impact of ATP funding to relevant technical and economic metrics. These metrics then inform processes for collecting data and estimating

measures of economic benefit. Data were collected from interviews with companies, industry experts, and technology adopters, as well as from literature reviews of the scientific, trade, and scholarly press.

3.1 ESTIMATING ECONOMIC BENEFITS FROM TECHNOLOGICAL CHANGE

Technological change generates economic benefits through the creation and use of entirely new goods and services and by improving existing products. Truly novel goods increase the overall satisfaction of purchasers by delivering experiences previously unobtainable; by improving buyers' levels of nutrition, comfort, security, or happiness; and by offering additional variety. Improved products generate benefits by providing a given level of service at a lower opportunity cost to the consumer, by offering higher quality or a higher level of performance, or by delivering a broader array of services.

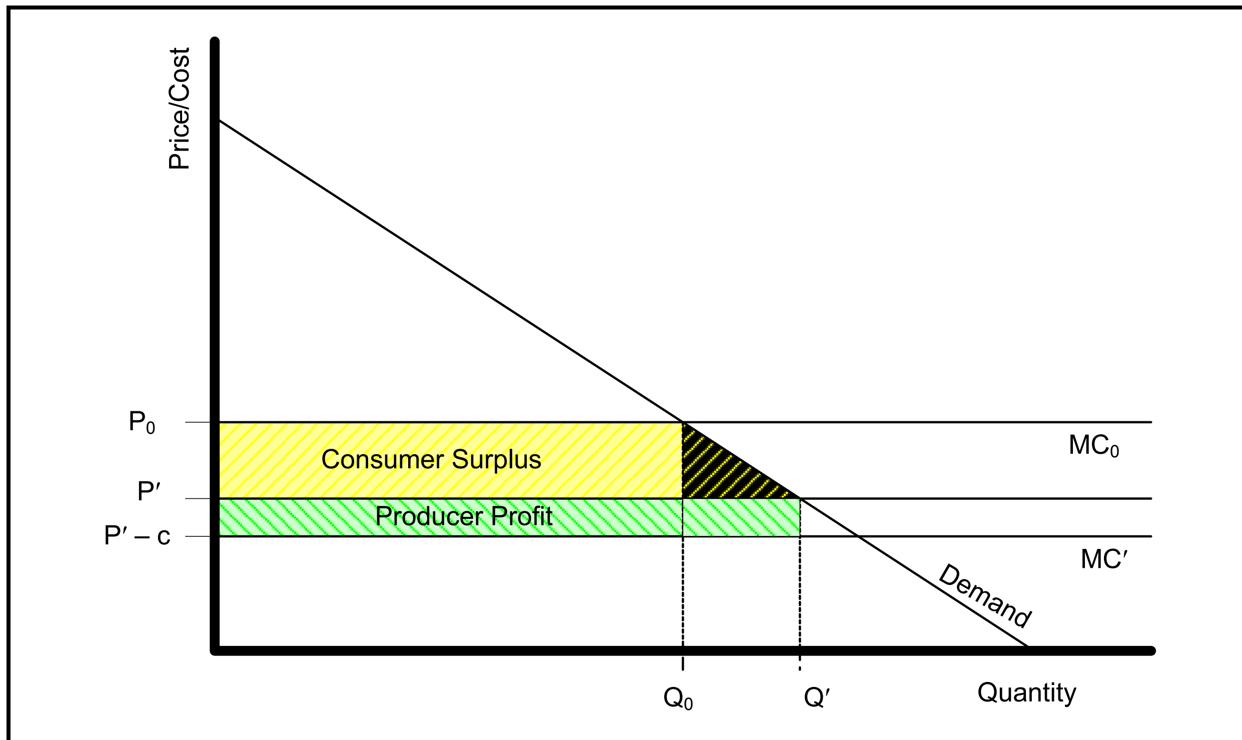
A variety of analytical methods can be used to measure these types of improvements. The degree of complexity or sophistication depends on the difficulty of each specific measurement task. For new goods and improvements in multidimensional products and services, discrete choice models are often used (Berry, Levinsohn, and Pakes, 1995; Trajtenberg, 1989). If one or more dimensions of quality or performance are improved, price index (Austin and Macauley, 2000) or hedonic modeling approaches (White, 2000) can be used.

When cost or price reduction to the innovation's end user is the primary result of the improvement, a straightforward algebraic approach can be used, such as that described in Mansfield's classic paper on rates of return from industrial innovations (Mansfield et al., 1977).

Figure 3-1 illustrates Mansfield's approach. Under the assumption of perfect competition, profit-maximizing producers set price (P) such that it is equal to the marginal cost (MC) of production. Initially the market is at equilibrium where the quantity demand and the quantity supplied are equal for a price P_0 and quantity Q_0.

A technological innovation that affects an input or production process lowers the producer's marginal cost of production from MC_0 to MC'. Because the firm faces a downward-sloping demand curve, where consumers demand greater quantities at lower prices, it will reduce its

Figure 3-1. Mansfield's Approach for Evaluating the Benefits of Technological Change



price. If the producer reduces its price from P_0 to P′, output and sales will increase from Q_0 to Q′, all other things equal.

If the producer is able to set price above its marginal cost of production it is able to appropriate returns from the innovation. Figure 3-1 presents this graphically where the price consumers pay is illustrated by P′, but the marginal cost of production is MC′, which is the new price P′ less the cost savings resulting from the innovation (line P′ – c).

The economic benefits from the innovation include all of the shaded areas in the figure, which, taken together, represent the total gain to society from the innovation. The individual shaded areas represent the following:

- **Consumer surplus:** If the producer passes savings from the innovation to consumers through lower prices, reducing the price from P_0 to P′ creates a surplus for its customers.
- **Efficiency gains:** The small, most darkly shaded triangle represents the gains society accrues from more efficient allocation of resources.

- **Producer surplus (profit):** If the innovating firm can set a price above its costs, it can earn a profit on each unit sold, realizing private benefits from its actions. The producer surplus, or profit, is represented by the shaded area between P' and $P' - c$.

Most ATP projects yield new technologies that are later embodied in commercial products and services that create a cost, quality, or speed impact on the commercial, research, or industrial customers that purchase them, just as in the firms that Mansfield studied in the 1970s. Measures of quality and speed (technical measures) can be translated into cost measures by monetizing technical measures with dollar-denominated economic ones.

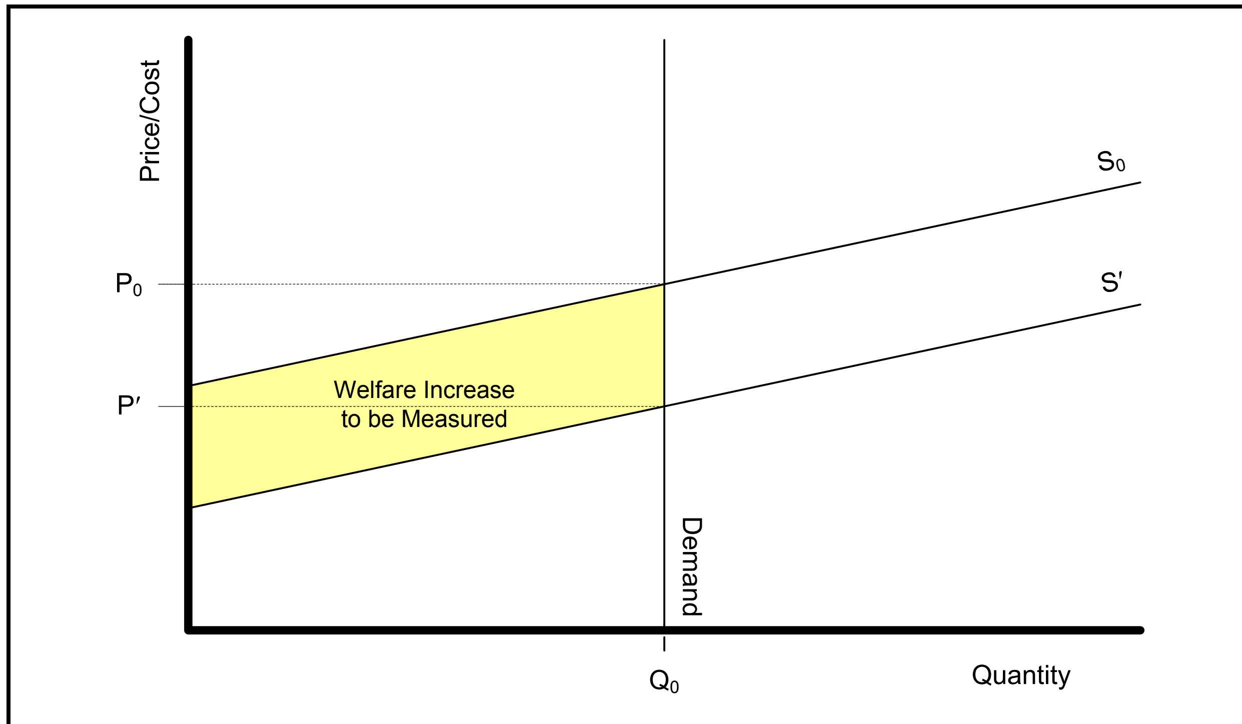
Analysts estimate the benefits from the innovation by constructing a counterfactual scenario and comparing it to the actual costs incurred by the adopting firms. In conventional product and service markets, the innovation-induced price reduction will cause an increase in the quantity supplied in the final product market, either through expansion of the firm or market entry.

Figure 3-2 illustrates such an example, with a slightly more realistic upward-sloping supply curve replacing Mansfield's assumption of constant marginal cost. A vertical demand curve holds demand constant, permitting the benefits from the innovation to be calculated as the difference in price (or cost) multiplied by the number of products sold or quantity of services demanded.

The equilibrium with the defender technology—the technology that the ATP-cofunded innovation supplants—in Figure 3-2 shows the price on the supply curve at P_0 and quantity fixed at Q_0. Substitution of products containing the new technology allows a reduction in costs to the supply curve S', with price falling to P' in equilibrium.

The economic benefit from the innovation is represented by the shaded area between the supply curves, with quantity remaining constant. This can be shown algebraically to be equal to $(P_0 - P')\, Q_0$. Thus, to operationalize this type of model, RTI needed only to estimate the economic benefits for each product or service unit and multiply those savings by the entire affected population.

Figure 3-2. Simplified Equilibrium Diagram of a Fixed-Quantity Market for Goods and Services in the Case of Cost-Reducing Technological Change



3.2 PUBLIC VERSUS PRIVATE BENEFITS AND COSTS

The concept of public and private costs and benefits from new technologies concerns how the development of new technologies is funded and who benefits from the technologies' use, either directly or indirectly, in the form of lower costs or prices. Simply stated, public benefits and costs accrue to everyone except the innovator, and private benefits and costs accrue only to the innovators. When summed, these four impact categories equal the social benefits discussed in the preceding section.

The distinction between public and private benefits and costs, producer surplus, and consumer surplus is made because this report presents performance measures of the public investment in ATP projects—public benefits compared to public costs:

- **Public benefits** are the sum of incremental past and future resource savings consumers reap from adopting a new technology, with consumers broadly defined as those who did not directly invest in the R&D of that technology. Public benefits

are presented net of consumers' cost to adopt or install the new technologies. Consumer surplus is the increase in value consumers gain by employing the new technology.

- **Private benefits** are the past and expected future profits for innovators that invested in the R&D. Private benefits are those incremental returns that accrue to the innovating firms, as a result of setting prices above their total average costs.
- **Public costs** are those costs borne by society for a technology's development; in this analysis, public costs would be ATP's technology development awards.
- **Private costs** are the innovator's R&D costs. In this analysis, these are the private companies' own R&D funds invested in their ATP projects. Project costs may also include additional investments innovators make to complete development and bring the technology to market.

Profit-maximizing companies will only be willing to innovate if they anticipate, *ex ante*, that they will be able to make a return that compensates them for expenditures on R&D and for acceptance of technical and economic risks. For innovating firms in highly competitive markets, however, their *ex post* realization of profits may be small or even nonexistent. This is most likely if their rivals can quickly imitate their innovations and drive prices down to zero-profit, equilibrium levels.

3.3 DEVELOPING HYPOTHESES ABOUT THE IMPACT OF ATP FUNDING

There is a large body of literature that discusses potential economic benefits that may accrue from governmental support of new technology development. In previous studies for ATP, RTI outlined a number of these impacts and provided quantitative estimates of several types of ATP contributions (White and Gallaher, 2002; White and O'Connor, 2004). In this study, RTI developed hypotheses about three specific types of benefits: correcting for missing markets in the provision of high-risk funding to small and start-up firms, accelerating the rate of technological development within firms, and facilitating knowledge spillovers both within and across industry/technology segments.

3.3.1 Missing Markets in Funding

It is well established that small firms and start-up ventures have a great deal of difficulty obtaining early-stage, high-risk funding for technology development. Entrepreneurs typically report that common sources of funding for more well-established entities (i.e., cash generated through sales and services, bank loans, and venture capital funding) may not be

available to the smallest and newest firms at a cost start-up firms are able to accept.

The Tools for DNA Diagnostics focused program provided cost-shared financial support to a number of these entrepreneurs, including the founders of MT, CuraGen, Nanogen, and Third Wave. As presented later in this report, these firms cited the challenge of securing early-stage funding for novel technology concepts.

3.3.2 Acceleration of Technology Development

Even though some firms may have internal financial resources or access to external sources of funding, it may be difficult for them to adequately fund early-stage technology development. This is especially important when it is not yet evident how the new technologies may be embodied in products or services that can be marketed profitably by the innovating firms.

A firm's finance managers must compare expected returns on R&D investments with the rate of return demanded by its investors. If the projected rate of return, inclusive of anticipated technical and market risks, does not exceed the rate demanded by investors, finance managers will likely not approve the high-risk project. In this case, investment in the form of angel financing or ATP-type cost-sharing funding may significantly accelerate the pace of R&D and subsequent technology development.

3.3.3 Knowledge Spillovers

Whenever new technical accomplishments are communicated to practitioners inside or outside the specific field of research, the knowledge shared has the potential to provide economic benefits to other researchers and firms. These spillover benefits, although very difficult to model and quantify, form an important contribution to society by those responsible for creating the knowledge.

ATP projects permit awardees to retain the intellectual property rights to their ATP-cofunded innovations, but ATP encourages awardees to publish and present their research. In the case of the Tools for DNA Diagnostics projects, ATP provided funding to many of the key players in the molecular diagnostics field. ATP awardees often presented their research findings in academic journals and trade publications. Thus, knowledge spillovers are not purely internal to the awardee. The presentation of novel technologies in product and service offerings and

the dissemination of research findings contribute to the collective knowledge of the industry.

Where possible, RTI used cash flows from licensing revenues that innovators accrued from other companies as lower-bound measures of private economic benefits from knowledge spillovers.

3.4 DEVELOPMENT OF TECHNICAL AND ECONOMIC METRICS

Economic benefits were quantified by pairing quantitative measures of a new technology's technical impact, called technical metrics, with economic metrics, which are measures whose unit values are denominated in dollars.

Technical metrics included incremental labor hour savings related to improving or eliminating manual processes. The paired economic metric is the cost of those labor hours as measured by the wage rate for employees performing those processes. When paired, the technical and economic metrics yield the economic benefit of eliminating a manual labor process.

Table 3-1 presents example technical and economic impact pairings. The final technical and economic metrics are presented in the quantitative analysis section of each case study.

Table 3-1. Example Technical and Economic Impact Metrics

Benefit Categories	Technical Impact Metric	Economic Impact Metric
Equipment cost savings (losses)	Net avoided laboratory equipment expenditure	Equipment prices
Labor savings	Reduction in labor hours for improved or eliminated manual processes	Hourly wage rates for relevant labor categories
Materials savings	Net reduced materials usage, including reagents, gels, sample volumes	Market price of materials
More efficient data analysis	Reduction in labor hours for output data warehousing and analysis	Hourly wage rates for relevant labor categories
Higher data quality	Reduction in number of repeated analysis runs	Materials prices, equipment prices, and labor wages

Technical and economic impact metrics exclude sales revenue (i.e., unit volume multiplied by price) because it is not considered an economic benefit. Prices facilitate the exchange of resources between demanders and suppliers. Profits may accrue to the innovator as a private benefit; however, there are no resource savings, such as labor hours or less equipment usage, to society through sales revenue.

3.5 PRIMARY AND SECONDARY DATA COLLECTION

Data to inform the technical and economic impact metrics were collected from both primary and secondary data sources. Primary data sources included representatives of the funded firms, end users of their products, and individuals with significant domain expertise in and historical knowledge of these technologies and the events surrounding their development.

Secondary sources included published articles in scholarly journals and trade publications and reports prepared by government agencies. In addition to the quantitative data needed to calculate measures of economic return, RTI gathered qualitative information and anecdotes to add richness and detail to the final report and conclusions.

To the extent possible, RTI reconstructed historical events using these resources to model the projects' technology outcomes as accurately as possible in the market and scientific context in which the innovations were generated. Where experts, company representatives, and the end users provided conflicting reports and data, RTI worked to develop a consensus view.

3.6 PERFORMANCE MEASURES

Performance measures permit ATP and its stakeholders to objectively review, assess, and compare project performance in a manner similar to investment analysis. In this case, the investment is the project cost. However, a number of considerations must be kept in mind when reviewing performance measures.

A principal shortcoming of performance measures is that all benefits and costs may not have been quantified. This is particularly true when historical project expenditures are readily available, but calculating historical and future benefit streams requires information that may be

highly nuanced and difficult to collect. As a consequence, performance measures may undervalue the true economic performance of a project. In economic assessments such as this one in which all benefit streams may not be quantified it is important to note that the performance measures that are calculated are likely to be conservative.

A second consideration is that there is a distinction between public and social performance measures that parallels the earlier discussion of public versus private benefits and costs. Measures of public return include only the time series of public costs and benefits. These performance measures identify and reflect only the benefits attributable to ATP's involvement in the project.

Total social benefits include public benefits arising from the cost savings achieved by consumers and any private benefits from additions to innovator profits. Social performance measures reflect these benefits as well as combined public and private project costs.

Project benefits and costs are presented as a time series of annual cash flows. Project costs represent the investment in the project and can be considered negative benefits or cash outflows. Project benefits are cash inflows and are typically positive. Benefits may be negative if technology adoption costs exceed technology usage benefits in the same year. Each year in the time series has a net economic benefit represented by net cash flows.

When acceleration benefits are being estimated, the actual streams of costs and benefits are arrayed as a time series. The delayed expenditures and benefits that would have occurred in the absence of ATP funding are subtracted from these actual cash flows to create the net impact of government funding, both on an annual basis and across the entire time period covered by the actual and hypothetical durations. It is these net cash flows and their timing that are used to calculate each of the performance measures using Microsoft Excel or another software package.

Three benchmark measures—benefit-to-cost ratio (BCR), net present value (NPV), and internal rate of return (IRR)—provide estimates of the net economic benefits created by the investment (public alone or combined public and private, that is, social).

3.6.1 Benefit-to-Cost Ratio

The BCR calculated in this analysis is the ratio of the NPV of benefits to the NPV of costs, which accounts for differences in the timing of cash flows (which has implications for the real value of $1 in one time period versus another).

The BCR uses the annual time series of quantified benefits derived from new products and services enabled by the technologies developed during the ATP project. Letting B_t be the net benefits accrued in year t by technology users and C_t the total funding for the project in year t by ATP and industry, then the BCR for the program is given by

$$(BCR) = \frac{\sum_{i=0}^{n} \frac{B(t+i)}{(1+r)^i}}{\sum_{i=0}^{n} \frac{C(t+i)}{(1+r)^i}} \qquad (3.1)$$

where

t is the first year in which benefits or costs occur,

n is the number of years the benefits and/or costs occur, and

r is the social discount rate.

In this study, r was set at 7%, the OMB-specified level.[2] Because benefits and program costs may occur at different time periods, both are expressed in present-value terms before the ratio is calculated. Essentially, a BCR greater than one indicates that quantified benefits outweigh the calculated costs. A BCR less than one indicates that costs exceeded benefits, and a BCR equal to one means that the project broke even.

3.6.2 Net Present Value

The NPV of the investment in a project is calculated as

$$NPV = \sum_{i=0}^{n} \left[\frac{B(t+i)}{(1+r)^i} - \frac{C(t+i)}{(1+r)^i} \right] \qquad (3.2)$$

where the terms have the same meanings as identified for the BCR determination. Any project that yields a positive NPV is considered economically successful. Projects that show a positive NPV when analyzed using Office of Management and Budget's (OMB's) 7% real discount rate are socially advantageous. A negative NPV would indicate

[2]See OMB Circular A-94.

that the costs to society outweigh the benefits, and a NPV equal to zero would indicate a breakeven point.

3.6.3 Internal Rate of Return

The IRR on an investment is the compound annual return on an R&D project, which may incur costs over multiple years, over the projected lifetime of the innovation before the innovation itself becomes a defender technology. In mathematical terms, the IRR is the value of r that sets the NPV equal to 0 in Eq. (3.2).

The IRR's value can be compared with conventional rates of return for comparable or alternate investments. Risk-free capital investments such as government bonds can be expected to yield rates of return under 5% in real terms, while equities seldom return more than 10% over an extended period of time. In academic studies of the diffusion of new technologies, however, real rates of return of 100% or over have been found for significant advances with broad social benefits. It should be noted that in cases for which costs exceed benefits, an IRR cannot be calculated.

If only public benefits and costs are used to calculate the IRR, the IRR is known as the public rate of return. When both public and private costs are used, the IRR is called the social rate of return. The social rate of return includes the net benefits to the innovator in addition to the benefits accruing to those who reap savings from using those technologies.

4 Case Study: MIND Development—The Joint Affymetrix-Molecular Dynamics Project

In 1994, ATP awarded the largest technology development project in its history to a joint venture (JV) between two young California companies: Affymetrix, a DNA microarray manufacturer, and Molecular Dynamics, a molecular biology instrument manufacturer. The 5-year, $31.5 million award was among ATP's first Tools for DNA Diagnostics projects.

The project's goal was to combine Affymetrix's expertise in DNA microarrays and Molecular Dynamics' expertise in instrumentation to develop a handheld Miniature Integrated Nucleic Acid Diagnostic (MIND) device. This device would enable doctors to rapidly analyze patients' blood samples in the office and output the data from a handheld unit to a desktop reader that would determine a clinical diagnosis. The core of the handheld device would be an Affymetrix microarray tiled with thousands of microscopic DNA probes that would bond with matching DNA or mRNA samples from a patient. Molecular Dynamics would develop the instrumentation surrounding the microarray, including capillary electrophoretic sample preparation.

The MIND Development project was envisioned as an ambitious, broad-ranging effort to overcome technical and market barriers to point-of-care diagnostics. In the mid-1990s, biotechnology companies saw point-of-care diagnostics—the use of miniaturized molecular diagnostic devices and processes in a medical office setting to provide medical diagnoses—

as the next major market opportunity. Though many technical concepts had been proposed, the actual technologies required to make practical diagnostic tools possible had yet to be developed. The companies' proposal set an overall goal of developing the full suite of instrumentation, assays, protocols, and data analysis and management systems.

The award remains ATP's largest. Affymetrix and Molecular Dynamics' original project budget was $63 million for 1995 through 2000. ATP and the two companies would each contribute $31.5 million. The project was not as costly as originally planned—spending amounted to $57.2 million—and ATP's cost share was $2.9 million less than expected.

This case study presents the economic analysis of the JV's commercialized technology outcomes and the impacts the project had on the molecular diagnostics industry. RTI interviewed third-party experts and end users, reviewed the genomic science and engineering literature, and reconstructed historical events to gather the data needed to define the counterfactual scenario and inform the analysis.

RTI evaluated the technologies by estimating cash flows under the constraints of a counterfactual scenario in which the ATP grant was not awarded and the technologies' introductions were delayed. The focus was on public benefits relative to ATP's investment. Private benefits and costs were difficult to evaluate because the incremental returns to the companies attributable solely to their JV activities could not be estimated as reasonably. Approximations are included later in the case study for reference.

4.1 PROJECT OVERVIEW

The MIND Development project was an ambitious, comprehensive effort to develop the first point-of-care molecular diagnostic device. Affymetrix believed that these devices would one day be one of the largest segments of the biotechnology industry. Upon initiation of ATP's focused program, Stephen Fodor, Robert Lipshutz, and others at Affymetrix began to strategize how to develop integrated miniaturized devices for fast, efficient, and cost-effective diagnoses of patients' DNA samples.

Lipshutz presented the MIND device concept to ATP in a 1993 white paper submitted in response to ATP's request for participation from industry, academia, and government to help scope the goals of the proposed focused program. That paper, "Technology for the Genetic

Revolution," presented the technologies and concepts that Affymetrix believed were yet to be developed but necessary to enable practical applications of genomics.

In the following year, Affymetrix approached Molecular Dynamics to submit a joint proposal for the focused program's first competition. Molecular Dynamics possessed complementary instrumentation and engineering expertise. The two companies had a preexisting working relationship because Molecular Dynamics had built Affymetrix's first microarray scanner. Together, the two firms believed they would be able to advance the MIND device further than by going it alone.

Apart from their complementary technologies, a teaming effort made good sense for a number of other reasons. The proposal's scope was too ambitious and broad for a single company award; both firms' expertise was required. The breadth of the project also meant that it would be a costly endeavor, and a JV award was not subject to the $2 million funding cap applied to individual awards. The availability of ATP funding drove the genesis of the project: both firms stated that they would not even have considered the project if ATP funding had not been a possibility.

Lipshutz headed up Affymetrix's team and David Barker, Molecular Dynamics' Vice-President of Research and Business Development, served as the lead investigator for his company's ATP activities. The project also enlisted researchers at the California Institute of Technology, the Lawrence Livermore National Laboratory, Stanford University, the University of Washington, and the University of California, Berkeley through subcontracts to increase the team's scientific expertise.[3]

ATP cofunding was awarded in the 1994 competition. Though the project's official period of performance was February 1995 through January 2000, this analysis simplified that period to whole calendar years. ATP projects are awarded on a cost-sharing basis, and Affymetrix and Molecular Dynamics matched $18.5 million and $10.1 million, respectively. Table 4-1 presents the audited annual expenditures for 1995 through 1999.

[3] Molecular Applications Group joined the JV briefly as a partner with limited rights; however, its participation in the project was brief.

Table 4-1. Annual MIND Development Project Expenditures

Year	ATP to Affymetrix	Affymetrix Matching Funds	ATP to Molecular Dynamics	Molecular Dynamics Matching Funds	Total Funding
1995	$1,248,000	$1,248,000	$1,882,000	$1,883,000	$6,261,000
1996	2,240,000	2,240,000	2,371,000	2,372,000	9,223,000
1997	4,614,000	4,616,000	2,499,000	2,500,000	14,229,000
1998	5,295,000	5,297,000	1,435,000	1,436,000	13,463,000
1999	5,143,000	5,145,000	1,859,000	1,860,000	14,006,000
Total	18,539,000	18,547,000	10,046,000	10,050,000	57,183,000

Source: ATP.

Note: The total value of the ATP award was $31.5 million, but the JV did not spend $2.9 million of that amount. Affymetrix's grant funds and cost share include those of Molecular Applications Group. Dollar values in this table were not adjusted for inflation. Sums may not add to totals because of independent rounding.

4.1.1 Overview of Affymetrix

Affymetrix, Inc. developed and commercialized the first DNA microarray, a revolutionary diagnostic tool tiled with probes made of genetic sequences on a glass wafer the size of a thumbnail. Researchers use microarrays to investigate large numbers of genes simultaneously (see Figure 4-1).[4]

Figure 4-1. Affymetrix GeneChip Microarray

Source: Courtesy of Affymetrix.

[4]Affymetrix's DNA microarrays are also known as GeneChip® microarrays. "GeneChip®" is Affymetrix's brand name and trademark under which Affymetrix markets its DNA microarray products and analysis systems. To prevent confusion, this case study uses the engineering terms "DNA microarrays" or "microarrays."

Until microarrays' introduction in 1994, scientists used $100 blood tests and other laborious diagnostic procedures to identify individual genes. A microarray permits thousands of those experiments to run simultaneously. Experiments that only a decade ago took weeks, months, or perhaps years to run now take only a couple of days (Malik, 2003). This speed has had a profound effect on the way medical research is conducted.

In a microarray experiment, researchers introduce a specially prepared blood or tissue sample to a microarray and track gene expression patterns by analyzing matches between the sample and the microarray's probes. Each microarray contains thousands of probes that are single-stranded DNA reference sequences. Where an mRNA or DNA sequence from an experimental sample is complementary to a probe's sequence, the two will bind and emit a fluorescent signal. This process is called hybridization (see Figure 4-2).

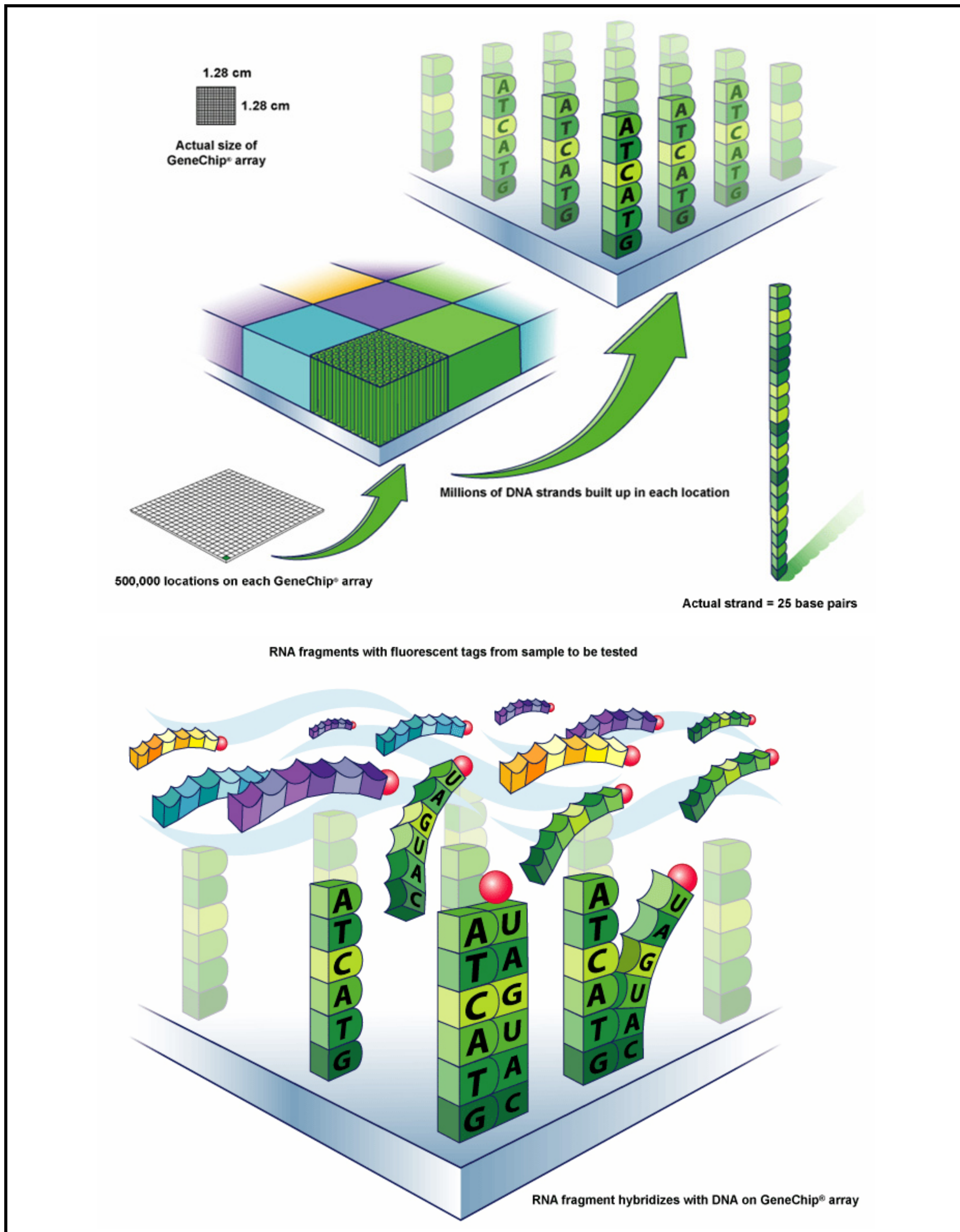
DNA microarrays are an important component of medical research because they document cells' responses to diseases and the effects of drug treatments (Gerhold, Jensen, and Gullans, 2002). They also take the vast amount of information from large-scale sequencing efforts and provide a platform from which DNA and mRNA samples can be tested against entire genomes.

Affymetrix's CEO, Dr. Stephen Fodor, led the team that developed the first DNA microarray technology. Their breakthrough combined photolithographic manufacturing techniques from the semiconductor industry with advances in combinatorial chemistry (Fodor et al., 1991; Affymetrix, 2005).

In simplified terms, Affymetrix's photolithography technique alternates lithographic masks, chemical solutions, and light exposure to build DNA sequences vertically on glass surfaces. Only those areas exposed to light receive the next nucleotide in a desired sequence when the entire surface is flooded with a chemical solution. Microarrays are manufactured in a wafer format and then are diced into individual units.

In late 1993, Affymetrix was a small private company in the development stage, readying for the initial sale of its microarrays on a commercial basis. Affymetrix had recently completed two stages of venture capital financing, and its R&D dollars were earmarked for lower-risk, near-term

Figure 4-2. DNA Hybridization



Source: Courtesy of Affymetrix.

opportunities. Although much of the proposed research under MIND Development would be complementary to Affymetrix's R&D plans, high-risk subprojects such as sample preparation and systems integration were not. Affymetrix's financiers were intent on speedy commercialization of its existing technology and the development of Affymetrix's manufacturing capability.

Ultimately, the ATP project played a pivotal role in the company's R&D program, funding the company's high-risk R&D and accelerating the company's total R&D program (see Table 4-2). The significance of the ATP project is illustrated by the share of Affymetrix's R&D budget allocated to it. The sum of its ATP funds and its cost share constituted between one-fifth and one-third of its total R&D budget during the 5-year project.

During the project period, Affymetrix underwent significant growth both scientifically and financially (Table 4-3). Today Affymetrix is the largest and most prominent producer in the microarray market and is the acknowledged pioneer of DNA microarray technology (Harbert, 2005). In 2005, the company earned revenues of $368 million, $198 million of which was from microarrays (Affymetrix, 2006).

4.1.2 Overview of Molecular Dynamics

Founded in 1988, Molecular Dynamics was an engineering-focused company that developed, manufactured, and marketed high-resolution scanners and other molecular biology instruments. The company's focus was on developing instrumentation to automate analytical procedures

Table 4-2. Affymetrix Project Spending, as a Percentage of Corporate R&D

For the Period Ended	Total R&D Spending[a]	Company Cost Share	ATP Funds	Total Project Funds (% of R&D Spending)
12/31/1995	$12,420,000	$1,248,000	$1,248,000	20%
12/31/1996	18,762,000	2,240,000	2,240,000	24%
12/31/1997	28,168,000	4,614,000	4,616,000	33%
12/31/1998	38,433,000	5,295,000	5,297,000	28%
12/31/1999	43,524,000	5,143,000	5,145,000	24%

Source: RTI estimates and Affymetrix SEC Forms 10-K for fiscal years 1996 through 2005.

[a]For 1995 through 1999, Affymetrix accounted for the ATP funds as research revenue and not as a credit to its R&D expenses. The total R&D expenditures for 1995 through 1999 are not net of the ATP grant.

Table 4-3. Affymetrix's Revenue History

	Year	Revenue (millions)	Net Income (millions)	Employees
	1993	$1.41	–$5.59	Data unavailable.
	1994	1.57	–9.68	Data unavailable.
ATP Award Period	1995	4.62	–10.75	66
ATP Award Period	1996	11.97	–12.22	161
ATP Award Period	1997	19.76	–22.52	242
ATP Award Period	1998	52.02	–23.13	321
ATP Award Period	1999	96.85	–23.08	519
	2000	200.83	–53.99	744
	2001	224.87	–33.12	905
	2002	289.90	–1.60	877
	2003	300.80	14.30	871
	2004	346.00	47.60	907
	2005	367.60	57.52	1,101

Source: Affymetrix SEC Forms 10-K for fiscal years 1996 through 2005.

Note: Affymetrix's annual revenues during the award period include the ATP cofunding.

and permit researchers to visualize, quantify, and analyze genetic information.

By the end of 1996, Molecular Dynamics had delivered over 3,000 instruments to customers around the world. The bulk of these were gel and blot scanning systems that used lasers to analyze electrophoresis gels marketed under the "Storm" brand name (Molecular Dynamics, 1997).

ATP cofunding permitted Molecular Dynamics to develop the first high-throughput DNA sequencer, accelerating the HGP and other large-scale sequencing efforts (see Figure 4-3). The ATP project accounted for more than half of Molecular Dynamics' R&D budget for 1995 through 1997. Molecular Dynamics' R&D expenditures for 1998 and 1999 were not available because the company was acquired. The audited Molecular Dynamics and ATP matching funds for those years are included in Table 4-4 for reference.

Figure 4-3. MegaBACE 1000 DNA Sequencer

Source: Courtesy of GE Healthcare.

Before the award, Molecular Dynamics did not have the financial resources to invest in a high-risk project alone. According to Barker, Molecular Dynamics' lead investigator, as a small public company, the firm needed to balance its R&D expenditures against its revenues. Yet executives also recognized that the payoff would be significant if the project successfully developed the first diagnostic device for the point-of-care health care market. The company's leadership was willing to stretch and invest in the research if ATP awarded the project cofunding. Without the JV award, Barker believes Molecular Dynamics would have invested their R&D dollars in their existing product portfolio.

In 1997, the last full reporting year in which Molecular Dynamics was an independent company, the company earned net income of $4.9 million on revenues of $55.7 million and had 286 employees (Molecular Dynamics, 1998). Revenue totals for the 2 preceding years were $49.4 million and $38.9 million, respectively (see Table 4-5).

The JV activities had a profound effect on Molecular Dynamics, transforming it from an engineering-based organization to a biotechnology tools company. Molecular Dynamics later invested heavily in research into instrument systems for genomics, pharmaceuticals, agriculture, and clinical diagnostics.

Table 4-4. Molecular Dynamics Project Spending, as a Percentage of Corporate R&D

For the Period Ended	Total R&D Spending[a]	Company Cost Share	ATP Funds	Total Project Funds (% of R&D Spending)
12/31/1994	$4,953,000			
12/31/1995	7,064,000	$1,883,000	$1,882,000	53%
12/31/1996	8,573,000	2,372,000	2,371,000	55%
12/31/1997	8,940,000	2,500,000	2,499,000	56%
12/31/1998		1,436,000	1,435,000	
12/31/1999		1,860,000	1,859,000	

Source: RTI estimates and Molecular Dynamics SEC Forms 10-K for fiscal years 1992 through 1997.

[a]Molecular Dynamics accounted for the ATP grant as a credit to its R&D expenses and presented net expenses in its 1995 through 1997 annual reports. To simplify presentation, Table 4-4 presents gross R&D expenses.

In the years following the ATP award, Molecular Dynamics was absorbed into increasingly larger organizations (see Table 4-5). In 1998, Molecular Dynamics was acquired by long-time strategic partner and reagents supplier, Amersham Pharmacia Biotech (APB), largely on the strength of Molecular Dynamics' ATP-cofunded technology portfolio.

APB later changed its name to Amersham Biosciences, one of the principal businesses of Amersham plc, a $2.5 billion a year British biotechnology firm specializing in diagnostic imaging, protein separations, and discovery systems. GE Medical Systems completed its $9.5 billion acquisition of Amersham in 2004. The resulting business was renamed GE Healthcare.

This case study continues to refer to the organization as Molecular Dynamics because it was Molecular Dynamics' executives, engineers, and scientists who successfully developed, marketed, and introduced the MegaBACE system at a time when these tools were critically important to the HGP and other biotechnology efforts.

4.1.3 Project Research and Development Goals

The MIND Development project involved core technology R&D and integrated systems design and development. The device would initially include a handheld reader and a desktop diagnostic unit. The plan called for the two pieces to be integrated into one unit in the long term. The MIND device would be supported by reagents, protocols, and data analysis and management software. The project's primary focus was to

Table 4-5. Molecular Dynamics' and Successors' Revenue History

	Year	Company Name	Revenue (millions)	Performance Measure[a] (millions)
	1992	Molecular Dynamics	$28.2	$1.9
	1993	Molecular Dynamics	38.0	4.0
	1994	Molecular Dynamics	33.9	–4.7
ATP Award Period	1995	Molecular Dynamics	38.9	–3.0
ATP Award Period	1996	Molecular Dynamics	49.4	3.4
ATP Award Period	1997	Molecular Dynamics	55.7	4.9
ATP Award Period	1998	Amersham Pharmacia Biotech[b]	744.6[c]	90.3
ATP Award Period	1999	Amersham Pharmacia Biotech	878.1	93.5
	2000	Amersham Pharmacia Biotech	988.2	83.2
	2001	Amersham Biosciences[d]	1,127.2	98.6
	2002	Amersham Biosciences	1,085.0	64.1
	2003	Amersham Biosciences	1,029.4	24.3
	2004	GE Healthcare[e]	13,456.0	2,286.0
	2005	GE Healthcare	15,153.0	2,665.0

Source: Molecular Dynamics, Amersham, and General Electric SEC Forms 10-K and 20-F for fiscal years 1992 through 2005.

[a]The profit measure for Molecular Dynamics is net income, earnings before interest and taxes for Amersham, and business segment profit for GE Healthcare.

[b]Amersham Pharmacia Biotech acquired Molecular Dynamics in 1997 and was part of Nycomed Amersham.

[c]Amersham's financial data were translated into U.S. dollars using the average annual U.S. dollar and British pound exchange rate.

[d]Amersham Biosciences was created when Nycomed Amersham reorganized as Amersham.

[e]GE Medical Systems acquired Amersham to create GE Healthcare in 2004.

develop the core science and component systems that would eventually make the integrated device possible.

The team would begin by independently developing individual components and then bring them together into a system as they were developed. Affymetrix focused its efforts on broadening and adapting its microarray technology and designing data management and analysis software, attempting to integrate sample preparation and amplification into its microarray technology. Molecular Dynamics focused on the CAE instrumentation and would automate and miniaturize DNA labeling and capillary electrophoresis.

When assembled, the planned device would accept a patient's blood sample, extract DNA from the blood cells, amplify the DNA, and then analyze the sample using one of two techniques: DNA-probe array hybridization or CAE (ATP, 1994). DNA from the sample would hybridize with the microarrays probe. Alternatively, CAE, a method for sequencing DNA in tiny capillary tubes, would be used to separate, size, and sequence the resulting DNA fragments for output into an analysis system.

Molecular Dynamics enlisted Richard Mathies of the University of California, Berkeley to develop and adapt his concepts for high-throughput CAE. The JV would also develop the software to efficiently analyze the data output and determine a clinical diagnosis.

The MIND development project sought to overcome many technical barriers, including the following:

- specimen acquisition and handling,
- sample preparation and DNA extraction,
- selection or amplification of DNA sequences,
- fluorescent labeling of DNA samples,
- fragmentation of the DNA sample,
- hybridization or separation of DNA fragments,
- reading of the array,
- data analysis, and
- diagnostic interpretation.

Researchers had investigated some of these barriers before but not in the miniaturized, integrated environment needed for the device. The project team knew that sample preparation would be an especially difficult problem because of the variability in sample types, volumes, and the requirements for care handling. Preexisting sample preparation technologies were too expensive and unwieldy for high-volume clinical applications.

Integrating these procedures presented its own set of technical risks. Compatible chemistries were needed for the individual components to work together. Another significant technical challenge was posed by microfluidics, the behavior of fluids at volumes thousands of times smaller than a common droplet. When working with very small volumes of fluid, those volumes can become so small that they are difficult to

analyze and control. These risks were serious enough that without ATP support, the companies would not have tried to overcome these barriers.

The project team decided that each firm should work within its domain of expertise and commercialize technology milestones as they were achieved.

4.1.4 Joint Project Effectiveness

Representatives of Affymetrix and Molecular Dynamics believe that the JV was more productive than if each firm had pursued the same research objectives individually. Both firms cite their regular technical briefings and technology strategy meetings as beneficial. In the words of one participant, these exchanges enabled significant "cross-fertilization and cross-motivation" that inspired and drove many efforts to achieve technology milestones.

During the 5-year period of performance, challenges in developing molecular diagnostics for the point-of-care market shifted the market opportunity toward research applications and clinical diagnostics, particularly as the imminent completion of the HGP refocused the scientific community's interest on gene expression, genotyping, and sequencing. Affymetrix and Molecular Dynamics successfully demonstrated the individual components of the MIND device; however, the MIND device originally proposed was not developed.

Point-of-care diagnostics proved to be a significant challenge—one that persists as of this writing—because of the challenge of collecting and preparing samples, the variety of sample types, and the need for strictly controlled environments. The point-of-care market's usability, reliability, and accuracy requirements greatly exceeded what biotechnology companies could deliver at a reasonable cost.

Molecular Dynamics developed a microarray technology for gene expression and analysis during the award period that was a competitive threat to Affymetrix's technology. Molecular Dynamics' technology was available on a precommercial basis through its Microarray Technology Access Program (MTAP). The availability of genomic data from the progress of the HGP and other large-scale sequencing efforts made gene expression the most attractive near-term market opportunity for microarrays, and the JV partners found themselves in direct competition.

As in many emerging industries characterized by rapidly evolving technology platforms and application space, the biotechnology industry is

amorphous and dynamic. Changes in the competitive landscape, technological breakthroughs, and usage trends can lead to market space convergence. Strategic partners may find themselves in direct competition, as was the case with Affymetrix and Molecular Dynamics.

The two companies reduced their level of collaboration, although not their commitment to the project. They ultimately operated the JV at arm's length to prevent the unintentional disclosure or dissemination of competitive information or positions. Initially meeting quarterly, the two firms began to meet biannually and reduce the volume of information exchanged to a level that met the ATP's quarterly technical reporting requirements.

4.2 ANALYSIS OF AFFYMETRIX'S TECHNOLOGY OUTCOMES

Figure 4-4. Affymetrix GeneChip Microarray

Source: Courtesy of Affymetrix

Affymetrix's ATP-cofunded research led to advancements in chip design and manufacture, sample labeling, and assay protocols as well as in the software used to analyze data output. The project accelerated the development of process technologies that made microarray production more efficient and the chips of higher quality (see Figure 4-4).

Through the ATP cofunded project, Affymetrix was able to identify and resolve many of the key research questions and production issues related to microarrays. The firm continues to leverage derivatives of methodologies and proofs of concept from the JV to drive innovation and R&D internally. The Affymetrix and ATP funds invested between 1995 and 2000 created a better end-use experience, characterized by greater data production volumes per chip and more sophisticated software and hardware systems.

The ATP award had a significant influence on Affymetrix as a company and on the biotechnology industry as a whole. Without the award, Affymetrix believes that the company's growth would have been slower. Receiving the award helped Affymetrix secure additional funding from venture capitalists and increased interest in Affymetrix's initial public offering (IPO) by validating the company's efforts. Affymetrix believes the award and the project's success also invigorated investor interest in the biotechnology sector.

Although project outcomes from Affymetrix's work have ongoing value for the organization and society, in terms of quantifiable benefits, this

analysis was only able to quantify a 1- to 2-year acceleration in the adoption of improved Affymetrix microarrays. This estimate is a conservative, lower-bound estimate of the economic benefits from Affymetrix's ATP cofunded technologies because the methodologies and analytic techniques also had synergistic impacts on other R&D efforts internally. However, RTI was unable to quantify benefits from these spillovers.

4.2.1 Technologies Developed with ATP Cofunding

The MIND Development project supported a broad research program at Affymetrix. For its technology to serve as the core of the handheld unit, Affymetrix needed to increase the processing power of its microarrays, expand the ability to analyze the data output, and devise new process technologies and methods for efficient manufacturing. In addition, Affymetrix needed to integrate sample preparation, assay, and data analysis steps.

The close fit between the ATP project and the balance of Affymetrix's research program permitted economies of scale in R&D, and Affymetrix moved significantly along the learning curve as a consequence. One of the main differences between what would and would not have happened during the project was that the MIND device required microarrays to have sophisticated technology for sample preparation that bypassed standard laboratory processes. In addition, the systems integration work was solely related to the ATP project.

Affymetrix successfully completed many subprojects, wrote papers, and demonstrated each piece of technology it proposed in 1994. Among Affymetrix's patents that cite ATP or NIST are those for its designs for the integrated nucleic acid device. However, because the market did not develop as expected, Affymetrix's management did not invest in completing the systems integration work. Rather, Affymetrix focused on finding commercial applications of component technologies.

Among Affymetrix's accomplishments that benefited from ATP funding were the following:

- **Reduction in microarray feature size.** When Affmetrix's DNA microarrays were first introduced in 1994, they had a feature (i.e., DNA probe) size of 100 microns. Affymetrix had reduced the size to approximately 50 microns, but the ATP cofunds assisted in reducing the size further to 25 microns. This innovation increased the power of each microarray four-fold. Equally notable is that the strength of each probe's signal

increased more than 20 fold but without a corresponding decrease in the signal-to-noise ratio.

- **Software for computation and data analysis.** Much of the ATP project dollars were spent developing the IT infrastructure for working with the data output. The MIND device would need to analyze an enormous amount of data rapidly to yield a clinical diagnosis quickly. Furthermore, the increases in array density yielded complementary increases in the amount of data that had to be managed. Thus, increasingly sophisticated and powerful analysis software was a significant achievement.
- **Process development for microarray manufacture.** Prior to the JV, Affymetrix's photolithography technology for manufacturing DNA microarrays had been proven in the laboratory and in small-scale production. During the first 2 years of the JV, ATP cofunding helped Affymetrix develop industrial-scale photolithography for microarray production and improved manufacturing techniques.
- **Encapsulation and miniaturization of front- and back-end technologies.** Affymetrix integrated sample preparation, hybridization, data analysis, scanning, and visualization processes. Affymetrix's research into sample preparation integration would have been delayed as long as 10 years. Although Affymetrix hosted four classes of assays on the integrated system, and each of the technical pieces worked as expected, there was not yet a viable commercial market for this integrated preparatory technology, and final integration was put off indefinitely.
- **New protocols and assays.** Affymetrix developed new protocols, test methods, and measurement techniques for microarray end users and for internal applications. For example, they developed the wet chemistry for labeling that is still used today.

The methodologies and analytic techniques also had synergistic impacts on other R&D efforts internally: ATP-cofunded technologies, best practices, proofs of concept, and processes flowed into the rest of the company. The ATP award also helped the firm develop a product roadmap.

Affymetrix applied for and received many patents for innovations that were supported in whole or in part by ATP cofunding (see Table 4-6). These patents cover topics ranging from device design, assays, software, and chemistry, and they illustrate the enduring impact of the award.

Finally, there were impacts beyond those for Affymetrix and the end users of its products. Through the development of data analysis and management software, Affymetrix and ATP helped validate and spur the

Table 4-6. Affymetrix Patents Citing ATP Support

Patent Number	Patent Name	Application Date	Issue Date
7,090,758	Capillary array electrophoresis scanner	October 31, 2002	August 15, 2006
6,965,020	Nucleic acid labeling compounds	September 11, 2001	November 15, 2005
6,957,149	Computer-aided probability base calling for arrays of nucleic acid probes on chips	April 1, 2003	October 18, 2005
6,881,836	Photocleavable protecting groups and methods for their use	January 22, 2003	April 19, 2005
6,864,059	Biotin containing C-glycoside nucleic acid labeling compounds	December 5, 2002	March 8, 2005
6,844,433	Nucleic acid labeling compounds	June 2, 2003	January 18, 2005
6,830,936	Integrated nucleic acid diagnostic device	December 31, 2000	December 14, 2004
6,699,659	Products and methods for analyzing nucleic acids including identification of substitutions, insertions and deletions	December 21, 1999	March 2, 2004
6,612,737	System and method for self-calibrating measurement	December 29, 1999	September 2, 2003
6,600,996	Computer-aided techniques for analyzing biological sequences	March 28, 1997	July 29, 2003
6,596,856	Nucleic acid labeling compounds	February 9, 2001	July 22, 2003
6,566,515	Photocleavable protecting groups and methods for their use	March 14, 2000	May 20, 2003
6,554,986	Capillary array electrophoresis scanner	May 25, 2000	April 29, 2003
6,545,264	Systems and methods for high performance scanning	August 26, 1999	April 8, 2003
6,326,211	Method of manipulating a gas bubble in a microfluidic device	March 10, 2000	December 4, 2001
6,261,431	Process for microfabrication of an integrated PCR-CE device and products produced by the same	December 28, 1998	July 17, 2001
6,228,593	Computer-aided probability base calling for arrays of nucleic acid probes on chips	January 14, 2000	May 8, 2001
6,546,340	Computer-aided probability base calling for arrays of nucleic acid probes on chips	March 20, 2001	March 20, 2001
6,197,595	Integrated nucleic acid diagnostic device	April 19, 1999	March 6, 2001
6,168,948	Miniaturized genetic analysis systems and methods	January 12, 1998	January 2, 2001
6,147,205	Photocleavable protecting groups and methods for their use	March 5, 1997	November 14, 2000
7,099,777	Techniques for identifying confirming mapping and categorizing nucleic acids	January 11, 1999	August 29, 2000
6,066,454	Computer-aided probability base calling for arrays of nucleic acid probes on chips	October 10, 1997	May 23, 2000
6,022,963	Synthesis of oligonucleotide arrays using photocleavable protecting groups	April 10, 1996	February 8, 2000
5,922,591	Integrated nucleic acid diagnostic device	June 27, 1996	July 13, 1999
5,856,174	Integrated nucleic acid diagnostic device	January 19, 1996	January 5, 1999
5,733,729	Computer-aided probability base calling for arrays of nucleic acid probes on chips	September 14, 1995	March 31, 1998

Source: U.S. Patent and Trademark Office.

development of an ecosystem of companies devoted to IT tools for the biotechnology, genomic, and pharmaceutical industries.

4.2.2 Commercialization Status and Products

Affymetrix aims to be the "Intel" of the DNA microarray market through its "Powered by Affymetrix" initiative. Affymetrix researches, produces, and markets single-use microarrays globally and offers its strategic partners access to precommercial technology.

Aside from microarrays, Affymetrix produces the entire suite of laboratory equipment and consumables, including scanners, reagents, and software. Affymetrix's products are used for two primary applications: monitoring gene expression levels and investigating genetic variation (including Single Nucleotide Polymorphism [SNP] analysis).

Affymetrix's products include the following:

- **Microarrays for gene expression and DNA analysis.** Microarrays can be used with whole and/or partial gene sequences for humans, mice, cats, dogs, and cows. Microarrays are also produced to study bacteria and insects (e.g., fruit flies, mosquitoes) and vegetation (i.e., rice, corn, poplar trees, and sugar cane).
- **Reagents.** Reagents are used to label DNA targets and to serve as primers and other chemical agents, such as those for wash and stain.
- **Instruments.** Affymetrix produces ovens for the hybridization process, sample preparation and insertion stations, and scanners for reading the microarrays.
- **Software.** Software products include data-mining tools, a software server, and a software developer's kit (SDK) for third-party solution providers.

The company has entered into a large number of strategic technical and marketing partnerships with universities, research laboratories, and pharmaceutical firms. Partners include Invitrogen (reagents), Perlegen Sciences (SNP genotyping), F. Hoffman-La Roche (molecular diagnostic products), the Broad Institute at the Massachusetts Institute of Technology, and Caliper Life Sciences (microfluidics).

4.2.3 End Users and Applications

Affymetrix's products are used by commercial, government, and academic research laboratories in several vertical markets, most notably those for pharmaceuticals, agrichemicals, biotechnology, and public

health. Microarrays have many gene expression and DNA monitoring applications in the life, food, and plant sciences, including

- human disease research,
- genetic analysis,
- pharmaceutical drug discovery and development,
- pharmacogenomics,
- molecular diagnostics,
- plant breeding,
- food testing,
- pathogen identification, and
- consumer genetics (Affymetrix, 2005).

One example of an Affymetrix microarray is the one developed for investigating Severe Acute Respiratory Syndrome (SARS), a severe and contagious respiratory syndrome that originated in China. In 2003, SARS killed nearly 1,000 people worldwide and hampered commerce in Southeast Asia for months. SARS is spread by close person-to-person contact and is fatal in 10% of cases (CDC, 2005).

Affymetrix produced a microarray with the single-stranded genetic sequence for SARS to diagnose new cases and to help detect new viral strains. These microarrays were developed specifically to assist pathogen research and infectious disease laboratories track genetic mutations in SARS (Valigra, 2004).

To conduct the experiment, a researcher must first prepare the sample—isolating the DNA to be tested from a blood or tissue sample, “unzipping” the double helix structure of the DNA, and using a chemical procedure to fluorescently label the bases in the sample. The sample is then washed over the microarray, and the entire microarray is inserted into an incubator for 24 hours. After the incubation period, fluorescent signals emit from the microarray’s probes where the DNA from the sample and from the probes have hybridized because they represent complementary sequences.

The microarray is then placed in a scanning or imaging instrument that reads the fluorescent signals. Because the location of the probes and their sequences are known, the researcher is able to use the data output to determine whether the DNA from the sample is complementary to the SARS viral genetic sequence that has been tiled on the microarray

(Malik, 2003). The relative strength of the fluorescent signals can also help the researcher determine any genetic variations.

Microarrays now facilitate research and discovery in cancers, cystic fibrosis, HIV, and many other chronic ailments and infectious diseases. As of this writing, microarrays—and the instrumentation required to read them—are used almost solely in the research market and are not commonly used by clinicians because they are still too expensive. Prices can range from $250 to $800 each for academic and nonprofit users to more than $2,000 each for commercial users. As in the semiconductor industry, prices are expected to fall even as the number of probes increases and the average feature size shrinks (Affymetrix, 2005).

The current cost barriers are coupled with barriers related to the need for careful sample handing and preparation and sophisticated data management and analytic tools (Valigra, 2004). Before widespread clinical use of microarray technology is possible, a more self-contained system needs to be available.

4.2.4 Competitive Landscape for DNA Microarrays

The biotechnology industry is a dynamic one in which firms frequently enter and exit within short periods of time. Key factors of success appear to be the ability to

- innovate and develop a strong intellectual property position;
- partner with other leading organizations;
- keep pace with emerging applications for gene expression, monitoring, and diagnostics; and
- establish the application as a platform of choice (Harbert, 2005; Moukheiber, 2001).

Analysts estimate that Affymetrix holds between 60% and 75% of the market for DNA microarrays (Harbert, 2005; Moukheiber, 2001). Since 1994, several organizations have entered this market, which is estimated to grow to $2 billion by 2008. Driving demand is the emergence of new applications, lower purchase costs, increased response time, and greater efficiency (Harbert, 2005).

Microarrays are popular for molecular diagnostics because of their versatility, comparatively low fixed investment requirements, ease of use, and sensitivity, which corresponds to enormous data production potential.

Affymetrix is the largest producer in a market in which service providers and other organizations now compete. Several firms—many of which were founded after the emergence of Affymetrix—now produce microarrays. The most notable firms are Agilent Technologies, Illumina, Nanogen, and CombiMatrix (see Table 4-7). Though Affymetrix's products are among the most expensive, they are also considered to be among the most robust (Harbert, 2005).

In a certain regard, the competitive landscape is defined not by the physical product produced, but rather by the gene expression and diagnostic data generated. In this sense, service organizations could be considered competitors for Affymetrix, Illumina, and other microarray producers because they offer platforms for achieving the same results.

In the past, microarray manufacturers differentiated themselves by feature density, feature size, price, end-use application, and the ability to produce custom products. Microarrays for the research market offer the ability to test a large number of genes simultaneously. In contrast, microarrays for the clinical diagnostics market test fewer genes but have test sites with a large number of redundant probes to prevent false positives or negatives. The exacting performance and reliability requirements of the market dictate such redundancy.

Table 4-7. DNA Microarray Manufacturers

Company	Location	Year Founded	Gene Expression Product Line's Brand Name
Affymetrix, Inc.	Santa Clara, CA	1991	GeneChip
Agilent Technologies, Inc.	Palo Alto, CA	1999	ChIP-on-chip
Applied Biosystems, Inc.	Foster City, CA	1937	Human Genome Survey Microarray V2.0
Bayer Healthcare LLC	Leverkusen, Germany	1897	TRUGENE, VERSANT
CombiMatrix Corporation	Newport Beach, CA	1995	Custom Arrays
GE Healthcare	Fairfield, CT	2004	Codelink
Illumina, Inc.	San Diego, CA	1998	Sentrix Gene-Specific Probe Arrays
Molecular Devices, Inc.	Sunnyvale, CA	1983	GenePix
Nanogen, Inc.	San Diego, CA	1991	NanoChip microarray
NimbleGen, Inc.	Madison, WI	1999	NimbleChips
Orchid Cellmark, Inc.	Princeton, NJ	1995	SNP-IT
Sequenom, Inc.	San Diego, CA	1994	Mass Array, Spectro Chip
Solexa, Inc.	Hayward, CA	1992	Clonal Single Molecule Array

Source: Hoovers.com, Datamonitor, and company Forms 10-K filed with the U.S. Securities and Exchange Commission. N/A = not available.

The current technology platforms for microarrays have begun to mature, resulting in commoditization. Consequently, manufacturers—including Affymetrix—increasingly support multiple product lines in both the research and the diagnostics markets.

4.2.5 Quantitative Analysis of Affymetrix's Technology Outcomes

The economic analysis of Affymetrix's project outcomes quantified the benefits of introducing a higher quality microarray, sooner. The public investment supplemented Affymetrix's R&D program and enabled greater economies of scale in high-risk research and discovery, contributing significantly to its microarray design and manufacture capabilities. In the absence of ATP funding, the company would have pursued some of this work undertaken as part of the JV project, although Affymetrix stated that the R&D investment cycle would have been longer.

Because the award affected nearly every aspect of the entire end-use experience, this analysis was able to approach the value end users gained by having a more efficient microarray sooner. The four-fold increase in probe density, which is the same as a four-fold increase in analytical capability, for the same price was the primary vector for quantifying economic benefits.

4.2.5.1 Benefits Estimation Methodology

Affymetrix's DNA microarrays and Molecular Dynamics' sequencer are tools for acquiring information. The counterfactual scenarios used to quantify net public benefits estimate the hypothetical costs of generating the same information using the processes they replaced. Therefore, net public benefits from the JV were estimated by measuring resource savings from adopting JV technologies, less adoption costs and the funds ATP invested in the project.

Resource savings encompass avoided equipment costs, fully burdened wages, and other expenses that end users would have incurred to achieve their actual data volumes. In other words, if data volume is held constant, the economic benefits would be the cost savings of using the more efficient microarrays instead of the old ones. Net public benefit estimates capture the value of having acquired the same information in the currency of the technology the JV superseded.

Over the course of this study, executives from Affymetrix provided some early guidance on potential areas of benefit; however, RTI collected

impact categories and run time, labor, and cost estimates from primary and secondary sources. Experts and technicians from private companies, nonprofit and government laboratories, and research universities were interviewed to collect technical and economic impact metrics.

Affymetrix believes that the microarrays' higher quality end-use experience was accelerated between 1 and 2 years as a result of ATP's cofunding. Therefore, the counterfactual against which benefits were measured was accelerating by 1.5 years—the midpoint of the estimate provided by Affymetrix—the introduction of DNA microarrays with smaller feature sizes and more sophisticated software tools and protocols. The first Affymetrix product with a 25-micron feature size was introduced in early 1999 (Affymetrix, 2006). Thus, this product enhancement would not have been introduced until approximately mid-2000 under the counterfactual scenario.

4.2.5.2 Quantifying Economic Benefits

Reducing a microarray's feature size from 50 microns to 25 microns increases its analytic capability fourfold: an end user reaps four times the amount of information with one microarray. The indirect value of what researchers are able to learn from analyzing the data output is unquantifiable. However, it is possible to value the reduction in the number of microarrays, amount of consumables, and labor hours needed to generate a comparable volume of data with microarrays with 50-micron feature sizes from 1999 through mid-2000.

RTI estimated the number of microarrays sold in 1999 and the first half of 2000 to be 98,000 and 87,500 units, respectively (see Table 4-8). Affymetrix's total full-year product sales are available from its filings with the Securities and Exchange Commission (SEC): $114.9 million (1999) and $196.1 million (2000).[5] Probe array sales accounted for approximately 40% of total product sales during this period (Affymetrix, 2001). The balance of product sales was for consumables and the instrumentation.

[5] Affymetrix's product sales data for 1999 and 2000 were converted to 2005 dollars using the CPI. Actual, reported product sales on the company's Forms 10-K were $98.2 million in 1999 and $173.5 million in 2000.

Table 4-8. Avoided Microarray Expense Benefits (2005$)

	1999	2000
Total product sales	$114,857,000	$196,107,000
Probe array sales	$45,943,000	$79,100,000
Average unit price	$468	$452
Estimated unit sales	98,000	87,500[a]
Avoided microarray assays	294,000	262,500
Maximum avoided microarray expenses	$137,592,000	$118,650,000

Source: RTI estimates.

[a] Estimated unit sales of 87,500 are for the first 6 months of the year only.

RTI estimated the unit sales presented in Table 4-8 by dividing Affymetrix's annual microarray sales by the average unit price reported by end users. Commercial customers often paid $2,000 or more per array before discounts, but academic and nonprofit researchers paid substantially less. The average price is estimated by participants to have been $400 between 1998 and 2000, or an inflation-adjusted $468 in 1999 and $452 in 2000.

Dividing probe array sales by the average price yields the estimated number of units sold, assuming that all units sold in the 1.5-year time frame benefited from the advances made during the ATP project.[6]

Using the estimated number of microarrays sold, RTI calculated the following benefits (see Table 4-9 and Box 4-1):

Table 4-9. Avoided Microarray, Consumables, and Labor Expense Benefits (2005$)

	1999	2000
Maximum avoided microarray expenses	$137,592,000	$118,650,000
Maximum avoided consumables expenses	$58,800,000	$52,500,000
Maximum avoided labor expenses	$21,268,000	$18,989,000
Benefits attributable to ATP (25%)	$54,415,000	$47,535,000

Source: RTI estimates.

[6] For 1999, $45.9 million was divided by $468 to arrive at approximately 98,000 units. Because only a half year of benefits are being claimed for 2000, the estimate of $79.1 million in microarray sales was first divided by 2; then $39.6 million was divided by $452 to arrive at 87,500 units.

Box 4-1. Avoided Microarray, Consumables, and Labor Expense Benefits Calculations

In 1999, 98,000 microarrays were sold. Benefits were calculated as:

Avoided microarrays = 98,000 x 3 avoided units per assay x $468 = $137,592, 000

Avoided consumables = 98,000 x 3 avoided assays x $200 = $58,800,000

Avoided labor expenses = 98,000 x 3 avoided assays x $36.17 per hour x 2 hours = $21,268,000

- **Avoided Microarray Expense:** If each microarray sold were able to do the work of four defender microarrays, researchers would have required three additional units to generate the same volume of information. The number of avoided microarray assays would be three times the number of units actually sold. Affymetrix believes that prices would have been no different if the feature size had been larger, as is also the case in the semiconductor industry. Implicit in claiming three times the actual number of units sold as a benefit is accepting the fourth unit as the public cost of adoption.
- **Avoided Consumables Expense:** Reagents, dyes, and other consumables are needed to work with each microarray. These consumables are an integral part of the entire assay. They were estimated to have cost $200 per avoided microarray in real, 2005 dollars.
- **Avoided Labor Expense:** Each microarray assay takes approximately 2 hours of manual intervention. Data collected by the U.S. Bureau of Labor Statistics reveals that the average unburdened wage for a laboratory technician in 2004 was $17.56 per hour (BLS, 2005). Adjusting for inflation and multiplying the result by 2.0 to account for benefits, payroll taxes, and employee administrative and overhead costs yields an average fully burdened hourly cost of $36.17. The labor expense benefit per avoided microarray experiment is $72.34.

4.2.5.3 Net Public Benefits Attributable to ATP

Affymetrix believes that its ATP activities accelerated its microarray R&D and moved the company significantly along the learning curve. However, as presented earlier in this chapter, the company estimates that three-quarters of the cofunded technology advances it *commercialized* would have been accomplished regardless of whether ATP funds were available, although the investment cycle would have been longer.

Affymetrix needed the software, protocols, and supporting technologies for the microarrays to gain market acceptance. If they did not have these, adoption would have lagged, and Affymetrix might have lost its first

mover advantage. Similarly, Affymetrix needed to shrink feature (probe) sizes because more densely tiled chips are more efficient for end users. Affymetrix needed early customers to require fewer chips for their analyses in order to sell more of them in the future. The software ATP supported facilitated effective use of the microarrays because without it the user experience would have been more cumbersome.

There are economies of scale in research; the complementarities between the ATP project and Affymetrix's own research program were a driver for the original proposal. Determining which research dollars were more effective is not possible.

If 75% of the commercialized work would have been undertaken without the award, then the remaining 25% approximates the ATP cofunding's contribution. Thus, the ATP share of the avoided microarray, consumables, and labor expense benefits presented in Table 4-9 is assumed to be 25%.Accordingly, the incremental value attributed to ATP funding was approximately $54.4 million in 1999 and $47.5 million in 2000 (undiscounted).

Table 4-10 summarizes the net public benefits realized from Affymetrix's work under the JV. Total public benefits were $101.9 million. The Affymetrix share of ATP's inflation-adjusted JV expenditures, inclusive of all subcontracts, totaled $22.4 million, and net benefits are estimated to be $79.6 million (undiscounted).

Table 4-10. Public Benefits, Costs, and Net Public Benefits—Affymetrix (2005$)

Year	Public Benefits	Public Costs	Net Public Benefits
1995		–$1,248,000	–$1,597,000
1996		–2,240,000	–2,777,000
1997		–4,614,000	–5,629,000
1998		–5,295,000	–6,354,000
1999	$54,415,000	–5,143,000	48,398,000
2000	47,535,000		47,535,000
Total	101,950,000	–22,375,000	79,575,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding.

4.2.5.4 Private Benefits and Costs

The core research undertaken under the ATP award broadened Affymetrix's scientific and technical capabilities and contributed to its body of knowledge and intellectual property portfolio. Affymetrix investigated sample preparation, manufacturing processes, microarray tiling, and integrated molecular diagnostics systems. Affymetrix accrued private economic benefits from these activities; however, those benefits cannot be reasonably estimated.

Affymetrix had operating and net losses until 2002. The company certainly did not lose any more money because of the ATP project. At a minimum, it is likely that the company's sales grew more quickly than they would have otherwise because its technology and microarray end-use experience were more sophisticated as a consequence of the project.

Quantifying incremental private benefits would require estimating how Affymetrix's losses would have been different without the ATP award and comparing the result to their actual losses. Generating a reliable estimate is difficult because it is not possible to reliably disentangle the impacts the project had from the perspective of end users, nor is it feasible, in practical terms, to understand how end users would have altered their consumption decisions if some more subtle product attributes were either different or unavailable. In addition, data on return on investment and profit margins are highly sensitive business information that could harm the company's competitive position if disclosed.

4.2.6 Impact on the Emergence of the Bioinformatics Software Market and Microarray Technology Adoption

ATP's impact on the software industry that emerged to serve the data analysis and management needs of microarray users cannot be estimated reasonably. Parsing out the specific software attributes ATP funded is not feasible. Furthermore, software design is an iterative process. It is possible that ATP-cofunded code and algorithms are no longer embedded in Affymetrix's software tools. Yet, Affymetrix credits ATP funding with helping it create more sophisticated software tools and ultimately with validating the market for them.

A review of Affymetrix's software partners illustrates the qualitative benefit of developing software tools and Affymetrix's work to encourage

software developers to develop new applications for use with its microarrays. RTI could not reasonably quantify the impact of ATP funding on reducing development costs at software companies.

Between 1999 and 2005, 25 software companies released 33 software applications that are compatible with Affymetrix's products. In addition to its own software products, Affymetrix offers a software development kit (SDK) that developers can use to permit their applications and Affymetrix's products to interact. The SDK is partly a collection of application protocol interfaces that software engineers use to program their software to use the facilities provided by another. Code available via the SDK may be a derivative of or include ATP-cofunded programming.

The cost of developing a new software tool, without using any prior art, is unclear. According to one participant, a tool may cost $1 to $2 million to develop. That figure may be higher or lower depending on whether the interface between the two software families had been written previously. The same participant suggested that an SDK could reasonably save between one and two full-time equivalent software engineers 1 year of programming. This equates to a cost of $200,000 to $250,000 for each company. A firm with multiple software products would likely enjoy economies of scale, reusing earlier code for each new tool.

ATP accelerated the adoption of microarray technologies by the scientific community, the downstream impacts of which are so broad that they were unable to be quantified in this study. Affymetrix's DNA microarrays are more effective and efficient and are supported by a more robust assay system as a consequence of ATP awards. The acceptance of microarray technologies, and the research they enabled, was accelerated by ATP support for the entire microarray research solution, including assay protocols, software, and equipment in addition to more robust microarrays.

4.3 ANALYSIS OF MOLECULAR DYNAMICS' TECHNOLOGY OUTCOMES

Molecular Dynamics' research led to the first high-throughput DNA sequencer, induced innovation at its main competitor, and consequently accelerated the HGP. The 96-capillary MegaBACE 1000 commercialized Molecular Dynamics' ATP-cofunded technology and concepts and technologies developed by and licensed from Richard Mathies of the University of California, Berkeley, who also served as a subcontractor on

the project. The research conducted during the award transformed the company into a biotechnology tools company. Molecular Dynamics' research staff evolved from a majority of engineers to nearly 50% engineers and 50% scientists.

The efficiency of the new sequencers as compared with the slab gel sequencers they replaced can be seen in their output. Slab gel instruments required an average of 6.5 hours to complete one sequencing cycle of 96 samples. Each sample was read to a typical length of 400 base pairs (bps), for a total of 38,400 bps or 5,900 bps/hr.

In contrast, Molecular Dynamics' MegaBACE required 2.5 hours to complete one cycle and could read 96 samples to an average readlength of 650. Researchers could acquire more data (62,400 bps), more quickly (24,960 bps/hr), and at a greater quality. The average percentage of that data that met quality standards was 98% for the MegaBACE versus 85% for the slab gel instrument.

Experts estimated that through 2003, when the finished draft of the HGP was completed, MegaBACE 1000s had been used to sequence approximately 30% of the human genome.

4.3.1 Technologies Developed with ATP Cofunding

Molecular Dynamics, collaborating with Mathies and Amersham Pharmacia Biotech (APB), investigated and successfully adapted capillary array electrophoresis techniques for high-throughput sequencing of DNA (Bashkin et al., 1996). When the project began, the defender technology for sequencing DNA, slab gel electrophoresis, was not conducive to a miniaturized diagnostic device. That technology required careful handling, pouring, and placement of sensitive gels. Capillary array electrophoresis (CAE), on the other hand, is a liquid-based system that analyzes DNA fragments placed in capillaries, avoiding gel electrophoresis' manual processes and toxic materials, and providing better data quality. The JV felt it could miniaturize the process of CAE and resolve problems with microfluidics.

The need for improved DNA sequencing technologies was apparent during the earliest years of the HGP. In the late 1980s and early 1990s, scientists were uncovering the genetic basis for many human and animal diseases. As their work progressed, the need for a new generation of diagnostic procedures, scientific instruments, and analytic tools became more pressing (Medlin, 1995). For researchers to achieve their goal of

understanding the link between human disease and certain genes, they first needed to decipher the sequence of the approximately 3 billion DNA base pairs contained in a human's 23 pairs of chromosomes. Determining genetic sequences was costly and time consuming; even the most well-equipped laboratories, operating state-of-the-art instrumentation, were only able to determine one genetic sequence every few days (Regis, 1995).

Scientists employed the sequencing strategies developed by Nobel prize winner Fredrick Sanger and his team in the 1970s. In simplified terms, DNA fragments are placed in individual lanes of a poured gel solution. The DNA molecules are separated via electrophoresis, a process that uses electrical current to separate molecules of different charge and size. Because the terminating base of each DNA strand is fluorescently labeled with an energy transfer dye to differentiate it from the other three bases, scanning or imaging equipment can identify each base because of the base-specific signal it emits.

Slab gel electrophoresis' lengthy and laborious processes did not provide the throughput needed to sequence the human genome within the time frame set by the HGP (Smith, 1993). A key barrier was that gel electrophoresis could not be automated sufficiently because gel preparation processes required great care. Furthermore, experiments often had to be rerun because of errors in gel placement, handling, or preparation (Hunkapiller et al., 1991). Lanes would wander horizontally on the gel, complicating lane tracking, which translated into an additional data verification step. Sequencing tools that avoided sensitive manual procedures, provided greater data fidelity, and sequenced large volumes of DNA in less time were needed.

CAE instruments provided a solution to these problems. Mathies had developed a method for reading fluorescently labeled DNA using laser beams inside 24-inch capillary tubes (Mathies and Huang, 1992). Molecular Dynamics enlisted Mathies as a subcontractor, licensed the early technology, improved it, and developed the remaining technologies and chemistry.

The team credits the ATP project with solving the technical impediments to producing a commercially viable, high-throughput CAE DNA sequencer. The team miniaturized capillaries and integrated complex chemical processes with the device engineering. The award also helped finance the development of high-resolution confocal lenses for scanning

over large areas on microarray slides (Mathies et al., 1994). These lenses were a key enabling technology because they permitted the microarray scanner to keep the entirety of a large flat area in focus for high-resolution, automated multicolor scanning and recognition. The ATP funds were also used to support the translation of the CAE technology onto glass microchips with etched capillaries for DNA separations (Liu et al., 2000a; 2000b).

Mathies' method used novel energy transfer dyes, which were commercialized by APB and used by Molecular Dynamics. Researchers also worked on several biochemistry projects, including

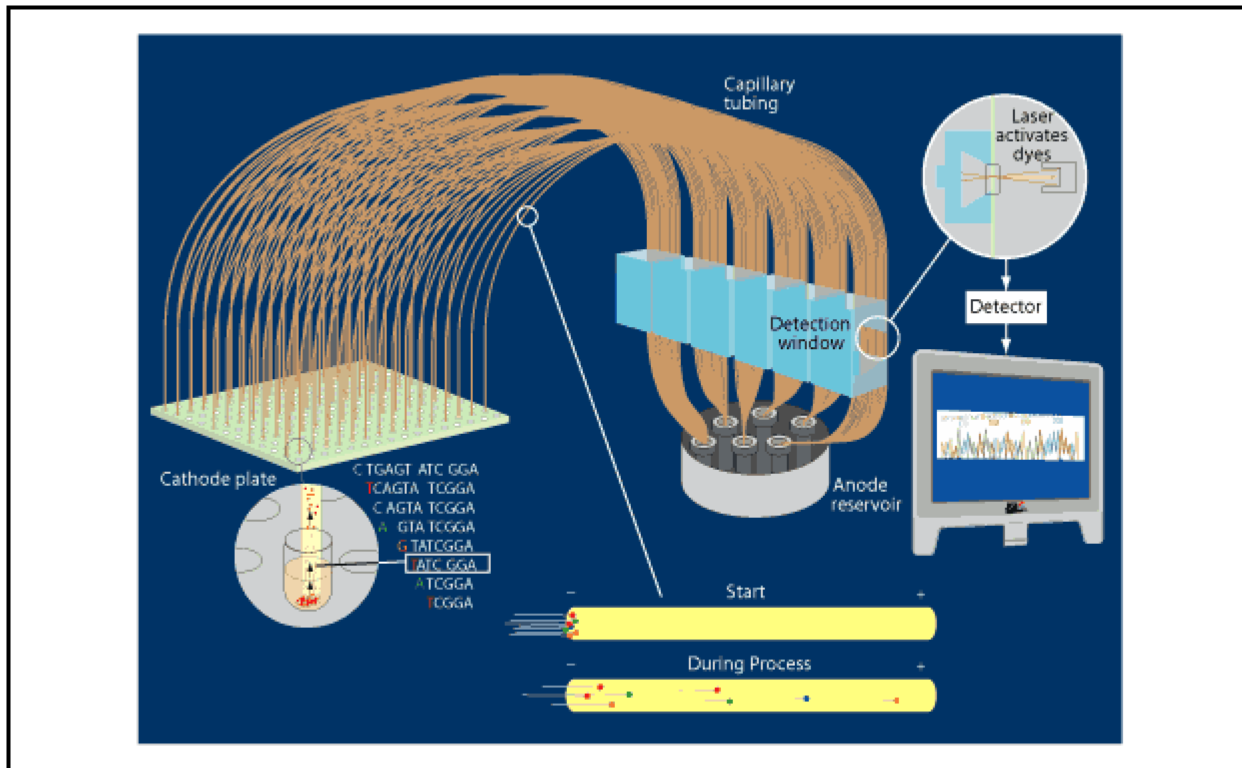
- a gel separation matrix that was pumped into the capillaries,
- new dye chemistry that provided higher label sensitivity for the sequencing primers, and
- coatings for the capillaries to extend their useful life to around 300 sequencing runs.

Molecular Dynamics' work on the scanning equipment, capillary arrays, biochemistry, and electrical engineering was successful. The company invested an additional $6 million in the sequencer to complete the industrial design and resolve engineering problems. However, all of the enabling technologies were developed or advanced using project funds.

CAE instruments eliminate the gel handling and casting procedures. Instead, a liquid separation matrix is injected into each capillary just before the DNA fragments are loaded into the machine. An electrical current is applied between the DNA samples and the end of the capillary, which causes the DNA ions to migrate into the capillary (Mardis, 1999). With the DNA fragments already fluorescently labeled, the instrument's scanner reads the bases in each capillary and outputs a data file with the completed DNA sequence (see Figure 4-5).

The instrument employs the Sanger method for sequencing, as does slab gel electrophoresis, but has a higher throughput because each of its 96 capillaries is a lane for sequencing DNA fragments. Most significantly, it can sequence more base pairs at a greater readlength and yield a higher pass rate for results. Readlength is the number of ordered nucleotides sequenced per sample. The pass rate is the percentage of resolved base pairs that meet quality standards. (Tables 4-14 and 4-15 in Section 4.3.6.3 presents comparative productivity measures for gel and capillary electrophoresis instruments.) Because the capillaries are

Figure 4-5. Capillary Array Electrophoresis



Source: Courtesy of the Joint Genome Institute.

separate from one another, there is no chance of interference from an adjacent lane.

4.3.2 Commercialization Status and Products

Molecular Dynamics commercialized its project outcomes via the MegaBACE 1000 DNA sequencers to take advantage of the market opportunity presented by genome centers' intense need for high-throughput instrumentation (see Figure 4-6). GE Healthcare continues to manufacture MegaBACE systems and sell a complete line of sequencing consumables. Notable early adopters included the Department of Energy's Joint Genome Institute and Incyte Pharmaceuticals.

Initial MegaBACE systems had 96 capillaries, but Amersham Biosciences also released instruments with 48 (MegaBACE 500) and 384 (MegaBACE 4000). The two other MegaBACE sequencers, the 750 and the 1500, are upgradeable. Customers can adjust the number of capillaries depending on their throughput requirements in intervals of 16 capillaries.

Figure 4-6. MegaBACE 1000 DNA Sequencer

Source: Courtesy of GE Healthcare.

4.3.3 End Users and Applications

Experts interviewed by RTI or who have published agree that the introduction of high-throughput CAE sequencing was a watershed event that accelerated the HGP, scientific discovery, and the downstream medical innovations that the completed sequence of the human genome enabled (International Human Genome Consortium, 2001).

Other important advances in laboratory automation contributed to the equivalent of DNA sequencing's industrial revolution. For example, laboratories began bar coding samples to reduce errors and redundant activity, and researchers developed robotics to handle sample preparation and loading (Hodgson, 2000). However, none of these had the same magnitude of impact as the sequencers.

High-throughput sequencers moved the HGP's target completion date for a finished draft forward from 2006 to 2003 (Hodgson, 2000). The project was supposed to be completed in 2006, but a first draft of 90% of the genome was completed in June 2000.

When initially introduced, the primary market was large genome sequencing centers and "core" facilities at research universities,

government laboratories, and pharmaceutical firms. Many of these labs operated 24 hours a day, 7 days a week to accumulate sequenced base pairs numbering in the tens of thousands. The MegaBACE and the competitive instrument from Applied Biosystems, Inc. (ABI), the Prism 3700, turned those units of measure into millions. ABI also received ATP funding; however, it was for technology development unrelated to the 3700.

Slab gel systems continued to be the platform of choice at smaller genomic research laboratories because of the relatively high cost of the $200,000 MegaBACE unit and the $300,000 ABI 3700. RTI estimates that since the MegaBACE launched in 1997 approximately 1,500 MegaBACE units have been sold.

Early adopters included some of the largest genome centers around the world that played an integral part in the mapping of the human genome. The world's largest publicly funded center, the United Kingdom's Sanger Centre, was one of the earliest adopters. In the United States, nearly all of the top five publicly funded centers installed MegaBACE systems, though some only beta tested them. The Department of Energy's Joint Genome Institute ultimately had an installed base of 86 units. Other high-profile early adopters included Washington University of Saint Louis, Incyte Pharmaceuticals, and the Beijing Genome Center.

4.3.4 Competitive Landscape for DNA Sequencers

In the late 1990s, only three companies had significant footholds in the market for DNA sequencing instruments: ABI and Molecular Dynamics and, to a much lesser extent, LI-Cor (see Table 4-11) . ABI had been the market leader ever since they introduced their slab gel instrument, the ABI Prism 377, in 1987. The 377 commercialized advances in DNA sequencing that were developed by Leroy Hood, the inventor of automated sequencing.

Table 4-11. DNA Sequencer Manufacturers (Sanger Method)

Company	Location
Applied Biosystems, Inc.	Foster City, CA
Beckman Coulter	Fullerton, CA
GE Healthcare (Molecular Dynamics)	Fairfield, CT
LI-Cor, Inc.	Lincoln, NE

ABI's market leadership with the 377 was not jeopardized until the MegaBACE 1000 started showing very good results in September 1997. At a meeting in Hilton Head, South Carolina, a noted researcher, Dr. Jingjue Ju, then with Incyte Pharmaceuticals, presented the first results from beta testing of the MegaBACE. Ju presented large volumes of data that had been generated in a short period of time. Ju was quoted in a 2000 article by Merrill Goozner as saying that "Applied Biosystems was very nervous to see the MegaBACE producing actual data [quickly]."

Eight months later, ABI announced that they had developed a 96-capillary machine, the ABI Prism 3700, but the first of these units did not enter service until January 1999 (Goozner, 2000; Hodgson, 2000).

Over time, the Prism 3700 significantly outsold the MegaBACE. ABI teamed with Craig Venter to form Celera Genomics, the organization that competed with the publicly funded program, for the first large initial sale of the 3700s. Celera Genomics is a subsidiary of Applera Corporation, as is ABI. During the time of the JV project, Applera was known as PE Corporation.

ABI also supplied the public HGP genome centers with the majority of their instruments. Although its sales initially outpaced ABI's, Molecular Dynamics only captured 30% of the global market at best. ABI succeeded in maintaining its market share, in part because they were the entrenched supplier with superior marketing and in part because the 3700 included robotics for automated sample loading (Hodgson, 2000).

The sequencer market experienced a prolonged period of softness after completion of the HGP (Coty, 2002). According to one interviewee, several centers did not purchase replacement units when the project was completed. In addition, a large number of used instruments were available as companies changed their research focus or shut down as contracts were completed.

Sales regained momentum in 2003 because of emerging applications beyond DNA sequencing in SNP genotyping, microsatellite genotyping, and fragment analysis. These applications were not for initial *de novo* sequencing of genomes but rather for comparing specific sequences against reference sequences. The assembly of such sequences is not as challenging given that the reference sequence is known. This means that new technologies that offer throughput on the order of millions of base pairs per day, but lower readlengths of 100 to 200 bases per sample, were commercially viable.

A near-term goal of the National Human Genome Research Institute (NHGRI) is to reduce the cost of sequencing a genome to $100,000 and eventually to $1,000. In 2004, NHGRI made $38 million in technology development grants to a mix of for-profit companies and research universities (NHGRI, 2004). NHGRI estimates that it costs $10 million to sequence a mammalian genome. Lowering that cost to $100,000 or less would allow researchers to sequence many peoples' genomes to identify disease-causing genes. If NHGRI can reduce the cost to $1,000 then each person could have his or her genome sequenced and use that information for health maintenance.

New entrants, such as 454 Life Sciences, Agencourt, and Solexa, use microfluidics and solid-state technologies and other completely different approaches to sequencing than Molecular Dynamics' and ABI's approaches (see Table 4-12). But the Sanger sequencing method is not considered outmoded because of its readlength advantage. Indeed, Microchip Biotechnologies, a company cofounded by three former Molecular Dynamics executives (and investigators on the ATP project) and Berkeley's Mathies, are developing a benchtop, integrated capillary sequencer that combines fully integrated sample preparation with microchip separations using Sanger chemistries.[7]

The consensus among study participants is that multiple platforms for DNA sequencing will emerge in the near term. These platforms will differentiate themselves by the readlength and throughput demands of the intended application. At the time of this writing, the newest technologies offer short readlengths of 100 bps and are appropriate for

Table 4-12. Next Generation DNA Sequencing Companies

Company	Location	Company	Location
454 Life Sciences, Inc.	Branford, CT	Microchip Biotechnologies, Inc.	Dublin, CA
Agencourt Biosciences Corp.	Beverly, MA	Pacific Biosciences, Inc.	Menlo Park, CA
Genizon BioSciences, Inc.	St. Laurent, Canada	Perlegen Sciences, Inc.	Mountain View, CA
GenoVoxx GmbH	Lübeck, Germany	Shimadzu Biotech	Kyoto, Japan
Helicos Biosciences Corp.	Cambridge, MA	Solexa, Inc.	Hayward, CA
Lucigen	Middleton, WI	Visigen Biotechnologies, Inc.	Houston, TX

[7]Microchip Biotechnologies was founded by Stevan Jovanovich, Roger McIntosh, and Dennis Harris (all of Molecular Dynamics) and Richard Mathies (UC Berkeley).

resequencing and genotyping, whereas *de novo* sequencing and complex analyses still require Sanger-based systems like ABI's and the MegaBACE.

In the long term, CAE will likely be fully supplanted when new platforms are able to achieve comparable or better readlength and accuracy. The competitive landscape may also consist of microarray manufacturers and service providers like Affymetrix's spin-off Perlegen Sciences, whose offerings can also be used in resequencing and genotyping.

4.3.5 Induced Innovation at Applied Biosystems, Inc.

The industry insiders, academics, and experts RTI interviewed agreed that ABI accelerated its R&D and production planning for its 96-capillary Prism 3700 instrument following the announcement that Molecular Dynamics was poised to bring the MegaBACE to market.

The ambitious goals of the HGP required a high-throughput sequencer, and it was inevitable that a company would introduce one. Study participants were unanimous in their opinion that ABI was best positioned to introduce it. All options for optimizing slab gel systems to increase sequencing output had been exhausted, and it was commonly known that ABI had a high-throughput sequencer at some stage of development.

CAE systems were the next logical step, and a paper on the subject that Mathies coauthored in 1992 had been widely read in the biochemistry and laboratory engineering community (Mathies and Huang, 1992). ABI introduced a 1-capillary instrument to the market in 1995, but its slab gel systems remained the platform of choice because of the capillary unit's low throughput capability.

Because their platform was the *de facto* standard, ABI had little incentive to migrate its customers to a new platform until the MegaBACE jeopardized ABI's position. Experts felt that if ABI had lost its market leadership, there would have been a significant downstream impact on the company because its most significant source of profits was generated by the sale of consumables for the instruments and not from the sale of the instruments themselves.

Interviewees were not expecting the first high-throughput capillary sequencer to be introduced by Molecular Dynamics, nor for it to be released as early as it was. They did not agree on the time frame under which ABI would have done so, but most thought it would have been 18

to 24 months later, perhaps in 2000 or 2001. This would have been 3 years or more later than when the MegaBACE beta-testing results were presented in 1997.

Interviewees suggested that following the Hilton Head meeting ABI began to rush the 3700 through development, licensing technology from Hitachi to meet the threat to their market dominance. ABI preannounced the 3700 in late 1998; the first 3700 sequencers would not ship for over 1 year (Goozner, 2000; Shreeve, 2004; Karow, 2006).

ABI is understood to have had 140 to 160 scientists and engineers working rapidly to complete the 3700. During the development process, Molecular Dynamics claimed ABI infringed on some of their patents, and later ABI claimed the same. The two firms settled their suits via cross-licensing agreements.

James Shreeve's *The Genome War*, a highly regarded account of the events and processes surrounding the HGP and the competing program at Celera Genomics, provides first-person accounts from insiders at ABI that the 3700 was accelerated by 1 year (2004). This 1-year acceleration estimate was employed in this study's quantitative analysis.

4.3.6 Quantitative Analysis of Molecular Dynamics' Technology Outcomes

This section presents net public benefits for MegaBACE 1000 instruments installed from 1997 through 2000. In addition, the 1-year acceleration of the release and use of the ABI Prism 3700 was attributed to the introduction of the MegaBACE 1000.

The counterfactual scenario was that the best-in-breed slab gel instrument, the ABI Prism 377 with a 96-lane capacity, would have remained the technology leader through the counterfactual introduction date of the 3700 sometime in 2000.

Molecular Dynamics' production of the MegaBACE allowed end users to acquire capillary instruments for their projects when they otherwise would have had to purchase the less efficient ABI 377, or forgo high-throughput sequencing altogether. RTI estimated that this continued through the end of 2000, at which point the sequencer market slowed following completion of the draft human genome (Coty, 2002).

The public economic benefits were the additional costs of using slab gel sequencers to achieve the same throughput as capillary sequencers.[8] Additional investments in equipment, extended work shifts, and/or new hires might have been needed, and the work might have taken 2 years or more instead of 1 year.

Public benefits were calculated by estimating the raw data output in the base case (with capillary sequencers) and calculating the corresponding raw data output slab gel sequencers would have had to sequence. The incremental annual costs of using slab gel sequencers from 1998 to 2005 was the public benefit.

Over the course of this study, the lead investigators from Molecular Dynamics provided some guidance on potential areas of benefit. However, RTI collected impact categories and run time, labor, and cost estimates from primary and secondary sources. Experts and technicians from private companies, nonprofit and government laboratories, and research universities were interviewed to collect the data to inform technical and economic impact metrics.

4.3.6.1 Installed Base of MegaBACE 1000 Sequencers

The MegaBACE first entered service in late 1997, but commercial shipments did not begin until 1998. By the time ABI's capacity was able to supply the entire sequencer market, Molecular Dynamics had shipped approximately 780 instruments (see Table 4-13).[9]

American manufacturers have a near monopoly on the global DNA sequencer market. Consequently, there was a high export rate from 1997 to 2000 to supply foreign labs: 40% for Molecular Dynamics and 50% for ABI (Molecular Dynamics, 1998; Applera, 2000).

Of the 780 MegaBACE units installed globally by the end of 2000, about 470 were in the United States. Therefore, the installed base for which

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[8] It is important to note that cash flow analysis does not consider noncash outflows or inflows, such as depreciation or amortization. Cash flow analysis accounts for equipment purchases fully in the year in which the expenditures are made. Implicit in this approach is that resources are consumed in the same year in which they are acquired. For example, reagents purchased in 1999 are assumed to be consumed in 1999. It is assumed that equipment has no residual value beyond its expected life. Cash flows that cannot be directly tied to the adoption or acceleration of a technology are excluded. It would not be appropriate to use the data herein as the sole basis from which to estimate the total engineering cost of sequencing a base pair.

[9] Detailed information on the growth in the global installed base of the MegaBACE 1000 is available in the annual reports of Amersham plc, which acquired Molecular Dynamics and its parent, Amersham Pharamacia Biotech (GE Healthcare, 2006).

benefits accrued peaked at 470. RTI estimates that the U.S.-installed base of MegaBACE sequencers was 920 instruments in 2005. However, benefits cease to accrue to units installed beyond 2000, and these units were excluded from Table 4-13.

Benefits are not calculated for MegaBACE sequencers installed after 2000 because a review of ABI's financial statements and press releases suggests that the company's available production capacity was sufficient to supply the entire market. Benefits accruing to end users when few alternatives are available, such as during the tight market for sequencers in 1999 to 2000, can be claimed. However, once a competitive product is available in sufficient quantity, public benefits attributable to ATP must end. Beyond 2000, if the MegaBACE had not been available, end users would have chosen the 3700 instead and would have received the same benefits as from the MegaBACE sequencers.

Both the MegaBACE and the 3700 were estimated to have a useful life of 5 years, after which they would have no residual value. The initial MegaBACE units installed in 1997 and 1998 began to reach the end of their useful life 2 years after the installed base peaked.

Table 4-13 details the rate of retirement for the U.S. installed base, which would be total global sales minus exports, minus U.S. sales from 5 years

Table 4-13. U.S. Base of MegaBACE 1000 Sequencers Installed in 1998 through 2000

Year	MegaBACE Unit Sales	MegaBACE Exports	MegaBACE Retirement	Cumulative U.S. MegaBACE Installs	Midpoint of U.S. MegaBACE Installed Base	Midpoint of Combined MegaBACE and ABI 3700 Installed Base
1998	150	60		90	45	45
1999	280	110		260	175	425
2000	350	140		470	365	865
2001				470	470	970
2002				470	470	970
2003			90	380	425	925
2004			170	210	295	545
2005			210	0	105	105

Source: RTI estimates.

Note: The installed base of MegaBACE and ABI sequencers includes 500 ABI 3700s installed in 1999 that were later removed from service in 2004.

earlier. Instruments that came online in 2000 would have reached the end of their useful lives by the end of 2005, for example. Thus, the cash flow of benefits attributable to the project stopped in 2005.

The end date of 2005 was coincidental yet made the cash flow estimation for both Affymetrix's and Molecular Dynamics' work retrospective analyses.

The installed base was assumed to have grown linearly during any given year. At the end of 1998, 90 units were installed, then 170 units were added during 1999, and the 1999 year-end installed base reached 260. To simplify calculations, the midpoint of the installed base for each year was employed as a base from which to extrapolate public benefits and costs that were calculated on a per-unit basis.

4.3.6.2 Installed Base of ABI Prism 3700 Sequencers in 1999

ABI shipped 1,000 Prism 3700 sequencers in 1999, approximately 50% of which were for export markets (O'Neil, 1999; Applera, 2000). Because the availability of these units was induced by the introduction of the MegaBACE, the benefits from the initial 500 U.S. sequencers from the first year of production were attributed to the JV. These sequencers were accounted for under the same assumptions as the MegaBACE sequencers. Installations in 1999 and decommissions in 2004 were assumed to follow a linear path, and full-year benefits were calculated for 250 sequencers for those 2 years. A base of 500 was used for 2000 through 2003. These units were added to the U.S.-installed base of MegaBACE sequencers in Table 4-13.[10]

Hereafter, when this case study refers to the "installed base," it is referring to the MegaBACE 1000 sequencers installed through 2000 and the ABI 3700 sequencers installed in 1999.

4.3.6.3 Productivity Gains of High-Throughput Capillary Sequencers

End users at several laboratories estimated the labor-hour requirements of manual processes for the slab gel instrument and the capillary instrument (see Table 4-14). The capillary sequencer requires 65 fewer

[10] Although the 3700 sequencers are assumed to be functionally the same as the MegaBACE, the 3700 differed from the MegaBACE in one important aspect: the instrument was capable of automatically loading the next plate after finishing one complete run. The 3700 could sequence samples from four plates before an operator needed to return to load the next four plates. The MegaBACE required an operator to return after each run. This assumption makes the analysis results more conservative.

Table 4-14. Hands-On Time Comparison of Slab Gel and High-Throughput Capillary Sequencers

Manual Labor Process	Slab Gel Electrophoresis (ABI Prism 377)	Capillary Array Electrophoresis (MegaBACE 1000)
Manual processes		
Gel preparation and pouring (minutes)	20	
Instrument loading and instrument operation (minutes)	20	15
Gel plate cleanup (minutes)	15	
Postrun lane retracking (minutes)	25	
Total manual labor time (minutes)	80	15

Source: RTI estimates.

minutes of manual intervention than the slab gel sequence. End users told RTI (and the literature confirmed) that eliminating gel preparation and pouring and postrun lane retracking offers substantial productivity benefits (Mardis, 1999; Meldrum, 2000; Hodgson, 2000).

One of the most significant advantages was the reduction in run time that permitted more instrument runs to be completed in one 8-hour shift (see Table 4-15). The slab gel instrument required an average of 6.5 hours to complete a sequencing cycle in which 96 samples were read in 96 lanes. Each lane would contain one sample, and each sample was read to a typical length of 400 base pairs (bps). In contrast, the MegaBACE required 2.5 hours to complete a run and would yield an average readlength of 650 bps in each plate's 96 wells.

Table 4-15. Productivity Comparison of Slab Gel and High-Throughput Capillary Sequencers

	Slab Gel Electrophoresis (ABI Prism 377)	Capillary Array Electrophoresis (MegaBACE 1000)
Instrument run time	6.5 hours	2.5 hours
Combined instrument run time and manual intervention time	6.83 hours	2.75 hours
Number of lanes	96 lanes	96 lanes
Average readlength	400 bps	650 bps
Pass rate	85%	98%
Consumables cost per sample	$0.50	$1.25

Source: RTI estimates.

Data quality was significantly higher as well: the average pass rate was 98% for the MegaBACE versus 85% for the slab gel instrument.[11] Although the cost of consumables per sample was higher with the capillary instrument, end users stated that they willingly paid more for consumables and the instrumentation to achieve the productivity and data production and quality benefits afforded by the instrument.

4.3.6.4 Impact of High-Throughput Capillary Sequencers on Laboratory Operations

The majority of capillary sequencers purchased between 1999 and 2000 were installed at major genome centers and research laboratories that had adopted an industrial-scale production environment to sequence human, mouse, rat, wheat, and other genomes of significant scientific and commercial value. Private-sector laboratories were concurrently seeking out new genes for drug discovery. Many of these laboratories operated 24 hours a day, 7 days a week, every week of the year. However, units were also installed at smaller laboratories. Assuming that all units were operating around the clock would overstate benefits.

It was assumed that before completing the draft human genome sequencers were operated two shifts a day, 5 days a week (through 2000), on average, which was 4,000 hours per year per instrument. Following the completion of the human genome, beginning in 2001, many operations slowed their production rates. End users said that, on average, most sequencers were operating one and a half shifts per day (beginning in 2001).

Estimated Data Production Rates

Estimated data production rates and total production volumes were needed to quantify the value generated by introducing capillary sequencers. The following is an example of how to estimate the annual raw data production of a capillary sequencer running two shifts per day.

Dividing the total number of shift hours per year (4,000) by the sum of the instrument's run and manual intervention times (2.75 hours) yielded the number of runs one instrument sequenced in two shifts per year: about 1,455 runs. Each run sequenced one plate of 96 samples, each of which would be read to 650 bps, on average. Under these operating

[11] The ABI Prism 377's settings could be changed to perform extended runs. When run time was extended to between 10 and 14 hours, laboratories could achieve an average readlength per sample of 1,000 bps. This was not an efficient setting for large-scale sequencing projects.

conditions, one MegaBACE produced 90.8 million bps of raw data output per year (see Box 4-2).

Substituting the values for a slab gel instrument yielded 22.5 million bps per year for one ABI 377 operated in two shifts. Thus, according to data supplied by interviewees, one MegaBACE produced more than four times the amount of data in one shift than the 377 produced.

The impact of this productivity gain was illustrated by the change one laboratory experienced. The lab converted one workspace from 20 slab gel instruments to 35 capillary ones without changing square footage and reaped significant productivity gains. The MegaBACE and the ABI 377 have roughly the same footprint, but one technician could oversee all 35 units because less workspace was required for employees. The lab had a staff of five to six people working in two shifts operating twenty 377 sequencers. In addition, a team of three people performed the postrun lane retracking to check for data that may have bled into adjacent lanes.

Estimated Data Production Volumes

The total number of acceptable base pairs the installed base was able to sequence each year, given the above operating parameters and those in Table 4-15, was the volume of data delivered. The incremental cost of

Box 4-2. Annual Capillary Sequencer Data Production Volume Calculations

For 2000, data production for one MegaBACE 1000 operating in two shifts was estimated as follows:

Annual runs in two shifts = 4,000 hours ÷ 2.75 hours per run ≈ 1,455 runs

Raw data output = 1,455 runs x 96 samples/run x 650 bps/sample ≈ 90.8 million bps

Acceptable data output = 90.8 million bps x (1-0.02) ≈ 88.9 million bps

With 865 sequencers operating in 2000, the total data output was 78,511 million bps, or 76,940 million bps in acceptable data. Under the same operating conditions, one slab gel sequencer could produce:

Annual runs in two shifts = 4,000 hours ÷ 6.83 hours per run ≈ 585 runs

Raw data output = 585 runs x 96 samples/run x 400 bps/sample ≈ 22.5 million bps

Acceptable data output = 22.5 million bps x (1-0.15) ≈ 19.1 million bps

achieving that same data production volume with the ABI 377 was equivalent to the public benefit of the innovation.

Table 4-16 presents the installed base for which benefits were quantified and the total amount of acceptable sequenced base pairs these instruments would have produced under the operating assumptions (see Box 4-2). Acceptable data output would be the total amount of raw data minus the data that did not pass. For the capillary instrument, unacceptable data output was estimated to have been 2%. The same figure for the slab gel instrument was 15%. Thus, to achieve the same data volume, the slab gel instrument would have needed more raw data output to compensate for its lower quality reads.

In 2000, the raw data output requirement from slab gel sequencers would have been 90,518 million bps instead of 78,511 million bps needed from capillary sequencers. This means that, under the counterfactual scenario, end users would have required more than 1 million additional runs (2.357 million instead of 1.258 million) on slab gel instruments to achieve the same volume of clean data as with 865 capillary sequencers running two shifts per day.

4.3.6.5 Public Benefit-Cost Estimates

RTI calculated the differences in labor, consumables, and additional equipment expenses to estimate benefits from introducing high-

Table 4-16. Estimated Annual Volume of Genetic Data Sequenced by the Installed Base of Year 1998 through 2000 Capillary Sequencers (1998–2005)

Year	Midpoint of Installed Base of Capillary Sequencers	Acceptable Data Output (million bps)	Number of Runs—Capillary Instruments (thousands)	Raw Data Output—Capillary Instruments (million bps)	Raw Data Output—Slab Gel Instruments (million bps)	Number of Runs—Slab Gel Instruments (thousands)
1998	45	4,003	65	4,084	4,709	123
1999	425	37,803	618	38,575	44,474	1,158
2000	865	76,940	1,258	78,511	90,518	2,357
2001	970	64,710	1,058	66,031	76,129	1,983
2002	970	64,710	1,058	66,031	76,129	1,983
2003	925	61,708	1,009	62,967	72,598	1,891
2004	545	36,358	595	37,100	42,774	1,114
2005	105	7,005	115	7,148	8,241	215

Source: RTI estimates.

Note: Installed base includes both MegaBACE and ABI instruments.

throughput sequencers. The analysis used the number of additional slab gel runs needed to yield the same volume of "clean" base pairs as the capillary ones.

Avoided Labor Expense Benefit

As presented in the productivity comparison in Table 4-14, each run on a capillary instrument required about 15 minutes of manual intervention compared with 1 hour and 20 minutes for a slab gel instrument. The incremental labor hours required were monetized using the same fully burdened wage rate for laboratory technicians used in the Affymetrix analysis: \$36.17 per hour. Labor benefits peaked at more than \$102 million in 2000 during the race to complete the first draft of the human genome (see Table 4-17 and Box 4-3).

Table 4-17. Avoided Labor Expense Benefits

Year	Number of Runs—Capillary Instruments (thousands)	Labor Cost (2005\$)	Number of Runs—Slab Gel Instruments (thousands)	Labor Cost (2005\$)	Incremental Labor Benefits (2005\$)
1998	65	\$592,000	123	\$5,899,000	\$5,307,000
1999	618	5,590,000	1,158	55,716,000	50,126,000
2000	1,258	11,377,000	2,357	113,398,000	102,021,000
2001	1,058	9,569,000	1,983	95,372,000	85,803,000
2002	1,058	9,569,000	1,983	95,372,000	85,803,000
2003	1,009	9,125,000	1,891	90,948,000	81,823,000
2004	595	5,376,000	1,114	53,585,000	48,209,000
2005	115	1,036,000	215	10,324,000	9,288,000

Source: RTI estimates.

Note: Installed base includes both MegaBACE and ABI instruments.

Box 4-3. Avoided Labor Expense Benefits Calculations

Using the data for 2000 from Tables 4-16 and 4-17 as an example, the labor cost of sequencing 76,940 million bps was calculated as follows:

Slab gel sequencers labor cost = 1.33 hours/run x \$36.17/hour x 2.357 million runs ≈ \$113,398,000

Capillary sequencers labor cost = 0.25 hours/run x \$36.17/hour x 1.258 million runs ≈ \$11,377,000

In 2000, the labor benefit of using capillary sequencers was therefore \$102,020,000.

It is important to note that the total number of shifts required per year under the counterfactual scenario would have exceeded three shifts per day. This means that many additional technicians would have been needed and additional slab gel sequencers would have been required. This analysis assumed that when a technician was not setting up an instrument for a run that he or she would be free for activities in gel preparation, cleanup, and postrun lane retracking. Despite this assumption, additional 96-lane ABI 377 sequencers would have been required.

Avoided Consumables Expense Benefit

The capillaries and reagents used by the MegaBACE and the 3700 were more expensive than the 377's gels and other consumables. Laboratories measure the cost of consumables as the cost per lane, which was the cost of sequencing one DNA fragment in one capillary or gel lane once.

As shown in Table 4-15, the cost of all consumables for slab gel instruments was estimated to be $0.50, including raw materials, expected breakage of glass plates, and other items. Consumables were more expensive for the capillary instruments at $1.25 per lane, which included replacement capillaries, dyes, and reagents. The consumables benefit was negative in all years because of the resulting $0.75 incremental cost per lane. Labs accepted higher consumables costs to reap the benefits from capillary sequencers' increased speed, quality, and productivity.

Using data from 2000 as an example, if there had been 2.357 million runs on slab gel instruments, the cost would have been $37,834,000 less than the cost of 1.258 million runs on the capillary instruments (see Box 4-4).

Box 4-4. Avoided Consumables Expense Benefits Calculations

Using the data for 2000 from Tables 4-15 and 4-16 as an example, the consumables costs of sequencing 76,940 million bps was calculated as follows:

Slab gel sequencers = $0.50/lane x 96 lanes/run x 2.357 million runs ≈ $113,148,000

Capillary sequencers = $1.25/lane x 96 lanes/run x 1.258 million runs ≈ $150,982,000

In 2000, the incremental consumables costs of using capillary sequencers were $37,834,000.

Net Avoided Equipment Expense Benefit

The net equipment benefit was the difference between the savings on avoiding additional slab gel instrument purchases and the cost of adopting capillary instruments. As explained below, U.S. laboratories would have required 1,823 additional slab gel instruments between 1998 and 2000.

To achieve the volume presented in Table 4-16, the minimum number of slab gel instruments required would be some number beyond the preexisting installed base. Under the counterfactual scenario, it was assumed that labs initially would have had the same number of slab gel instruments as capillary instruments. The number of additional slab gel instruments needed would be the number required to meet the capillary instruments' data production volumes (see Table 4-18 and Box 4-5).

In 1998, 123,000 runs were required, and 45 slab gels operated three shifts a year, they would only be able to complete around 39,000 runs. The deficit would need to be met by installing at least 95 more ABI 377s to perform the remaining 84,000 runs in 1998.

Units installed in earlier years were available in later ones because of the 5-year equipment lifetime. Thus, additional installations from 1998 were available through 2003. Labs would have needed to install an additional 801 units in 1999 and an additional 927 in 2000. Beyond those years, the

Table 4-18. Avoided Equipment Expense Benefits

Year	Raw Data Output—Slab Gel Instruments (million bps)	Number of Runs Required—Slab Gel Instruments (thousands)	Maximum Number of Runs—Preexisting Slab Gel Instruments (thousands)	Number of Additional Slab Gel Instruments Required	Avoided Equipment Expenditures (2005$)
1998	4,709	123	39	95	$14,220,000
1999	44,474	1,158	373	801	120,079,000
2000	90,518	2,357	760	927	139,039,000
2001	76,129	1,983	851		
2002	76,129	1,983	851		
2003	72,598	1,891	811		
2004	42,774	1,114	478		
2005	8,241	215	92		

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding. All dollar values are in real 2005$.

Box 4-5. Avoided ABI Prism 377 Equipment Expense Calculations

Using the data from Table 4-16 showing the number of runs required, the avoided equipment cost of sequencing 76,940 million bps in 2000 with slab gel sequencers was calculated as follows, assuming each sequencer operated three shifts per day (6,000 hours/year):

Runs/year per slab gel sequencer = 6,000 hours ÷ 6.83 hours of run time and set up ≈ 878 runs/year

In 1998, if labs had the same number of slab gel sequencers as capillary ones (45), they would have been able to complete only 39,510 runs (878 runs x 865 capillary sequencers). 123,000 runs were needed, requiring 95 additional slab gel sequencers [(123,000 – 39,510)/878].

Similarly, in 1999, 801 additional sequencers would have been needed, bringing the total available in 2000 to 895 slab gel sequencers, which were capable of 1,546,000 runs. The deficit of 811,000 runs in 2000 would have required 927 more, bringing the total number of supplemental installations to 1,823.

Avoided equipment expenditures in 2000 = 927 slab gel sequencers x $150,000 ≈ $139,050,000

cumulative capacity would have been sufficient to match capillary sequencers' data production volume under the counterfactual scenario.

This estimate of 1,823 instruments is conservative because it is assumed that all those instruments would be operated three shifts a day. The 1,823 units represented additional purchases beyond those preexisting units required to match the capillary instruments' data production volumes. The cash outflows for these purchases occurred in those 2 years, although the expected life of the instruments was 5 years.

RTI collected estimates of the average price paid for the 96-lane ABI 377, the MegaBACE 1000, and the ABI Prism 3700. The avoided equipment benefit in Table 4-19 was reduced by the costs of the capillary instruments, which were approximately $150,000 for the 377, $234,000

Table 4-19. Net Avoided Equipment Expense Benefit (2005$)

Year	MegaBACE 1000 Costs	ABI Prism 3700 Costs	ABI Prism 377 Avoided Equipment Benefit	Net Equipment Benefits
1998	–$21,060,000		$14,220,000	–$6,840,000
1999	–39,780,000	–$165,500,000	120,079,000	–85,201,000
2000	–49,140,000		139,039,000	89,899,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding. All dollar values are in real 2005 dollars.

for the MegaBACE, and $331,000 for the 3700 in constant 2005 dollars (Mardis, 1999).[12]

Table 4-19 presents the net equipment benefits for 1998 through 2000. The negative net benefits for 1998 and 1999 reflected the net public equipment cost of adopting the capillary sequencers.

Assembling the labor, consumables, and equipment benefits into one time series yields the cash flows presented in Tables 4-20 and 4-21. Table 4-20 presents each benefit category individually. Table 4-21 separates benefits into those associated with the MegaBACE and those for the ABI 3700 for reference. It is important to recall that the number of 3700s installed in 1999 exceeded the cumulative installations of MegaBACEs installed between 1997 and 2000.

Total net benefits the public realized from Molecular Dynamics' project work were estimated to be $280.2 million, with more than half of those accruing during 2000, the year in which the initial draft of the HGP was completed.

4.3.6.6 Private Benefits and Costs

As with Affymetrix, private benefits such as net profit margins by product line are confidential business information. Private benefits could not be calculated reasonably, but a rudimentary estimate was developed by analyzing Molecular Dynamics' 1997 Form 10-k filing.

A crude profit per unit was estimated by comparing net income with total revenues. This assumed that all of a company's products had the same net margin after all cash and noncash expenses and taxes. In 1998, Amersham Pharmacia Biotech's net profit margin was about 13%, as was ABI's. Given that the list price for the MegaBACE 1000 was $200,000, the estimated profit per unit (in nominal terms) was $26,000.

The annual private benefit Molecular Dynamics received from the project would be the profit estimate per unit multiplied by the number of units sold, including exports. Exports were included because profits accrued to the innovator (see Table 4-22). Similarly, the year-end 2000 cutoff for

[12] In nominal terms, the ABI Prism 3700 price was $100,000 more than the MegaBACE 1000 at $300,000. The incremental difference in price was partly explained by the fact that the 3700 had the automatic loading feature discussed in an earlier footnote. ABI had substantially more brand presence; an established reputation; and a more extensive sales, marketing, and service infrastructure than Molecular Dynamics had during the period covered in this analysis.

Table 4-20. Avoided Labor, Consumables, and Net Equipment Expense Benefits (2005$)

Year	Midpoint of Installed Base of Capillary Sequencers	Labor Benefits	Consumables Benefits	Net Equipment Benefits	Total Benefits
1998	45	$5,307,000	–$1,968,000	–$6,840,000	–$3,501,000
1999	425	50,126,000	–18,589,000	–85,201,000	–53,664,000
2000	865	102,021,000	–37,834,000	89,899,000	154,085,000
2001	970	85,803,000	–31,820,000		53,983,000
2002	970	85,803,000	–31,820,000		53,983,000
2003	925	81,823,000	–30,344,000		51,479,000
2004	545	48,209,000	–17,878,000		30,331,000
2005	105	9,288,000	–3,444,000		5,844,000
Total		468,380,000	–173,699,000	–2,142,000	292,540,000

Source: RTI estimates.

Table 4-21. Public Benefits, Costs, and Net Benefits—Molecular Dynamics (2005$)

Year	Public Benefits—MegaBACE 1000	Public Benefits—ABI Prism 3700	Public Costs—ATP Cost Share	Net Public Benefits
1995			–$2,409,000	–$2,409,000
1996			–2,940,000	–2,940,000
1997			–3,049,000	–3,049,000
1998	–$3,501,000		–1,722,000	–5,223,000
1999	14,285,000	–$67,950,000	–2,175,000	–55,839,000
2000	37,984,000	116,101,000		154,085,000
2001	26,157,000	27,826,000		53,983,000
2002	26,157,000	27,826,000		53,983,000
2003	23,652,000	27,826,000		51,479,000
2004	16,418,000	13,913,000		30,331,000
2005	5,844,000			5,844,000
Total	146,996,000	145,544,000	–12,295,000	280,245,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding.

public benefits did not apply because private benefits do not face the same cutoff from the availability of comparable alternatives.

Annual profits were calculated for MegaBACE sales through 2005. As noted earlier, Molecular Dynamics invested $6 million in industrial engineering and production systems to commercialize the sequencer. These costs were assumed to have been incurred in 1997 and 1998 when the MegaBACE was in beta testing and its first year of commercial sales. The estimates in Table 4-22 are included herein for illustrative purposes only.

4.4 NET ECONOMIC BENEFITS AND QUALITATIVE IMPACTS OF MIND DEVELOPMENT

According to the experts RTI interviewed, Affymetrix and Molecular Dynamics developed technologies that were significant contributions to society. The MegaBACE 1000 fulfilled the need for a new, high-throughput and low-cost DNA sequencing technology, induced innovation at ABI, and put the completed map of the human genome in scientists' hands years earlier than expected. The quality and power of Affymetrix's revolutionary GeneChip microarrays were enhanced by ATP-cofunded research into shrinking feature sizes, improving assays and protocols, and enhancing the software that enabled interpretation of the microarrays' enormous data production capabilities.

Table 4-22. MegaBACE 1000 Cumulative Sales and Estimated Annual Molecular Dynamics Profits

Year	Estimated Annual Sales	Cumulative Unit Sales	Estimated Annual Profits
1998	150	150	$3,900,000
1999	280	430	7,280,000
2000	350	780	9,100,000
2001	150	930	3,900,000
2002	150	1,080	3,900,000
2003	150	1,230	3,900,000
2004	150	1,380	3,900,000
2005	150	1,530	3,900,000

Source: RTI estimates.

More broadly, ATP's support of two small biotechnology companies validated a new industry and moved the technologies being developed by Affymetrix, Molecular Dynamics, and other firms like them from the periphery to the spotlight.

4.4.1 Time Series of Public Benefits and Costs and Performance Measures

RTI valued benefits relative to the technologies the ATP project superseded, analyzing the achievement of the same accomplishments with the less-effective and less-efficient technology, and then calculated the savings.

In the case of Affymetrix, the defender technology was its own microarray products, which would not have become as robust as quickly. If there had been no JV, society would not have benefited from Molecular Dynamics' introduction of the MegaBACE 1000 in 1997 and the acceleration of the ABI 3700. Consequently, genome centers and research laboratories would not have acquired the amount of information they did as quickly. The human genome project and other large-scale sequencing projects would likely have been completed during 2005 or 2006, as planned.

Public economic benefits totaled $359.8 million. Table 4-23 presents a time series of public benefits from the combined JV and from each company individually. When adjusted for inflation, ATP's contribution was $34.7 million, of which Affymetrix received 65% and Molecular Dynamics 35%.

The NPV for the entire project was $215.6 million, and the project had an internal rate of return of 84% and a benefit-cost ratio of 8.7 (see Table 4-24). For every $1 ATP invested, the public realized $8.70 in benefits.

The social rate of return expands a review of the JV's performance to include the additional costs and benefits Affymetrix and Molecular Dynamics incurred to bring the JV technologies to market, their JV cost share, and the profits they earned.

Table 4-23. Public Benefits, Costs, and Net Benefits—MIND Development JV Project (2005$)

Year	Molecular Dynamics Benefits (Public)	Affymetrix Benefits (Public)	Total Benefits (Public)	Total ATP Cost Share	Net Public Benefits
1995				–$4,007,000	–$4,007,000
1996				–5,717,000	–5,717,000
1997				–8,678,000	–8,678,000
1998	–$3,501,000		–$3,501,000	–8,076,000	–11,577,000
1999	–53,664,000	$54,415,000	751,000	–8,192,000	–7,441,000
2000	154,085,000	47,535,000	201,620,000	—	201,620,000
2001	53,983,000		53,983,000	—	53,983,000
2002	53,983,000		53,983,000	—	53,983,000
2003	51,479,000		51,479,000	—	51,479,000
2004	30,331,000		30,331,000	—	30,331,000
2005	5,844,000		5,844,000	—	5,844,000
Total	292,540,000	101,950,000	394,490,000	–34,670,000	359,820,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding.

Table 4-24. Public Performance Measures—MIND Development Project

Public benefits (2005 $ millions)	394.5
Public costs (2005 $ millions)	–34.7
Net public benefits (2005 $ millions)	359.8
NPV of net public benefits (2005 $ millions)[a]	215.6
Benefit-to-cost ratio	8.7
Internal rate of return	84%

[a]To compute NPV, net public benefits were discounted to 1995 using a 7% annual discount rate.

Source: RTI estimates.

Assuming incremental profits for Affymetrix were zero and employing the rudimentary profit estimates for Molecular Dynamics suggested a social rate of return of 59% for the MIND Development project. This social performance measures is lower than the 84% public rate of return because of the innovators' costs.

4.4.2 MIND Development's Contributions to Molecular Biology

The industry experts interviewed for this study believe that benefits from early completion of the HGP and development of the analytic capabilities of DNA microarrays cannot be overestimated. These achievements are

perhaps best understood in terms of their impact on drug development, public health, or lives saved by having these technologies sooner.

Sequencing moved from a cumbersome process to a highly automated process that produces several times the amount of data with near-perfect accuracy. Once the human genome was mapped, there was an enormous improvement in controlling and understanding gene expression and other applications. Improved data quality and production also had significant downstream impacts on data analysis, outcomes, and research.

When the HGP began, the cost to sequence one base pair ranged from $5 to $10. All along, researchers anticipated that technical and organizational advances would enable the project to be completed on time. They also believed that the cost per sequenced base would drop from $2 to $5 per finished base pair to $0.50 or less per pair (Hodgson, 2000). Now that cost is $0.01.

GenBank, a database supported by NIH, contains more than 56 billion finished DNA sequences. These sequences are for more than 300 completed genomes; an additional 750 genomes are currently being sequenced, including those for cancers (Bonetta, 2006).

NHGRI continues ATP's work, pushing to reduce costs even further by supporting technology development efforts for the next generation of DNA sequencing, and announced grants of $83 million to develop technologies that can sequence a human genome for $100,000 and $1,000 (NHGRI, 2004).

Having the finished sequence of the human genome enables downstream innovations in microarrays and other technologies because they require the reference sequence that Molecular Dynamics accelerated. These data make SNP analysis, genotyping, gene expression, and resequencing possible.

Affymetrix leverages mapped genomes to create diagnostic tools that in turn yield invaluable information about the presence of genes, genetic mutations, and the efficacy of medical therapies for patients of varying genetic backgrounds. Affymetrix believes that microarrays enable hypothesis-free testing because so much genetic information is acquired from one assay rather than from the gene-by-gene methods that the microarrays replaced.

The JV moved medical science closer to the era of personalized medicine in which patients will have medical therapies recommended to them based on their genetic makeup. Doctors' ability to identify the genetic basis of many diseases and pharmaceutical companies' ability to develop new drugs have been greatly advanced.

5 Case Study: Molecular Tool and Orchid Cellmark's SNP-IT Technology

In 1994, a small Maryland biotechnology firm known as Molecular Tool received a contract to determine the lineage of racehorses through DNA testing. Believing that they could significantly improve on the state-of-the-art technology for performing these tests by using a single-based primer extension (SBPE) technology they had pioneered, MT applied for an ATP award. MT was awarded approximately $2 million to develop a set of new single nucleotide polymorphism (SNP) analysis techniques that might reduce the processing time of a DNA test from 30 minutes to about 5 minutes. Reducing the processing time would yield substantial labor and materials savings as well as greatly improved throughput capabilities.

MT later applied for a second ATP award to create a complete analysis system using, in part, their proprietary analysis technology invented during the first project. By the time ATP cofunding was awarded, MT had been purchased by Orchid Cellmark (Orchid), which supported the nascent project. Combining MT's SBPE technology and Orchid's microfluidics expertise permitted Orchid to develop an efficient, high-throughput method for conducting DNA testing with potential applications in forensic analysis, paternity testing, and potentially diagnostic medicine.

Orchid licensed the resulting ATP-cofunded technology, named SNP-IT, to several organizations. Beckman Coulter (Beckman) acquired the rights to use SNP-IT in its SNPStream line of genotyping instruments.

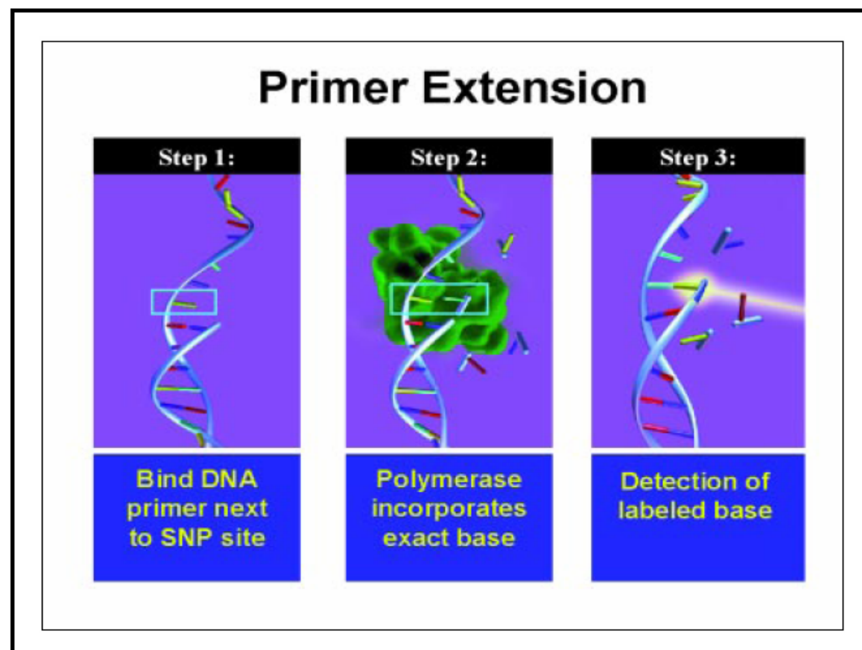
5.1 OVERVIEW OF MOLECULAR TOOL/ORCHID CELLMARK PROJECTS

Philip Goelet, Mike Knapp, and Stephen Anderson founded MT in 1988, with the intention of developing SBPE technology to enable faster and cheaper genetic analysis based on identifying SNPs—genetic variations found in DNA. In the early 1990s, they created a set of biochemical processes to enable SBPE, which they named genetic bit analysis (GBA).

GBA was a semiautomated process that identified and analyzed any variations in DNA (i.e., SNPs). MT's early GBA analyses used individual polymerase chain reaction (PCR) amplifications conducted in each well of 96-well microtiter plates, hybridization capture of PCR-generated templates, and genotyping of the captured template by primer extension sequencing. Figure 5-1 illustrates this process.

In the early 1990s, the Jockey Club of America became MT's first major customer. At the time, the standard technique for determining a horse's lineage was through protein analysis. Protein analysis investigates antibodies and provides the most accurate method of identification; however, it was (and remains) expensive and slow. MT provided much faster SNP-based tests in the spring of each year when hundreds of

Figure 5-1. Genetic Bit Analysis Procedure



Source: Courtesy of Orchid Cellmark, Inc.

thousands of tests were needed. MT soon acquired a small number of clients in human hereditary testing and forensics.

5.1.1 Overview of Molecular Tool and Orchid Cellmark

Despite MT's innovations, the cost of GBA and the labor requirement per test remained too high for most research applications. Although the use of standard chemistry lab plates allowed some level of automation in this process, sample preparation, hybridization, and analysis were all conducted manually. A standard GBA analysis took approximately 30 minutes, a technical barrier that prevented MT from attracting new customers.

MT recognized the need for an automated system that could conduct parallel genetic analysis procedures in a miniaturized format, allowing more cost-effective and faster analyses. At the time, some SNP services were being used for paternity testing; however, the cost per analysis was too high to compete with analyses looking at single tandem repeats, or STRs.

When compared with STR analysis, SNP analysis could provide an increase of approximately 50% in "linkage information content" resulting from analysis (Schaid et al., 2004). Still, in the mid- to late-1990s, STR analysis had become the marker of choice for parentage and most forensic testing because it was both inexpensive, accurate, and relatively fast using higher-throughput analysis methods (Gray, Campbell, and Spurr, 2000). SNP analysis could not compete with STR analysis on a widespread basis until it became less expensive.

MT believed that clinical research would be the largest market for SNP services, though the research community demanded low prices to afford the large volume of genotyping that would be undertaken. MT's GBA technology was not yet capable of meeting those cost or volume requirements, and MT sought ATP cofunding to develop a high-throughput automated system for SNP analysis.

At the time of the first ATP project award, MT had 20 employees and did not have the resources to continue R&D into GBA. MT was unable to secure external funding because of the technical and market risks associated with their technology strategy. No research had yet been successful at miniaturizing genetic analysis processes, and it was very uncertain whether such technical capabilities could achieve commercial success.

Executives with the company at this time indicated that MT would not have been able to conduct this research without the ATP cofunding. In the absence of the award, MT would have continued to market its existing GBA analysis technology with which they had had very limited success.

The first ATP award provided MT with immediate financial resources with which to conduct risky, exploratory research, which resulted in several significant technical developments and a feasibility demonstration of a high-throughput SNP analysis instrument. Further, former MT executives interviewed by RTI believe that they were able to attract additional investors because ATP's investment validated the potential of MT's technology.

At the time of the second ATP project award, MT had grown to 30 people but still did not have the cash flow to finance high-risk research. The company wanted to develop the tools and technologies necessary to create an integrated analysis system. Although MT had merged with GeneScreen since the completion of the first award, funding remained limited for additional research aimed at miniaturizing and encapsulating the GBA analysis process.

The second ATP award aimed to develop a platform to house their SNP analysis technology and create a cost-effective miniaturized, automated analysis system. MT was acquired by Orchid in the second half of 1998 before the project began.

Orchid was a recent spin-off from the Sarnoff Corporation and had extensive expertise in developing automated microfluidics processors. It bought MT with the intention of using GBA as an application for their microfluidics platform. Orchid's original focus was on technology research and development and eventually commercialization.

5.1.2 Project Research and Development Goals

MT/Orchid developed the first commercial platform for high-throughput SNP genotyping. ATP's investment helped the company overcome technical barriers to rapid genotyping analyses. Between 1995 and 2001, a total of $5.1 million was invested in the two 3-year ATP projects, $3.6 million of which was contributed by ATP (see Tables 5-1 and 5-2).[13] The balance of this section discusses each project's R&D goals.

[13]Company executives stated that this budget proved to be sufficient to meet the projects' technical objectives.

Table 5-1. Molecular Tool Project Costs: Integrated Microfabricated Devices for DNA Typing, 1995–1998

Year	ATP Funding	MT/Orchid Matching Funding	Total Funding
1995	$267,000	$125,000	$392,000
1996	1,143,000	340,000	1,483,000
1997	511,000	208,000	719,000
1998	18,000	12,000	30,000
Total	1,939,000	685,000	2,624,000

Sources: ATP.

Note: All values in actual dollars.

Table 5-2. Orchid Cellmark Project Costs: Polymerase Signaling Assay for DNA Variation Detection on Universal Processor Arrays, 1999–2001

Year	ATP Funding	MT/Orchid Matching Funding	Total Funding
1999	$690,000	$394,000	$1,084,000
2000	603,000	344,000	946,000
2001	662,000	377,000	1,039,000
Total	1,955,000	1,115,000	3,069,000

Sources: ATP.

Note: All values are in actual dollars.

5.1.2.1 Integrated Microfabricated Devices for DNA Typing

MT's main goal was to develop an approach to analyzing SNPs more quickly, cost effectively, and accurately than PCR or sequencing techniques using the company's GBA process as a starting point. The research team aimed to develop a microfluidics process that would allow GBA processes to be conducted in parallel in a miniaturized format on 96-well titer plates.

The team had three key technical objectives:

- **Develop a microfluidics analytic system to enable genotyping of single genetic bits.** MT intended to reduce the size of each stage of the analysis process, including reagent addition and fluorescence identification, while ensuring sample integrity and high reproducibility of results.
- **Develop a GBA microdevice.** MT proposed to identify and investigate the use of a platform by which GBA could be conducted on a microscale. MT had already been using 96-well

plates, but they intended to increase the density of GBA processes that could be conducted on one plate.

- **Develop the feasibility of creating a 1,000 GBA microdevice.** MT planned to develop the capabilities to create a system in which a high density of GBA processes could be conducted on a very small surface.

MT planned a proof-of-concept instrument that would allow 1,000 GBA in 96-well plates. The new system would encompass several steps. First, a DNA probe would be created, and multiple copies of the same probe would be attached to a glass or silicon plate, each in a separate well. Polymerase, an enzyme that assists in DNA replication, and a different set of broken nucleotides would be added to each well. Fluorescent reagents would be added, and the researcher would look for reactions to specific broken nucleotides. If no SNPs were present, only one probe would "fluoresce," indicating that the nucleotide was present. If SNPs were present, there could be multiple reactions of fluorescence.

To meet this ultimate goal, the focus of this research project was to investigate the problems that might occur when GBA processes were miniaturized.[14]

5.1.2.2 Polymerase Signaling Assay for DNA Variation Detection on Universal Processor Arrays

Although MT's first ATP award focused on conducting GBA analysis in a miniaturized format and investigating the feasibility of conducting multiple such analyses in parallel, this second project aimed to develop a microfluidics-based SNP analysis system using GBA analysis techniques.

With the second ATP research award, MT aimed to develop a prototype SNP analysis instrument. Thus, they needed to develop several key technologies/processes:

- a universal array, including a comprehensive set of DNA probes;
- expanded digital imaging capabilities to quickly capture information from the miniaturized analysis process;
- pattern-matching software to quickly provide the results of the analysis to researchers; and
- miniaturization and systems integration.

[14]More specifically, they planned to investigate liquid cross-talk (the potential leakage of fluid between channels) and liquid handling (the parallel distribution of liquids of different types across 30 parallel channels).

At a high level, this project required developing the systems integration techniques necessary for various microfluidics processes to work together and the imaging technology and software needed to quickly and accurately characterize the results of each analysis.

In 1998, research in integrated miniaturized instrumentation was a new area. Several processing steps had never been integrated in a single chip. Heterogeneous phase biochemical reactions, or reactions using different inputs, had never been performed on a chip either. The chemical sensitivity of oligonucleotides to miniaturized processes would require the research team to design new technical procedures.

5.2 ANALYSIS OF MOLECULAR TOOL AND ORCHID'S TECHNOLOGY OUTCOMES

MT had largely completed its major proposed technical objectives by the end of the first ATP project: they developed a DNA probe attachment chemistry, increased array density, and produced a universal "DNA processor" that allowed for rapid and accurate imaging and data analysis.

Former executives indicated that the imaging capabilities represented a major improvement over scanning technologies that had been used in the past. Imaging techniques adapted from the semiconductor industry allowed for much faster image capture and analysis than the linear collection of information gathered through scanning. Other improvements from the first project included improved biochemistry for primer extension. Software improvements allowed more efficient data analysis, and the biochemical improvements enabled processing savings through a reduction in time and materials.

The second project was a distinct effort that led to new biochemistries and processing capabilities that could be encapsulated in a stand-alone instrument. The resulting prototype was capable of conducting GBA with 12-plex arrays on 96-well plates.

The SNP-IT technology enabled an increase in the accuracy of hereditary DNA analysis from one in a million to one in several billion and a cost reduction of approximately $1 per genotype, or half that of common PCR and sequencing techniques used at the time.

5.2.1 Commercialization Status and Products

To lower the high cost and improve the accuracy of genetic analysis, MT and other companies worked throughout the mid- to late-1990s to develop high-throughput SNP analysis techniques based on several biochemical processes. These processes included SBPE, allele-specific oligonucleotides hybridization (ASO), and allele-specific primer extension (ASPE). Some of these techniques were direct detection methods of genotyping (e.g., SBPE), while others were indirect techniques (e.g., ASO and ASPE).

In 1999, Orchid Cellmark released one of the first commercially available products able to conduct high-throughput SNP analysis. The SNPStream25k was based on the direct detection methods MT developed during the first ATP-cofunded research project and automation procedures from the second ATP project, collectively called the SNP-IT technology. Orchid also built a facility, called the MegaSNPatron, to offer contract-based SNP analysis services using SNPStream products. This facility has conducted millions of SNP analyses since it first opened in 1999.

Orchid's commercialization strategy was to place its proprietary technology in products already on the market. In 2000, as part of its "Platform Propagation Strategy," Orchid succeeded in placing a variety of license and partnership agreements. In a company press release in 2000, Orchid stated, "Together, the two [license] agreements [with PE Biosystems and Amersham Pharmacia Biotech] are making Orchid's SNP-IT technology available to researchers to perform genotyping analyses on an estimated 90% of the installed base of DNA sequencers already available in laboratories today" (Orchid, August 10, 2000b).

In 2001, 17.1% of Orchid's revenue came from products and 82.9% from services. At the time, they held 70 U.S. patents and 78 foreign patents. In 2002, Orchid divested its instrument businesses and became exclusively a service provider, retaining the rights to its SNP-IT primer extension intellectual property.

During the transition, Beckman purchased Orchid's instrument business and today offers a line of SNP analysis instruments, marketed as the GenomeLab SNPStream genotyping product line, enabled by the SNP-IT technology.

Licensees in 2000 included PE Biosystems, Amersham Pharmacia, PerkinElmer, Beckman Coulter, Affymetrix, and Luminex (Orchid, 2001a). In 2001, Orchid issued additional licenses to and formed collaborative agreements with Asper Biotech, AstraZeneca, DNALink, Hitachi MirairBio, Quest Diagnostics, and Invitrogen (Orchid, 2002b).

5.2.2 End Users and Applications

SNP analysis is important to pharmaceutical and biotechnology companies interested in pharmacogenomics research and to academic, government, and nonprofit research institutions interested in identifying disease genetic characterizations. Orchid's SNPStream product line targeted all of these markets.

Reductions in time and improvements in accuracy have been important factors in the increased use of SNP analysis over the past 10 years. According to experts in academia and the biotechnology and pharmaceuticals markets, cost reductions have probably had the largest impact.

In 1994, the price of SNP analysis was around $5, and by 1999, early high-throughput technologies (including Orchid's) improved this cost to approximately $1. Currently, industry experts estimate that a SNP analysis costs as little as $0.15 in some cases. This represents over a 30-fold reduction in cost.

Orchid and Beckman sell SNP analysis products to three main customers—biotechnology companies (40%), pharmaceutical companies (20%), and research and government laboratories (40%). These products were generally used for three broad applications:

- *disease discovery* to understand specific genetic attributes of complex diseases (mainly biotech companies),
- *drug testing, or pharmacogenetics,* to improve the efficacy of pharmaceuticals (mainly pharmaceutical companies), and
- *genetic identification* to identify genetic profiles for humans, animals, and other organisms (mainly research/government labs).

In the disease discovery and drug testing (pharmacogenetics) markets, high-throughput SNP analysis provided a cheaper and faster way to conduct analyses previously performed using conventional gel-based DNA sequencing. This is where the first major market developed.

Orchid worked with and sold SNP-IT-based products and services to several companies for disease discovery research. For example, in 2001 Orchid developed a service agreement with Oklahoma Medical Research Foundation (OMRF) to conduct high-throughput SNP scoring on samples provided by OMRF to help determine the genetic characteristics of lupus. OMRF researchers had conducted extensive research into this area, but by using Orchid's technology, they hoped to accelerate gene discovery in lupus[15] (Orchid Cellmark, September 25, 2001b). That same year, Orchid began a partnership with Ellipsis Biotherapeutics Corporation to perform SNP analyses related to the genetic characteristics of inflammatory bowel disease (Orchid Cellmark, October 10, 2001c).

In the genetic identification market, SNP analysis products were competing mainly against STR analysis, which had already become well entrenched in the United States because of its widespread use in forensics. However, SNP analysis is the preferred technology for more challenging gene identification analyses.

Following the World Trade Center disaster, for example, the Office of the Chief Medical Examiner of New York City spent almost an entire year working to identify victims based on genetic material gathered at the site. When STR analysis was unable to identify 49% of the victims, New York City researchers turned to SNP analysis methods. The remaining DNA was too damaged or degraded for STR analysis.

New York City contracted with Orchid and several other public and private laboratory facilities to conduct more robust analysis using SNPs (Orchid Cellmark, November 9, 2000c). First, researchers tested the 6,000 or so reference samples—using victim's genetic information from toothbrushes, hairbrushes, etc.—and created a database, and then they took genetic material collected at the World Trade Center site and compared the resulting samples (Hand, 2002).

The Federal Bureau of Investigation (FBI) awarded Orchid two contracts in 2003 to develop high-throughput SNP analysis techniques for forensic identification applications. The first contract involved developing a panel of SNP markers that could identify male DNA specifically by measuring polymorphisms on the Y chromosome. Measuring polymorphisms on the

[15] According to a September 25, 2001, press release from Orchid, "Lupus affects approximately one in 1,000 people in the United States. Ninety percent of people who develop lupus are women between the ages of 18 and 40. African American women have the highest risk of developing the disease, approaching a prevalence of 1 in 250. Lupus can be highly debilitating and causes early death, especially in the absence of treatment, in many of those affected."

Y chromosome would allow the FBI to create a profile of human male DNA from a degraded sample and enable differentiation between male and female DNA when samples contain mixtures of DNA. The second contract was to create an "expanded panel" of SNP markers that would double the number of SNPs Orchid was using and increase its ability to identify individuals using degraded DNA (*Forensic Focus,* 2003).

Another gene identification application of Orchid's technology is in animal husbandry. Much of Orchid's genetic identification work has been conducted in the United Kingdom (UK) as part of a large government project to help British farmers breed sheep with a reduced likelihood of developing scrapie, an untreatable and fatal disease. The UK has 40 million sheep that could be decimated by an outbreak of the disease. This project, started in 2001 and renewed in 2004, accounted for over 20% of Orchid's revenue in 2004 (Orchid's 2005 SEC 10-K filing).

5.2.3 Competitive Landscape for SNP Analysis

SNP analysis has become a competitive market in recent years, and the market stratified as new users and analysis needs have emerged. Some technologies and processes, including SNP-IT, focus on small, customized analyses, while others are designed for use with larger samples. Table 5-3 provides an overview of the major SNP analysis products on the market, the technologies on which they are based, and basic information on costs and capabilities.[16]

In this highly competitive market, Orchid's SNP-IT technology is predominantly used for DNA-based human identity and agriculture testing. New techniques have been developed by competing equipment companies to allow rapid SNP analyses, and alternative methods, such as DNA sequencing, are still being used by some for SNP analysis.

In broad terms the SNP market is broken out into two categories of analysis:

- **Direct SNP analysis**—includes traditional sequencing techniques offered by GE Healthcare and Applied Biosystems (ABI), as well as DNA polymerase-based methods offered by Orchid, Pyrosequencing, and Sequenom.

[16] Although Third Wave and Nanogen both produce SNP analysis products, the Invader and NanoChip, respectively, these are not included in Table 5-3 because adequate information for comparability is not available. Also, it is important to note that several companies included in Table 5-3 received ATP funding, but not to help develop competing products. Third Wave and Nanogen did, however, receive funding from ATP directed at developing alternative approaches to SNP analysis, which now compete with Orchid's SNP-IT technology.

Table 5-3. Commercially Available SNP Analysis Tools (2005)

Product	Company	Tech-nology	SNP Selection	Type of Detection	Initial Setup Cost	Per-Sample Cost	Max SNP per Reaction	Assay Time	Throughput Samples/Day
GeneChip Human Mapping 500K Array Set	Affymetrix	ASO	Fixed set	Indirect	$250,000	$500–$1,000	500,000	2–3 days	48
BeadArray	Illumina	ASPE	Fixed set	Indirect	$300,000	$60–$800	250,000	2–3 days	8–1,000
GeneChip Targeted Genotyping Array	Affymetrix	ASO	Customized	Indirect	$250,000	$60–$300	20,000	2 days	48–96
FlexMAP	Luminex	ASPE	Fixed	Indirect	$65,000	$20–$25	50	4 hours	384
SNPPlex	ABI	PCR	Fixed set	Indirect	$300,000	$2.00–$2.50	48	2.5 days	200,000
GenomeLap 48-Plex SNPStream	Beckman Coulter	SBPE	Customized	Direct	$150,000–$200,000	$3.80	48	1.5 days	384–55,000
MassARRAY system	Sequenom	Mass spec.	Customized	Direct	$289,000 (compact MS)	$1.12	29	1–1.5 days	3,000
Pyrosequencing	Biotage	Pyroseq	Customized	Direct	$100,000 (PSQ HS 96)	$0.21	3	10 minutes	4,000
TaqMan	ABI	PCR	Customized	Indirect	$92,000 (7900 HT)	$0.15–$0.20	1	1 day	25,000–50,000

Note: This information is based significantly on Spinney (2005) and Syvänen (2005).

- **Indirect SNP analysis**—includes hybridization arrays developed by Affymetrix, Genometrix, Illumina, and Nanogen and enzyme-enhanced hybridization techniques developed by ABI, GE Healthcare, and Third Wave.

Sequenom and ABI introduced products in 2000 (MassARRAY) and 2001 (Taqman), respectively, that competed with Orchid's SNPStream. Although Orchid and Sequenom were the main competitors in 2000 and 2001, the market now includes Nanogen, Illumina, Luminex, and Third Wave, among others.

Beckman's SNPStream fits between the least expensive products (e.g., Taqman and Pyrosequencing), which offer relatively low throughput, and the more expensive microarray products, such as those offered by Illumina and Affymetrix, which offer very high throughput.

One advantage to users of the SNP-IT technology is that Beckman's products are customizable, which allows more targeted analyses at a lower cost. In contrast, Affymetrix's high-throughput product is a fixed array set, which in many cases will result in unnecessarily high per-sample costs if only certain SNPs are of interest.

After 2003, when the Human Genome Project was completed, some believed that the DNA sequencing market would essentially die out; however, today, DNA sequencing accounts for $500 million in annual revenue.[17] Industry experts have suggested that the SNP analysis market could grow to be several times as large. For example, drug companies are currently conducting SNP analysis on every clinical trial sample, and experts estimate that approximately 30 million samples are generated by clinical trials each year. Tens of millions of tissue samples are generated by tumor biopsies, among other such analyses, providing evidence of a significant addressable market.

GlaxoSmithKline has indicated that they plan to use SNP analysis for all lab processes to improve drug testing and prevent drug interactions. Additionally, recent increases in lawsuits related to drug interactions have generated increased interest in SNP analysis, and SNP analysis of newborns could allow early identification of genetic conditions.

[17] In a June 21, 2005 letter to shareholders, Solexa CEO John West cited this figure and noted that total revenues from DNA sequencing and genetic analysis account for more than $1 billion per year. Solexa is a major DNA sequencing provider. The letter can be accessed at http://www.solexa.com/pdf/Letter_to_Shareholders_2005_06.pdf.

5.2.4 Quantitative Analysis of Moledular Tool/Orchid's Technology Outcomes

Based on interviews with MT and Orchid executives, RTI concluded that MT would not have completed development of the SNP-IT technology without ATP funding of both projects. Consequently, SNP-IT users would have spent considerably more labor and materials on DNA analyses. These analyses would have generated less accurate results and would likely not have been as numerous.

Although genotyping analysis would likely have been more costly for researchers without ATP's support of MT/Orchid's research, the overall view of benefits must be interpreted cautiously. Within 1 year of the release of Orchid's SNPStream, Sequenom launched its MassARRAY system,[18] which offered similar cost savings and functionality as the SNPStream. Thus, Orchid can be credited with providing benefits to users for only the 1-year period when the SNPStream was the sole instrument for high-throughput genotyping. This includes instruments used to provide contract analysis services at the MegaSNPatron facility.

The counterfactual scenario was that without ATP's investment in both projects, users would have been able to purchase a product that enabled automated genotyping analysis with similar cost savings to the SNPStream by mid-2000. Public benefits were limited to cost savings from SNPStream installations and service agreements during 1999.

Public benefits were calculated over the useful life of SNPStream instruments. End users continued to accrue economic benefits from SNPStream instruments even after alternatives were introduced because they had a sunk investment in the instruments. The technology alternatives were introduced after users made their investment decisions. As rational actors, they would not adopt an alternative technology if that alternative's fixed costs exceeded the potential savings in variable costs. The technologies Sequenom and ABI introduced are not believed to have offered enough cost savings for SNPStream users to switch.

Locked into their investment, SNPStream users expected to accrue benefits relative to the technologies and systems the SNPStream supplanted. Thus, RTI calculated the benefits users were estimated to have accrued over the entire 5-year expected life of the equipment.

[18] Sequenom announced that its MassARRAY product was officially available for purchase beginning in late 1999; however, interviews indicated that they were not competitive with Orchid's product until early 2000 when they started delivering units of their MassARRAY instrument.

In the case of the MegaSNPatron, users did not bear an investment cost, and the benefits were considered as a per-genotype cost savings for the 1-year acceleration period. The cost savings measure RTI used was net of the incremental purchase price and maintenance costs of operating the MegaSNPatron's instruments.

It is important to remember that the SNP-IT technology has been used in Beckman's products since 2001. Orchid continued to license the technology, which led to additional use (and related user cost savings) in other companies' products. However, potential downstream benefits from such use were not included in this analysis.

5.2.4.1 Quantifying Economic Benefits

During 1999, Orchid sold approximately six SNPStream 25K instruments and leased one additional instrument, which was later purchased by the leasing organization. Given the rapid introduction of alternatives, RTI only estimated benefits from these seven SNPStream installations. Benefits from these instruments were calculated over their approximate useful life of 5 years, as described above.

Based on the technical capabilities of the SNPStream 25K instrument first sold in 1999 and information gathered from users and former Orchid executives, RTI estimated that firms that purchased this instrument conducted on average 200,000 SNP genotyping analyses per year for the first 3 years, followed by approximately 2 years of reduced use estimated at 100,000 analyses per year.[19] At first these instruments were purchased for specific research projects, but later these SNPStreams were supplemented by other instruments. As such, the number of analyses conducted with SNPStream instruments decreased.

In 1999, only half of the 200,000 analyses per year (or 100,000) were conducted with each instrument. Over the next 2 years (2000 to mid-2002), 200,000 analyses were conducted per instrument per year; then for 2 years (mid-2002 to mid-2004), only 100,000 analyses per instrument were conducted per year. Table 5-4 provides a breakdown of the approximate number of analyses conducted annually.

At the time these instruments were purchased, the average total cost to users of conducting such analysis through "defender" techniques, such as PCR and sequencing, was more than $2 per genotype. When Orchid

[19]SNPStream25ks have an estimated useful life of 5 years after which they have no residual value.

released the first SNPStream, its technology enabled users to decrease the cost of each genotyping exercise significantly—down to less than $1 per genotype. This figure was inclusive of the equipment adoption expense of $250,000 per SNPStream.

For the cost-benefit calculations, RTI used the $1 estimate per SNP analysis in 1999, or $1.17 per analysis in real, 2005 dollars.

By using the SNP-IT technology, SNPStream customers, including Bristol-Myers Squibb, GlaxoSmithKline, and DNAprint genomics (Orchid 2001a), were able to see cost reductions in two key areas:

- labor cost savings—sequencing and PCR processes are very labor intensive (this accounted for approximately one-third of the cost savings) and
- material cost savings—by miniaturizing the processes, a much smaller amount of reagent is needed (this accounted for approximately two-thirds of the cost savings).

Table 5-5 provides the realized benefits that accrued to SNPStream users. Seven purchased or leased instruments resulted in a total of approximately $6.6 million in benefits.

Although SNPStream products were sold to only a relatively small number of laboratories and companies, Orchid used the same technology in their MegaSNPatron facility to conduct genotyping analysis for customers. According to Orchid executives, the relative savings to customers from this service are the same as those that accrued to users who purchased SNPStream products because of the lack of labor and overhead costs incurred by those who used the MegaSNPatron facility.

Interviews indicated that approximately 1,100,000 genotype runs were conducted during 1999 using the SNP-IT technology at the MegaSNPatron facility. Table 5-5 includes the annual benefits from SNP-IT-enabled services in 1999. Executives estimated that Orchid performed 1.1 million genotyping analyses for customers, and that each customer accrued the same $1.17 in net savings per analysis as equipment customers did. Total 1999 MegaSNPatron benefits were approximately $1.3 million. The total public benefits were estimated to have been $7.8 million.

Table 5-4. Number of Genotyping Analyses Conducted Using SNPStream Instruments Installed in 1999

Year	Installed Base of Instruments	Number of Analyses Conducted per Instrument	Total Number of Analyses Conducted
1999	7	100,000	700,000
2000	7	200,000	1,400,000
2001	7	200,000	1,400,000
2002	7	150,000	1,050,000
2003	7	100,000	700,000
2004	7	50,000	350,000
Total			5,600,000

Source: RTI estimates.

Table 5-5. Times Series of Public Benefits (2005$)

Year	Estimated Benefits to SNPStream Users—1999 Installations Only	Estimated Benefits to MegaSNPatron Subscribers	Total Public Benefits
1999	$819,000	$1,287,000	$2,106,000
2000	1,638,000		1,638,000
2001	1,638,000		1,638,000
2002	1,229,000		1,229,000
2003	819,000		819,000
2004	410,000		410,000
Total	6,552,000	1,287,000	7,839,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding.

In addition to the benefits quantified above, non-SNPStream end users benefited indirectly from ATP-cofunded technologies (and associated cost savings) via products developed by licensees of the SNP-IT technology. Although RTI did not determine the relative cost savings to these consumers, the existence of such benefits provides additional evidence that the public benefit calculations were conservative estimates. Section 5.3 provides a discussion of additional benefits that were not quantified as part of this study.

5.2.4.2 Private Benefits

Calculating private profits from an investment is difficult without access to confidential business information. However, an approximation of private

benefits can be calculated by reviewing license revenue related to a new technology and rudimentary measures of profits derived from new product sales.

Determining the exact profit made from SNPStream sales was more complex, so as a proxy for the profit made by Orchid on product sales, RTI used the price paid by Beckman to purchase the rights to the SNPStream product line as part of their acquisition of Orchid's instrument business. The price paid represented an NPV of future private benefits Orchid could have otherwise expected.

Beckman paid approximately $1.1 million and assumed $0.6 million in debt payments from Orchid as part of their acquisition deal. The $1.7 million deal included more than simply the right to develop and sell the SNPStream product line (Orchid, 2006). It has been estimated that the purchase price (i.e., $1.1 million) approximately represents the fraction of the total amount related to the SNPStream product line, so this amount was considered a direct private benefit to Orchid from their research.[20]

Orchid generated substantial revenue through licensing. Beginning in early 1999, Orchid conducted development work that resulted in several new patents.[21] Based on these patents, Orchid had the sole rights to the SBPE technology (often referred to by its trade name of genetic bit analysis, or GBA) and the SNP-IT automated GBA-based SNP analysis process (Orchid Cellmark, February 4, 2000d).

According to executives with the company during this period, almost all license revenue in 1999 and 2000 and a significant percentage thereafter was related to technologies developed during the ATP-cofunded project. Table 5-6 shows the total license revenue Orchid received from 1998 to 2005 related to patented technologies developed during the ATP-cofunded research; this revenue totaled approximately $13 million.

RTI investigated the possibility of future benefits generated by license revenue from the technology developed under these projects; however, Orchid's SEC filings indicate that the company does not anticipate significant future license revenue. For the year 2005, their license and grant revenue totaled $1.2 million.

[20]This acquisition included the rights to develop and sell products based on the SNP-IT technology, as well as some capital and materials.

[21]Interviews suggest that the ATP funds, along with the predetermined level of company matching funds for this research, provided the necessary resources to complete this development in early 1999.

Table 5-6. Times Series of Private Benefits (2005$)

Year	License Revenue from SNP-IT Technology	Sale Price from Beckman Purchase	Total Private Benefits
1999	$218,000[a]		$218,000
2000	1,130,000[b]		1,130,000
2001	2,503,000[c]		2,503,000
2002	3,678,000[c]	$1,174,000	4,852,000
2003	1,590,000[c]		1,590,000
2004	1,545,000[d]		1,545,000
2005	1,000,000[d]		1,000,000
Total	11,663,000	1,174,000	12,837,000

[a]Orchid Biosciences, Inc. 2001. Condensed Consolidated Financial Statements (in thousands except share and per share data) (unaudited). http://www.orchid.com/pdf/2000_q1.pdf.

[b]RTI Interviews.

[c]Orchid annual reports (2002a, 2003).

[d]Orchid SEC 10-K filings (2005, 2006).

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding. All dollar values have been adjusted to real 2005 dollars.

5.3 NET ECONOMIC BENEFITS AND QUALITATIVE IMPACTS

This section provides an annual breakdown of the public and social benefits that resulted from the two ATP-cofunded research projects. In addition, RTI qualitatively reviews additional benefits that resulted from ATP's investments but that could not be quantified.

5.3.1 Time Series of Public Benefits and Costs and Performance Measures

Public measures of performance are presented to evaluate the public return on only ATP's investments. Table 5-7 shows the time series of realized net public benefits. The net public benefits in each year are expressed as the sum of MT/Orchid's public benefits, less ATP's expenditures. The total net public benefit of the MT/Orchid research quantified in this analysis was estimated to be approximately $3.2 million.

Table 5-7. Time Series of Public Costs, Benefits, and Net Benefits—Molecular Tool/Orchid Projects, 1995–2005 (2005$)

Year	Public (ATP) Costs	Public Benefits	Net Public Benefits
1995	–$342,000		–$342,000
1996	–1,418,000		–1,418,000
1997	–624,000		–624,000
1998	–22,000		–22,000
1999	–807,000	$2,106,000	1,298,000
2000	–681,000	1,638,000	957,000
2001	–728,000	1,638,000	910,000
2002		1,229,000	1,229,000
2003		819,000	819,000
2004		410,000	410,000
2005			
Total	–4,621,000	7,839,000	3,218,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding.

ATP incurred project-related R&D costs from 1995 to 2001. As discussed previously, most of the benefits occurred following the final year of the second ATP award, when Orchid launched the SNPStream product line that contained technology from both projects. All public benefits had accrued by year-end 2004 because of the 5-year useful life of equipment installed in 1999.

Realized public benefits totaled approximately $7.8 million in 2005 dollars. After deducting public investment costs of $4.6 million, the realized net public benefits were $3.2 million.

Three separate measures of the projects' performance are provided in Table 5-8. The estimated value of net public benefits from the project exceeded ATP's investment costs. Using 1995 as the base year and a 7% discount rate, the NPV of realized net public benefits was $1.4 million. The public benefit-to-cost ratio was also 1.4, implying that for every $1 ATP invested, the public accrued $1.40 in benefits. The public internal rate of return was 19%.

Table 5-8. Public Performance Measures—Molecular Tool/Orchid Projects

Public benefits (2005 $ millions)	7.8
Public costs (2005 $ millions)	–4.6
Net public benefits (2005 $ millions)	3.2
NPV of net public benefits (2005 $ millions)[a]	1.4
Benefit-to-cost ratio	1.4
Internal rate of return	19%

[a]To compute NPV, net public benefits were discounted to 1995 using a 7% annual discount rate.

Source: RTI estimates.

5.3.2 Time Series of Social Benefits and Costs and Performance Measures

Net benefits to society, including the innovator's benefits and costs, more broadly provide a total return on investment picture of this research effort. In addition to the public costs and benefits included in the public measures of performance, MT and Orchid also used company funds for the research that led to the SNP-IT technology, and Orchid received private benefits from this research.

Private benefits included license revenue and profit from product sales, for which the price paid by Beckman to gain the right to develop and sell SNPStream products was used as a proxy.

Table 5-9 provides a summary of the private and public costs and benefits and the total net benefits (undiscounted), which were estimated to be approximately $13.9 million.

Table 5-10 presents social measures of the projects' performance by combining private benefits, private costs borne by MT/Orchid, public benefits, and public (ATP) costs. The NPV of net social benefits was estimated to be approximately $7.3 million. The social benefit-to-cost ratio was 2.4. For every $1 invested by ATP or MT/Orchid, society accrued about $2.40 in benefits. The social internal rate of return was 35%.

5.3.3 Impact of SNP-IT Technology on SNP Analysis Market

MT and Orchid's combined development of the SNP-IT primer extension technology resulted in significant benefits beyond those that could be

Table 5-9. Time Series of Public and Private Costs and Benefits, and Net Social Benefits —Molecular Tool/Orchid Projects, 1995–2005 (2005$)

Year	Public Benefits	Private Benefits	Public Costs	Private Costs	Net Social Benefits
1995			–$342,000	–$160,000	–$501,000
1996			–1,418,000	–422,000	–1,839,000
1997			–624,000	–254,000	–877,000
1998			–22,000	–14,000	36,000
1999	$2,106,000	$218,000	–807,000	–461,000	1,056,000
2000	1,638,000	1,130,000	–681,000	–389,000	1,699,000
2001	1,638,000	2,503,000	–728,000	–415,000	2,998,000
2002	1,229,000	4,852,000			6,080,000
2003	819,000	1,590,000			2,409,000
2004	410,000	1,545,000			1,955,000
2005		1,000,000			1,000,000
Total	7,839,000	12,837,000	–4,621,000	–2,113,000	13,942,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding.

Table 5-10. Social Performance Measures—Molecular Tool/Orchid Projects

Social benefits (2005 $ millions)	20.7
Social costs (2005 $ millions)	–6.7
Net social benefits (2005 $ millions)	13.9
NPV of net social benefits (2005 $ millions)[a]	7.3
Benefit-to-cost ratio	2.4
Internal rate of return	35%

[a]To compute NPV, net public benefits were discounted to 1995 using a 7% annual discount rate.

Source: RTI estimates.

quantified. In particular, two important benefits were not quantified:

- benefits (cost savings) to end users of competing products that used SNP-IT technology through license arrangements and
- profits made by companies selling products based on SNP-IT technology license.

The SNP-IT technology was developed as a "platform" technology that many organizations leveraged to enable rapid, cost-effective SNP analysis as part of their products. In addition to the license revenue that Orchid received (and still receives) from such arrangements, end users have benefited from being able to use the SNP-IT technology in products beyond the SNPStream line. And the companies that purchased these licenses benefited through the profits they generated.

Interviews and Orchid's SEC files indicate that Orchid licensed their technology to ABI, Quest Diagnostics, GE Healthcare (formerly Amersham Biosciences), Affymetrix, Hitachi MiraiBio, Invitrogen, Luminex, PerkinElmer, Quest Diagnostics, Thermo Biostar, and Asper Biotech. This list includes companies developing the most widely used DNA analysis technologies on the market today.

RTI's interviews suggest that some license arrangements were established to allow services to be offered (e.g., by Invitrogen and Quest Diagnostics) and Orchid's products to be resold (e.g., by Hitachi MiraiBio). Further, several companies used Orchid's technology as a key component to their products. As an example, ABI's SNaPshot SNP analysis product was largely based on the SNP-IT technology, and for approximately 3 years, this was ABI's main SNP analysis product. Further, as indicated above, by mid-2000, Orchid's technology was available in 90% of sequencers on the market as an add-on feature. Table 5-11 contains the names of companies and their product lines that licensed SNP-IT technology.

Table 5-11. Licensees of SNP-IT Technology

Company Name	Product Name
Asper Biotech	Genorama
ABI (previously Qwest)	PRISM SNaPshot Multiplex System
Beckman Coulter	GenomeLab SNPStream Genotyping System
GE Healthcare (formerly Amersham Biosciences)	Various reagent kits and software for SNP analysis (marketed as add on feature to sequencers)
Luminex	LabMAP assays[a]
Perkin Elmer	Various reagent kits and software for SNP analysis (marketed as add on feature to sequencers)
Thermo Biostar	SNP-IT features combined with BioStar's OIA® and thin-film biosensor technologies

[a]Evidence suggests that this product may have been discontinued or redesigned without the use of Orchid's SNP-IT technology.

Caliper, another small company that received an ATP award in the DNA diagnostics area, might also owe its existence to the MT/Orchid awards. It is very possible that this company might never have been created had it not been for MT's application for and the awarding of ATP cofunding in 1994. At the start of the first ATP project, two principals in the research effort, Mike Knapp and Mike Ramsey, left to form Caliper and develop products and services in the microfluidics arena. Although some of the technical developments made by Caliper were similar to MT's goals, it is impossible to determine where this research would have been conducted if MT had not received the ATP cofunding.

The increase in the accuracy and quantity of SNP analysis that resulted from Orchid's technology being used in their own products and services, as well as in other competing and noncompetitive products, has helped to increase the knowledge base of research on drug interactions and genetic diseases. Such research, experts suggest, has helped move the research community closer to being able to achieve the personalized medicine vision that has been described for many years.

6 Qualitative Analysis of ATP Projects at CuraGen, Nanogen, and Third Wave Technologies

The balance of this report's project review comprises five ATP-cofunded projects: two each at Nanogen and Third Wave Technologies and one at CuraGen. Like the Affymetrix-Molecular Dynamics and Molecular Tool/Orchid Cellmark projects, these projects entailed developing rapid, inexpensive diagnostics technologies.

Though there are similarities among the companies' business proposals, the technical proposals differed, and the technologies each company invented were distinct and sought to fulfill different market needs. CuraGen sought to develop a device that would be similar to the MIND device, but foresaw that microfluidics would be a challenge, and instead developed a microarray-based drug discovery platform. Nanogen developed the first microarray platform for the clinical diagnostics market during a period when its competitors were intent upon research applications. Finally, Third Wave Technologies invented easy-to-use genetic analysis test kits that could quickly identify the presence of genetic markers for several inherited and infectious diseases.

The R&D that ATP supported enabled these companies to bring technologies to market sooner than they otherwise would have. As discussed in this section, less efficient and effective technology platforms supported by larger market players dominated the market. In some instances, the technologies would not have been developed at all, and their contributions to science might not have occurred.

6.1 CURAGEN CORPORATION

CuraGen Corporation's joint venture (JV) project, "Integrated Micro-fabricated DNA Analysis Device for Diagnosis of Complex Genetic Disorders," sought to develop a self-contained, micro-fabricated device capable of performing the basic operations of DNA analysis. Much like Affymetrix and Molecular Dynamics' MIND Development project, CuraGen envisioned a device that would be capable of performing a variety of molecular analyses, including DNA sequencing, genotyping, and expression analysis.

As with Affymetrix and Molecular Dynamics projects, technical and market realities forced a change in CuraGen's strategy during the project. The financial resources available were insufficient to overcome the technical obstacles posed by sample preparation and microfluidics. CuraGen responded by seeking out alternative avenues for application of its successful project outcomes. Those technologies ultimately formed the primary components of CuraGen's GeneScape drug-discovery platform.

CuraGen's ATP-cofunded research not only led to the development of the company's drug discovery platform, but also indirectly to a new company. CuraGen established a subsidiary, 454 Life Sciences, Inc., in part to pursue technology solutions to the microfluidics problems it encountered during the ATP project. 454 develops next-generation DNA sequencers.

The importance of ATP cofunding in supporting these developments was voiced by CuraGen cofounder and 454 Chairman, Dr. Jonathan Rothberg, in a 2004 interview with *Nature BioEntrepreneur*, in which he was quoted as saying that "the ATP [award] led to CuraGen's success and indirectly to a new company" (Surendran, 2004).

6.1.1 Company Overview

Rothberg and Dr. Gregory Went founded CuraGen in New Haven in 1991 to harness the knowledge generated by the Human Genome Project in order to accelerate the discovery of new medicines and therapeutics (ATP, 2000).

During its first 2 years CuraGen focused on developing its proprietary technologies and preparing grant proposals. CuraGen received a $50,000 proof-of-concept research grant, its first source of external financing, from the National Institutes of Health's (NIH) Small Business

Innovation Research Program. The purpose of this grant was to demonstrate the feasibility of a DNA sequencer composed of easily updatable modules (ATP, 2000). Encouraged by this small effort's success, CuraGen applied for an ATP award in 1994 to move a broader vision of a DNA analysis device from the conceptual stage through technology development.

CuraGen approached Soane Technologies, Inc. (STI), later known as Aclara, to continue device development as an ATP-cofunded JV project. A JV project was advantageous for CuraGen because STI had been working on technologies for DNA fragment separation that could be incorporated into the gel electrophoresis component of the planned device—the part that would separate DNA fragments for analysis. STI also had potential connections with device manufacturers that could make commercializing technology outcomes easier.

Their project, "Integrated Micro-fabricated DNA Analysis Device for Diagnosis of Complex Genetic Disorders," ran from February 1995 through January 1998. The companies received $2.3 million in ATP funds and provided the balance of the total $5.17 million project cost. Included in CuraGen's cost share was a supplemental grant of $687,500 from Connecticut's Federal Technology Partnership Program (FTP), a program that provides state matching funds to companies that receive ATP awards so they can more easily meet the cofunding requirement (Feldman and Kelley, 2002).

The ATP project played a pivotal role in the company's research and development (R&D) activities. Using data obtained from CuraGen's SEC filings, RTI estimates that the ATP project accounted for 35% of the company's total R&D spending during the life of the project. The company employed 17 people when it received the ATP award in 1994. Today, it employs over 200 (CuraGen, 2006a).

6.1.2 Project Research and Development Goals

The integrated device would be capable of performing DNA sequencing, genotyping, and expression analysis without human intervention. The user would introduce an unprepared biological sample and the device would extract and separate the DNA on a gel electrophoresis plate. An optical imaging system would read the plate, transferring the data via an imaging system to bioinformatics software for analysis.

An integrated device that automated sample preparation and analysis would greatly reduce the amount of time spent performing procedures like DNA sequencing. This feature would make the device most attractive to research laboratories, CuraGen argued, because the urgency of the Human Genome Project would encourage research laboratories to adopt the fastest sequencing method available.

By making genetic analyses easier to perform, the device would also be attractive to clinical laboratories. In a clinical diagnostic setting, the device would enable routine DNA diagnostics that might improve the effectiveness of disease treatments by allowing physicians to detect diseases earlier and tailor therapeutics to patients' genetic compositions.

Researchers faced many technological challenges, including the fundamental issues of sample preparation and miniaturization. Specific tasks included developing

- design and fabrication techniques for sample handling and preparation device components,
- design and fabrication techniques for a miniaturized gel electrophoresis plate for sample separation,
- improved gel materials for use in the miniaturized electrophoresis plate,
- optical systems for reading the electrophoresis plate, and
- adaptive pattern-recognition software to interpret the data from the device.

Although CuraGen had conceptually started to address a few of the technical barriers before—CuraGen used the first NIH grant to demonstrate its sample separation concept—the bulk of the technology had yet to be developed. The two companies agreed that CuraGen would focus its efforts on developing the actual hardware and software of the device, while STI developed a new separation media. However, STI was unable to develop a suitable separation media and its role in the project effectively concluded.

As the project progressed, the challenges posed by microfluidics impeded progress. The project team shifted its strategy from an integrated device to a diagnostics platform. CuraGen acquired the best possible macroscopic robotics technology available to reduce sample volumes as far as possible and moved on with their research.

6.1.3 Technology Outcomes and Commercialization Status

CuraGen successfully developed a variety of genetic analysis technologies during the ATP award. Among them were GeneCalling, a differential gene expression profiling technology, and SeqCalling, a supporting technology that rapidly catalogs genetic sequences into databases. Both GeneCalling and SeqCalling were commercialized as part of CuraGen's GeneScape drug-discovery platform.

GeneCalling combines a pattern-recognition software program with a method for extracting DNA from tissue samples. GeneCalling first isolates DNA from two tissue samples and processes them into fluorescently tagged fragments. The system then separates the fragments by size and visualizes them as trace peaks. The pattern-recognition software compares the relative intensity of each sample's trace to identify any differences. If differences are found, the fragment to which each differential trace peak belongs is queried against a computer-generated gene database to identify the expressed gene it represents (Green et al., 2001).

The rapid identification of differentially expressed genes makes GeneCalling especially useful for research in drug discovery because researchers can quickly identify disease-related genes by comparing the expression profiles of two samples. For example, researchers can identify genes that are potentially related to a disease by first using GeneCalling to create a gene expression profile for a diseased sample and then comparing it to a control (i.e., healthy) sample's expression profile. Genes expressed in the diseased sample and not in the healthy sample are possibly connected to the disease itself.

GeneCalling has several advantages over defender expression techniques such as Serial Analysis for Gene Expression (SAGE), which are limited to detecting a single fragment for each expressed gene in a sample. Using a single fragment increases the probability that an expressed gene may be overlooked because of complications with the initial generation of the fragment. By contrast, GeneCalling generates an average of three fragments per gene. As a result, it typically identifies 95% of the genes expressed in a sample, while SAGE only identifies 92%. Generating multiple fragments also improves efficiency by increasing the significance of the initial GeneCalling assignments, thereby reducing the turnaround time for gene confirmation (Green et al., 2001).

SeqCalling is a high-throughput, industrial-scale sequencing technology that rapidly generates expression databases for any organism or tissue type. These databases expedite GeneCalling analysis by quickly providing researchers with entire sequences with which to identify expressed genes.

The GeneScape platform, which used both GeneCalling and SeqCalling, also included PathCalling (designed to analyze disease- or drug-related proteins) and SNPCalling (used to identify human genetic variations known as single nucleotide polymorphisms, or SNPs).

CuraGen developed a prototype of the DNA analysis device, the Niagara instrument. Niagara operated with GeneCalling and utilized software to process and analyze data. In 1997, CuraGen indicated that its scientists were developing an upgrade path for the Niagara instrument that would introduce components for sample preparation and DNA separation (CuraGen, 1997). But the instrument was never released commercially.

6.1.4 End Users and Applications

In 1997, CuraGen signed a collaborative research agreement with Pioneer Hi-Breed International to identify the genes responsible for agricultural crop performance using its GeneCalling technology (CuraGen, 1997). This agreement marked the beginning of CuraGen's business strategy of providing research services to biotech and biopharmaceutical companies using its GeneScape gene and drug-discovery platform.

As part of these collaborations, CuraGen proposed to use its GeneScape technology to analyze samples provided by the collaborator. For example, CuraGen could use the GeneCalling component of GeneScape to analyze expression profiles of a diseased blood sample provided by a collaborator and compare the sample with the expression profile of a normal blood sample to determine whether genes were being expressed in the diseased sample that were not being expressed in the normal sample (indicating a potential disease-related gene). Because GeneCalling had greater coverage and required smaller samples than established gene expression methods, the probability of finding these disease-related genes was much higher than with other methods.

Two other examples of CuraGen's collaborative efforts are described below:

- In October 1997, CuraGen entered into a collaborative research agreement with Biogen Inc. to discover novel genes and therapeutics across a range of Biogen-specified disease programs. As part of the agreement, Biogen had an option to acquire exclusive licenses to certain discoveries arising from the collaboration. In October 2000, the research collaboration was completed. As a result of the agreement, CuraGen discovered five novel drug targets and licensed these to Biogen (CuraGen, 2000).
- In May 1999, CuraGen signed an 18-month database product discovery and pharmacogenomics agreement with COR Therapeutics. Under the terms of this agreement, CuraGen applied their functional genomics technologies, related services, and pharmacogenomics expertise to identify new drug targets and develop novel cardiovascular drugs. During the research collaboration, CuraGen discovered an undisclosed number of novel drug targets (CuraGen, 2000).

Between 1997 and 2000, CuraGen entered similar business agreements with Abgenix Genentech, Glaxo, Roche Pharmaceutical, and Roche Vitamins (CuraGen, 2000).

In 2001, CuraGen announced it was no longer seeking research collaborations with other companies. The company shifted away from providing research services towards developing its own pharmaceuticals. Today, CuraGen is studying five oncology therapeutics in clinical and preclinical trials (see Table 6-1). These products are being evaluated for the treatment of cancer as both single agents (monotherapies) and as part of combined anti-cancer treatments.

CuraGen entered its first drug—Velafermin—into Phase I clinical trials in early 2003 (CuraGen, 2003). According to the Tufts Center for the Study of Drug Development, it takes a new drug 7 years to successfully complete clinical trials and receive FDA approval (Tufts, 2006). Therefore, CuraGen is expected to commercialize its first therapeutic product in 2010.

6.1.5 454 Life Sciences, Inc.

CuraGen's ATP-cofunded research not only led to the development of the company's drug discovery platform, but also indirectly to a new company. CuraGen established a subsidiary, 454 Life Sciences, Inc., in part to pursue technology solutions to the microfluidics problems it encountered during the ATP project.

Several researchers from the ATP project, including Jonathan Rothberg, moved to 454 and applied the lessons they learned in advanced

Table 6-1. CuraGen Drugs in Clinical Trials Discovered Using ATP-Cofunded Technology

Product	Indication	Date Entered Current Phase	Clinical Trials			
			Preclinical	Phase I	Phase II	Phase III
Velafermin	Oral Mucositis—Prevention	May 2006				
	Oral Mucositis—Treatment	January 2005				
PXD101	Multiple Myeloma	January 2005				
	Solid Tumors and Colorectal Cancer	September 2005				
	Solid Tumors and Ovarian Cancer	September 2005				
	T-Cell Lymphoma	January 2006				
	Multiple Myeloma (combined with Velcade®)	March 2006				
CR011	Metastatic Melanoma	June 2006				
CR014	Ovarian Cancer	January 2006				
	Renal Cell Carcinoma	January 2006				
CR012	Colorectal Cancer	January 2006				
	Ovarian Cancer	January 2006				

Note: PDX101 is being co-developed by CuraGen and the Danish biotech firm TopoTarget. This therapeutic is also being evaluated in five additional clinical studies that have been sponsored by the National Cancer Institute.

Source: CuraGen, 2006a, 2006b.

microfluidics technology for DNA sequencing. 454's scientists were ultimately able to overcome microfluidics barriers that impeded progress during the ATP project. These technological advancements were eventually incorporated into the company's Genome Sequencer 20 (see Figure 6-1).

The GS20 is the first DNA sequencing technology in 25 years that does not use the Sanger sequencing method (CuraGen, 2006a). An ultra-high throughput system, the sequencer is capable of rapidly producing readlengths of 100 base pairs (bps) with 200,000 reads per instrument run, meaning that each run yields 20 million bps. At that data production rate, a scientist can sequence a bacterial genome in less than 4 days (Bonetta, 2006). A Sanger-based system, like those from ABI and GE Healthcare, would take 1 month to produce the same amount of data.

Readlength is currently too short for de novo sequencing of a mammalian-sized genome, but 454 is advancing the technology to meet

Figure 6-1. 454 Life Sciences, Inc.'s Genome Sequencer 20

Source: Courtesy of 454 Life Sciences Inc.

400 bps or more per DNA fragment. According to some estimates, the instrument could resequence every gene in a person's body for an approximate cost of $300,000 (*Popular Science*, 2005). This is a remarkable improvement over conventional methods, which cost between $10 million and $15 million (Wade, 2006).

The system is in its first year of sales and the installed base remains small. However, Volker Pfahlert, head of Roche Applied Science, 454's manufacturing distributor, described the product launch as one of the company's most successful (CuraGen, 2006a).

6.2 NANOGEN, INC.

San Diego-based Nanogen, Inc. was formed in 1991 to develop cost-effective diagnostic products capable of analyzing thousands of genetic and infectious diseases. Like Affymetrix, Nanogen was developing microarray technologies, though Nanogen's technical approach differed. Nanogen sought to leverage its microarray technology to develop clinical DNA diagnostics systems.

Nanogen received two separate ATP awards (see Table 6-2). The first project, "An Integrated Microelectronic DNA Diagnostic System," aimed to develop an integrated microelectronic device for clinical laboratories to perform all aspects of DNA diagnostic tests from sample preparation to data analysis.

Table 6-2. Nanogen Project Spending

Project Title	Award Date	Performance Period	ATP to Nanogen	Nanogen Matching Funds	Total
An Integrated Microelectronic DNA Diagnostic System	July 1995	8/1/95–12/31/97	$2,000,000	$1,500,000	$3,500,000
A Portable Genetic Analysis System	March 1997	5/1/97–9/30/99	$2,000,000	$1,935,000	$3,935,000

Source: ATP.

As the first project was nearing completion, Nanogen won a second project to develop a portable DNA diagnostic device. These two awards were combined for the purpose of this analysis because Nanogen's microarray systems used today contain technology developed during both projects.

Nanogen was successful in automating sample preparation and integrating it with DNA diagnostics systems, and it credits the ATP award with enabling the company to conduct the necessary R&D. Technological advancements made during the projects contributed to the development and commercialization of Nanogen's two DNA diagnostic instruments.

6.2.1 Company Overview

During the company's early years, Nanogen's principal scientists primarily engaged in developing the company's microarray technology, which they believed would power future DNA diagnostic devices.

The technology, known as Automated Programmable Electronic Matrix (APEX), was an electronic silicon chip that used a novel method for multiplexed DNA hybridization analysis. The chip design included electronically charged test sites. By assigning each test site a specific charge, an electromagnetic field was created that directed charged DNA fragments to test sites where probes for specific DNA sequences would be attached. Independent, electronically controlled hybridization reactions occurred at each test site. Post hybridization, probes would emit a fluorescent signal that indicated whether the DNA sequence of interest was present in the sample.

Between 1994 and the spring of 1995, developments in Nanogen's microarray technology strengthened the company's financial growth. During this period, the company received more than $10.5 million from investors in two rounds of venture capital financing, moved into a larger

22,000-square-foot facility, and more than tripled its workforce from 7 employees in March of 1994 to 25 employees in April of 1995 (*Business Wire*, 1995).

As the company grew, Nanogen scientists became interested in broadening their research to address other important aspects of DNA diagnostic analysis, such as sample preparation. Nanogen's scientists wanted to automate the sample preparation and combine it with a microarray in a single diagnostic device. However, because of the inherent variability and complexity of sample preparation, there was a strong likelihood of failure and little chance of creating a near-term product. These high levels of technical and economic risk made it difficult for Nanogen to raise funds from private investors.

To fund the device's development, Nanogen submitted a proposal to ATP in 1994. The proposed project, titled "An Integrated Microelectronic DNA Diagnostic System," was accepted, lasted 2 years (from August 1995 to December 1997), and received a total of $2 million in ATP cofunding. Nanogen provided the remaining $1.5 million of the project's $3.5 million budget.

Nanogen submitted a second proposal to ATP in 1997. Researchers proposed a portable DNA diagnostic device for use in battlefield identification and forensic analysis, as well as in clinical diagnostic laboratories and research centers. This project was awarded in 1997, lasted 2 years (from May 1997 to September 1999), and received $2 million in ATP cofunding. Nanogen provided $1.9 million in additional financing.

Nanogen pursued a more diversified research program than it would have otherwise. For its integrated DNA diagnostic device to work, the company needed to solve the "upstream" problem of automating the process of preparing a sample, such as blood, so that it could be analyzed by the "downstream" microarray component. According to Nanogen scientists interviewed by RTI, the company would not have been able to devote nearly as many resources to studying the issue of sample preparation without ATP co-funding.

Today, Nanogen is the only commercial producer of electronic microarrays, employing 235 people and earning annual revenues of $12.4 million (Nanogen, 2006a).

6.2.2 Project Research and Development Goals

The diagnostic system Nanogen proposed in its first project was intended for use in clinical settings to provide rapid diagnostic results from analyses of tissue, blood, or other biological samples. The system would accept a sample from a patient, extract DNA from it, reduce the complexity surrounding the DNA, and then analyze it using DNA-probe hybridization techniques.

Having already developed the APEX microarray, which would serve as the system's analytic component, the research team focused on developing a sample preparation component. This task would be inherently difficult because of the variety of sample types and volumes faced in a clinical environment.

The research team began by developing the individual sections of the sample preparation component and then assembled them together into a single system as they were developed. The novelty of this approach was accompanied by uncertainty and technical risk. Few companies had attempted to address the sample preparation problem before Nanogen, and none of them had attempted to do so around an electronically active microarray. Components included the following:

- **Cell Selector**—After introducing a sample, such as blood, an electronic matrix selected cell types from which to extract target DNA. Undesired cell types were removed and the remaining cells lanced. The contents of these cells were transferred to the second component.
- **Crude DNA Selector**—The cell contents were received by an electronic array, which isolated the target DNA. This DNA was fragmented and forwarded to the final sample preparation component.
- **Complexity Reduction**—Not all of the DNA fragments generated during the previous step contained the genetic target for which researchers were testing. To increase the likelihood of detecting the target of interest, DNA fragments that did not contain the target gene were removed from the sample. This was accomplished through a preliminary hybridization process conducted on an APEX chip. The complexity reduction microarray would be equipped with DNA-probes that were designed to detect the target gene. DNA fragments in the sample that contain the target gene would be hybridized to these probes, leaving all the other fragments unhybridized and easy to remove. Next, the target fragments would be dehybridized and forwarded to the analytical component of the device.

The goal for the second ATP project was to develop a self-contained, portable DNA diagnostic device appropriate for use in forensics, battle-

field identification, and clinical diagnostics. The research team would need to accomplish three technical objectives to develop this device:

- create larger assay chips with more test sites to fully characterize the genetic code of an individual,
- integrate the sample preparation and complexity reduction components with the new assay chip onto a single module, and
- develop a microfluidics module for automated introduction of samples and reagents.

These tasks required the Nanogen team to increase the number of electronically addressable test sites on the APEX chip. Nanogen also needed to develop the necessary microfluidic systems for delivering and disposing of the sample and reagent material. Lastly, systems integration posed several hurdles.

6.2.3 Technology Outcomes and Commercialization Status

Nanogen developed a prototype of the integrated DNA diagnostic system and the portable device. By the close of the second project, Nanogen had built and tested the hardware for the device and found all components to be fully functional (Figure 6-2).

However these prototypes proved very difficult to commercialize. Experts interviewed by RTI explain that this is because one of Nanogen's major markets, clinical diagnostics, has a very low tolerance for false positives. When a company integrates the components of diagnostic analysis that were traditionally done by hand into an automated device, that company takes responsibility for those steps. As more steps are integrated into a device, there is more opportunity for errors to occur, which adds additional complexity to the process of making sure the entire device works appropriately.

Figure 6-2. Nanogen's Prototype Portable DNA Diagnostic Device

Source: Courtesy of Nanogen, Inc.

Recently, Nanogen announced that it has received a patent for a device that uses the company's electronic chip technology to integrate sample preparation, nucleic acid amplification, and detection. In the press release announcing this patent (U.S. Patent No. 6,989,086), Nanogen cited ATP as an early supporter of the company's research that led to this patent being issued (Nanogen, 2006b).

The time that elapsed between Nanogen's start in 1991 and the receipt of the patent in 2006, including both ATP projects, is indicative of the long incubation time for new biotechnologies. In the interim, Nanogen commercialized a variety of milestone genetic analysis technologies. Among these project-related innovations were improvements in Nanogen's microarrays.

When the first ATP project began, Nanogen's APEX microarray had a total of 25 test sites. By the end of the second project, Nanogen had developed a microarray with 100 test sites and another, more sophisticated microarray with 400 test sites.

The 100 test site microarray was developed into the NanoChip100, which became the analytical core of the NanoChip Molecular Workstation, released in 2000. The 400 test site microarray, which utilized a new chip architecture developed during the second ATP project, became the foundation for NanoChip400—the second generation of NanoChips and the analytical component of the NanoChip400 workstation instrument, released in 2005 (Nanogen, 2005).

The NanoChip Molecular Biology Workstation, Nanogen's first commercialized product, performs DNA diagnostics in clinical research settings (see Figure 6-3). While the majority of this process is automated, some things—such as sample preparation and attaching DNA-probes to the NanoChip—remain manual.

The NanoChip Workstation has been proven to be more accurate at SNP scoring than the "defender" technology, restriction fragment length polymorphism (RFLP), which was the industry standard for SNP genotyping during the 1990s (Nanogen, 1999). RFLP uses enzymes to cut DNA into fragments that vary in length between two individuals based on the genetic differences separating them. These fragments can be

Figure 6-3. NanoChip100 and NanoChip Molecular Workstation

Source: Courtesy of Nanogen, Inc.

measured using gel electrophoresis to determine the presence of SNPs (Sethi et al., 2004).

Nanogen's second generation instrument, the NanoChip 400 workstation, has also proven to be very accurate. The instrument features an increased number of test sites and automates some previously manual tasks, such as adding DNA-probes to the chip surface (Keen-Kim, Grody, and Richards, 2006).

6.2.4 End Users and Applications

The target market for Nanogen's Molecular Biology Workstation and NanoChip400 systems are clinical and research laboratories. Nanogen's diagnostic instruments provide these laboratories with genotyping results that are more accurate than competing technologies. The benefits of improved accuracy in a clinical setting, where misdiagnosis of a disease can lead to a patient's death, compensate for the higher cost of the instrument (Keen-Kim, Grody, and Richards, 2006).

Examples of Nanogen's customers include the following:

- The Mayo Clinic purchased two NanoChip systems in 2000 to perform a variety of clinically relevant research programs. Applications include pharmacogenomics, cancer, and epidemiologic studies. In a Nanogen press release, Dr. Dennis O'Kane of the Mayo Clinic said, "The NanoChip system may play an important role in bridging the gap between the discovery and

characterization of clinically relevant genetic information and its use in improving patient care" (Nanogen, 2000).

- The University of Alberta in Edmonton, Canada, purchased a NanoChip Molecular Biology Workstation in December 2000, which researchers at the institution intended to use in research programs in toxicogenomics and public health microbiology (Nanogen, 2001).

While the upfront purchase cost of the first generation NanoChip Workstation is higher than the defending RFLP technology, studies have shown the instrument to have comparable per-genotype operating costs. When using a new NanoChip cartridge and including reagent costs, the cost of detecting one SNP on the Workstation is $1.37 versus $1.09 using RFLP (Sethi et al., 2004). If one reuses a NanoChip, the cost per SNP falls to only include the reagent cost, which is less than half the cost of using RFLP (Table 6-3).

The second-generation NanoChip400 is less expensive for end users, on a per-genotype basis. The list price of the 100-test-site NanoChip used in the molecular workstation is $300 at the time of this writing, meaning the cost is $3 per sample when genotyping a single sample (assuming all test sites are used and excluding reagent cost). In contrast, the 400-test-site Nanogen400 is $400 per microarray, which reduces the price to only $1 per sample. As before, this cost will fall substantially if the chip is reused (Keen-Kim, Grody, and Richards, 2006).

Table 6-3. Cost Comparison of SNP Detection by RFLP, New NanoChips and Reused NanoChips

		Technician			
Method	**Supplies**	**Total Time Consumed[a] (hours)**	**Hands-on Time (hours)**	**Wages**	**Total Running Cost Per SNP**
RFLP analysis	$2.81	18	6.5	$0.49	$1.09
New microelectronic chip	$3.62	26	6.5	$0.49	$1.37
Reused microelectronic chip	$1.01	26	6.5	$0.49	$0.50

Source: Sethi et al., 2004.

Note: Costs of SNP detection cover operating costs only and do not include the instrument purchase cost. Monetary costs, originally reported in 2004 Euro, were converted to dollars using the yearly average exchange rate of $1.24 per Euro for 2004 (U.S. Embassy Paris, 2005).

[a] Hours of time consumed when genotyping 384 samples for three SNPs.

6.3 THIRD WAVE TECHNOLOGIES, INC.

Third Wave Technologies, Inc. (Third Wave) took a natural process in which certain enzymes cut DNA strands and turned that process into a biotechnology. Third Wave developed a faster, less expensive, and more accurate alternative to performing genetic analyses to identify disease markers in patients' blood. The technology's cost effectiveness made it possible to conduct similar research using samples from thousands of individuals.

ATP awarded Third Wave two projects. The first, "Development of a Generic Technology for the Targeted Detection and Cleavage of DNA," aimed to develop enzymes into a technology platform for molecular diagnostics. It was awarded in the 1994 competition and ran from the start of the following year through 1996 (see Table 6-4).

ATP awarded Third Wave a second project the same year that the first one ended. This effort, financed largely from sales of Third Wave's products containing technology from the first ATP-cofunded project, sought to develop Third Wave's technology into generic diagnostic and monitoring tools for point-of-care medical settings. These two awards were combined for the purpose of this analysis because the products end users consume today contain technology from both projects.

6.3.1 Company Overview

Third Wave was founded in Madison, Wisconsin, in 1992 to develop new genetic analysis methods. University of Wisconsin–Madison researchers and Third Wave's founders, James Dahlberg and Lloyd Smith, along with co-founder and former CEO Lance Fors, developed new methods for the

Table 6-4. Third Wave ATP Project Spending

Project Title	Award Date	Performance Period	ATP to Third Wave	Third Wave Matching Funds	Total
Development of a Generic Technology for the Targeted Detection and Cleavage of DNA and RNA	1994	01/01/1995 to 12/31/1996	$1,998,000	$771,000	$2,769,000
Simple, Generic, and Low Cost Genetic-Based Tools for Disease Detection, Intervention, and Monitoring	1997	10/01/1997 to 9/30/1999	$2,000,000	$2,093,000	$4,093,000

Source: ATP.

targeted detection and cleavage of DNA. These methods employed bacterial enzymes that Fors discovered could be tuned to detect predetermined genetic sequences.

Marketing its enzyme technology as Cleavase, Third Wave's early business plan was to develop and market diagnostic tests. Scientific and commercial opportunities arose in the analysis of genetic diversity because large-scale sequencing efforts like the Human Genome Project were releasing large volumes of reference genetic sequence. The more scientists understood genetic diversity, the more they would be able to accelerate the rate of discovery within the diagnostic and therapeutics fields (ATP, 2003).

Third Wave was the first company to develop a commercially viable, rapid method for analyzing genetic mismatches.

Major players, such as Switzerland's F. Hoffman-La Roche Ltd., dominated the genetic analysis market with resequencing products that used polymerase chain reaction (PCR). PCR used enzymes for target amplification, creating millions of copies of a DNA target. Once copies were made, they were sequenced and the output searched for SNPs. Although PCR was effective, it required several preparatory steps that were both time consuming and costly. Third Wave intended to decrease analysis time by reducing the number of steps needed for sample preparation and analysis.

ATP support made possible the development of Third Wave's approach from a set of diagnostic tests into a generic technology platform with applications in DNA testing and analysis, forensics, and agriculture. Insiders knowledgeable of the company's history have stated that if it had not been for the ATP award, Third Wave and its technology might not have even remained afloat, and medical science would not have benefited from the accelerated availability of inexpensive genetic analysis tools.

Little external private financing was available in the early 1990s. The 1994 ATP award was the single largest source of financing the company had received. According to Fors, most of the major market players had backed the PCR-based technologies, and there was little private funding for alternatives. Third Wave had received some SBIR grants, but these were for specific applications of the technology, not for core research into the technology itself.

Dr. Stephen Day, Third Wave's Director of Medical Affairs, believes the ATP award broadened Third Wave's core scientific capabilities. Day and Fors stated that ultimately most of Third Wave's technologies are derivatives or later generations of research conducted under the ATP awards. Until 1998, $7 million of Third Wave's $10 million in external funding originated from either ATP or SBIRs.

At the time of the second project, the company was bringing its first diagnostic tests to market and was not able to fund research solely with cash generated from ongoing operations. Nor were the company's VC backers interested in pursuing high-risk research opportunities.

Today, Third Wave is a $24 million a year company employing 154 people. Company executives trace the lineage of its Cleavase and Invader platforms—the trade names of its proprietary technologies— to the ATP awards.

6.3.2 Project Research and Development Goals

Third Wave's first ATP-cofunded project sought to develop specific diagnostic tools that could detect the presence of known and unknown DNA sequences using the Cleavase enzymes. The second project combined technologies from the first project with new, advanced chemistries to develop low-cost diagnostic tools for point-of-care settings.

6.3.2.1 Development of a Generic Technology for the Targeted Detection and Cleavage of DNA and RNA

The initial ATP project had three broad research goals. First, Third Wave aspired to develop the Cleavase technology into a more sophisticated nucleic acid cleavage system. The advantage of Cleavase enzymes is that end users can tune them to cut, or cleave, any predetermined genetic sequence. Where a Cleavase enzyme finds the reference sequence it seeks in a sample, Cleavase cleaves the DNA and emits a signal.

If the sample contains a sufficient number of the DNA targets, sensors can easily capture the test results. Where there are too few targets, Third Wave's Cleavase Detection Reaction (CDR) technology amplifies the signal from the detected sequences up to detectable levels.

Third Wave also aimed to develop a complementary method called Cleavase Direction Detection (CDD) that would assist in detecting the DNA or RNA sequence. CDR would be capable of rapidly detecting as few as 10 target sequences in the sample. CDD would be used when there were believed to be 1,000 or more targets in the sample.

The third diagnostic tool Third Wave proposed was Cleavase Fragment Length Polymorphism (CFLP). CFLP was an easy-to-use technique for identifying genetic variations, equally as accurate as conventional PCR analysis but several times faster and cheaper. CFLP is based on the Cleavase enzyme's ability to recognize secondary DNA structures that form as DNA cools after being heated. Cleavase cuts these structures, creating a unique "fingerprint" pattern of bands. This "fingerprint" is then read directly from the gel without the need for computer analyses. Genetic mutations in sample DNA are identified by comparing the fingerprint of the sample with a standard or "normal" DNA fingerprint.

6.3.2.2 Simple, Generic, and Low-Cost Genetic-Based Tools for Disease Detection, Intervention, and Monitoring

Whereas the first award sought to develop the Cleavase technology platform, the second ATP award proposed to develop generic, Cleavase-based tools for health care applications. The proposal spelled out four main technical goals:

- expand the recognition capabilities of Cleavase enzymes to enhance mutation scanning and viral bacterial and human identification by the cleavage of intramolecular structures (CFLP), which requires no prior sequence knowledge;
- discover and improve new and existing Cleavase enzymes and DNA chemistries to provide a simple cleavage platform, intermolecular structures (Invader) to cost-effectively detect and quantify small numbers of target molecules using simple instrumentation;
- explore the potential of new and existing Cleavase enzymes to enable new platforms to provide new solutions for disease management; and
- simplify the readout of these Cleavase enzyme-based platform technologies to increase throughput, and meet or exceed the cost/benefit requirements necessary to bring sensitive and specific nucleic acid tests to near patient and point-of-care testing.

The project would enable the creation of technologies for cost-effective preventive screening in medical care as opposed to the postsymptomatic

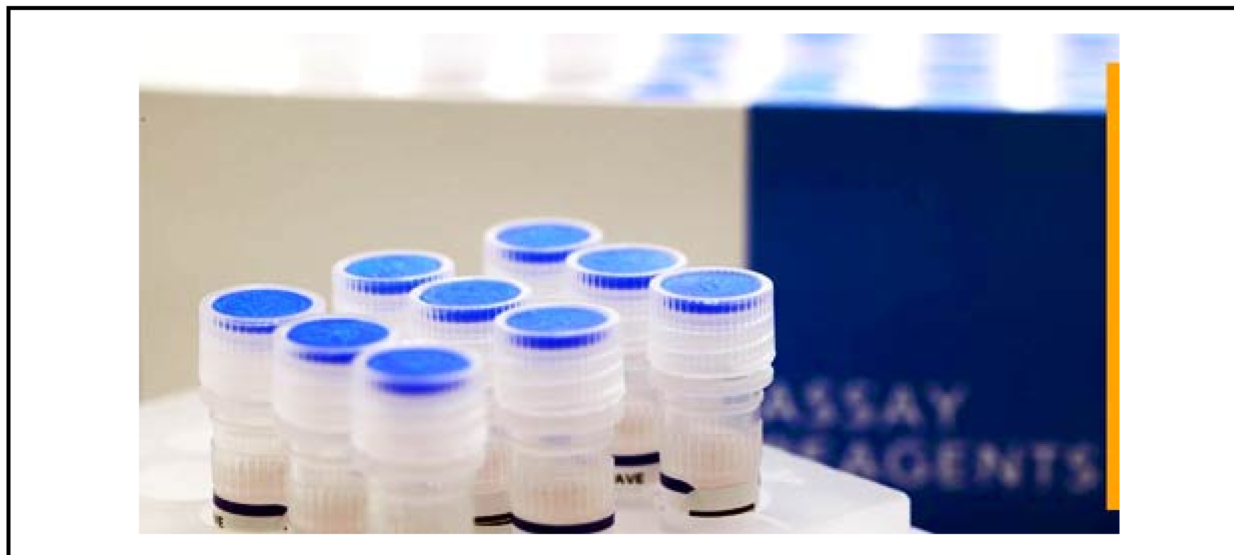
treatment system in place at the onset of the project. Third Wave proposed to explore potential for the Cleavase enzymes in disease management and gene expression monitoring, expanding their recognition capabilities and simplifying the analysis of assay results. Whereas the technologies they developed under the first award provided good test results in the control environments of research setting, the assays needed to be simplified for use in clinical or point-of-care locations.

6.3.3 Technology Outcomes and Commercialization Status

Third Wave met its goals for both ATP projects, releasing its first CFLP diagnostic kits in mid-1996. The first project also led to a preliminary version of Third Wave's Invader technology, which made CFLP seem comparatively cumbersome and with which Third Wave's executives later replaced CFLP.

The second award supported the development of Third Wave's signature Invader assay, which combined CFLP and engineered probes to identify SNPs. The Invader assay increased sensitivity and made the molecular diagnostic process more efficient. Primary and secondary reactions were now able to occur in the same test tube, offering great advantages to the medical diagnostic market (see Figure 6-4).

Figure 6-4. Third Wave Technologies' Cleavase-Based Diagnostics Tests



Source: Courtesy of Third Wave Technologies, Inc.

Invader offers substantial gains in quality and signal strength, providing end users more signal and easing analysis without requiring more sample DNA or RNA. Invader probes work by hybridizing to the sample DNA and creating a specific structure that is recognized by the Cleavase enzyme. Where the probes hybridize to target DNA, Cleavase enzymes cut the probes to begin a signal cascade that results in a target-specific fluorescent signal. In essence, end users benefited from a higher quality assay without incurring additional sample or analysis costs.

According to Third Wave's executives, all of the company's diagnostic and research products include either the Cleavase or the Invader technology platforms. Recently, the patents for PCR expired, and Third Wave now offers Invader Plus, which combines PCR, Invader, and Cleavase. Third Wave was issued patents that protect its intellectual property in the combination of its Invader chemistry and PCR (Third Wave, 2006).

Third Wave's technologies from the second award have found applications in the research and clinical diagnostic markets in 2000, but the technology is only now coming into the point-of-care market.

Third Wave, Shimadzu, and Toppan Printing plan to co-develop and commercialize a point-of-care device that aims to prevent adverse drug reactions (GenomeWeb News, 2006). Third Wave's technology will be used in the sample preparation stage, applying the Invader technology to interrogate genes. The other two companies will supply reagents and the chip-based platform. The group plans to bring a prototype to market for research use before the end of 2006.

6.3.4 End Users and Applications

Third Wave positions its molecular diagnostics products for the clinical and research markets as easy-to-use, inexpensive assay systems able to detect mutations and quantify specific genetic sequences. Independent studies of Invader assays have shown them to be easy to use and appropriate for the clinical settings. Industry experts cited the following economic benefits to end users:

- The Invader uses genomic DNA; therefore, there is no pre- or post-amplification as with PCR.
- Laboratories do not need to acquire equipment for pre-amplification or post-amplification processes. Not only does the lab save on equipment costs, but it also saves in equipment space allocation.

- There is no changeover in laboratory coats or booties—a process that is typically required to prevent contamination (time and materials savings).
- Setup time is only 20 minutes, as opposed to the multiple hours required to perform PCR. Time was available for technicians to work on other tasks.

The invader assay only needs an isothermal incubation source and a multiwell fluorometer. Traditionally, diagnostic PCR required 30 to 35 cycles and required significant control of contamination because the target might be amplified to as many as 34 billion copies. PCR combined with Invader (which Third Wave named Invader Plus) requires as few as 14 cycles, yielding only about 16,000 fold amplification. This comparatively low amplification dramatically reduced cross-contamination risks while at the same time enabling detection of as few as 10 copies of the target.

Laboratories like Quest, Chantilly, and Lab Corp use Third Wave's products for many applications, including SNP identification and analysis, inherited diseases, infectious diseases, and pharmacogenomics. Many of the products these labs use are analyte-specific reagents (ASRs), which are used for the detection of particular diseases or disease-associated genetic markers. For example, the Factor V Leiden ASR is designed for clinicians to determine whether a patient has the Factor V Leiden gene, which is linked to an increased risk of developing blood clots. One-quarter of the human genome's SNPs mapped in the international HapMap project were mapped using Invader coupled with PCR.

There are also applications beyond medical research and diagnostics. According to Day, in the field of agricultural genetics, SNPs serve as markers across the genome and allow plant and animal breeders, who use molecular diagnostic tools to identify markers and track the inheritance of simple and complex traits through the breeding process.

The adoption of molecular marker tools like Invader allows researchers to accelerate the pace and improve the accuracy with which they can advance traits. These genetic improvements are intended to increase agricultural yields, enhance crop quality, and produce agricultural products with desired physical traits.

7 Project Portfolio Performance and Review

ATP's molecular diagnostics projects brought new technologies to the market that have had a profound impact on genetic analysis and public health. This report profiled Molecular Dynamic's development of the first high-throughput DNA sequencer, the MegaBACE 1000, which accelerated the HGP and spurred innovation at other sequencer manufacturers. Third Wave, which may not have survived without ATP funding, developed inexpensive, easy-to-use diagnostic tests that were used to complete 25% of the International HapMap project.

Beyond these large-scale genomics research projects, ATP had an impact on the technologies used in medical research and clinical diagnostics everyday. Affymetrix's and Nanogen's DNA microarrays are more effective and efficient and are supported by a more robust assay system as a consequence of ATP awards. Many of Third Wave's products are approved by the Food and Drug Administration for clinical use, providing inexpensive, rapid diagnostic tests conducted in a test tube.

Orchid's customizable SNP analysis technology has enabled more cost-effective, accurate, and high quality forensics identification and genetic analysis to be conducted. In fact, Orchid's highly sensitive technology helped with identifying several hundred additional individuals' DNA from the World Trade Center disaster, when more traditional methods had failed.

CuraGen developed a drug discovery platform and now has several new biopharmaceuticals in clinical trials. In addition, the research into

microfluidics that the company tackled during its ATP project laid the groundwork for its next generation DNA sequencing subsidiary, 454 Life Sciences.

Ultimately, the principal beneficiaries of these technologies are the patients who receive more timely, better quality, and more effective health care because doctors, clinicians, and researchers have more powerful DNA diagnostic tools. The information generated—a sequenced genome, an expression profile of a diseased tissue sample, or an early warning of a gene that may make a patient more likely to contract an illness—have social impacts that are invaluable.

To provide quantitative measures for evaluating the success of these and the other Tools for DNA Diagnostics projects, Chapter 7 uses the economic benefits from the two case studies and uses them to calculate lower-bound performance measures for ATP's entire Tools for DNA Diagnostics portfolio.

7.1 PERFORMANCE MEASURES—ALL ATP TOOLS FOR DNA DIAGNOSTICS PROJECTS

Conducting an in-depth case study of each of the 42 Tools for DNA Diagnostics projects was not possible. However, the benefits quantified in the two case studies present a very conservative, lower-bound estimate of the return on ATP's investment in all 42 projects.

The public benefits from Affymetrix's, Molecular Dynamics', and MT/Orchid's ATP projects were compared with all 42 Tools for DNA Diagnostics project costs ATP incurred to calculate lower-bound measures of economic performance.

Performance measures reflect realized benefits that accrued through 2005. Cash flows were not purposefully stopped in 2005. The last of the products to which acceleration benefits are attributed reached the end of its useful life in 2005. Additional economic and scientific benefits from the technologies are expected to accrue indefinitely; however, these could not be quantified.

For the portfolio analysis, the entire dollar value of each project's award was allocated to the midpoint of each project's period of performance. This method simplified calculations while having little material impact on the performance measures.

Table 7-1 presents the time series of public benefits quantified in the two case studies. These public benefits were summed and reduced by ATP's inflation-adjusted annual spending on all 42 projects to derive net public benefits. In all, RTI calculated $402.3 million in public benefits, of which approximately 98% were contributed by ATP's investment in the Affymetrix-Molecular Dynamics JV.

ATP's investment was $164.2 million, which yields lower-bound net public benefits of $238.2 million. Thus, although only three projects were reviewed quantitatively, those projects alone realized benefits sufficient to yield positive net benefits for all 42 ATP Tools for DNA Diagnostics projects.

Admittedly, the Affymetrix-Molecular Dynamics project was selected for review because it was known qualitatively that the public benefited substantially from ATP's investment, though no quantitative measures had been calculated in advance of this economic analysis. The results of this retrospective analysis confirm what was known anecdotally and indicate that ATP helped introduce and accelerate new and innovative biotechnologies.

Table 7-1. Time Series of Public Benefits, Costs, and Lower-Bound Net Benefits—All Tools for DNA Diagnostics Projects (2005$)

Year	Public Benefits: Orchid Cellmark Case Study	Public Benefits: Affymetrix and Molecular Dynamics Case Study	Lower Bound Public Benefits	Public Costs for All 42 Projects	Lower-Bound Net Public Benefits
1995				–$1,994,000	–$1,994,000
1996				–47,849,000	–47,849,000
1997				–58,616,000	–58,616,000
1998		–$3,501,000	–$3,501,000	–18,937,000	–22,438,000
1999	$2,106,000	751,000	2,857,000		2,857,000
2000	1,638,000	201,620,000	203,258,000	–21,926,000	181,332,000
2001	1,638,000	53,983,000	55,621,000	–4,831,000	50,790,000
2002	1,229,000	53,983,000	55,212,000		55,212,000
2003	819,000	51,479,000	52,298,000	–2,120,000	50,178,000
2004	410,000	30,331,000	30,740,000	–6,136,000	24,604,000
2005		5,844,000	5,844,000	–1,762,000	4,081,000
Total	7,839,000	394,490,000	402,329,000	–164,171,000	238,158,000

Source: RTI estimates.

Note: Sums may not add to totals because of independent rounding.

Using the data presented in Table 7-1, RTI calculated lower-bound measures of performance for ATP's molecular diagnostics projects. Using 1995 as the base year, when a discount rate of 7% is applied to the time series of net public benefits, the minimum NPV is $119.7 million. This NPV is smaller than that calculated for the Affymetrix-Molecular Dynamics project alone because the latter calculation included the costs for only the MIND Development project.

The public rate of return was 28%. The benefit-cost ratio was 1.9. This means that for every $1 ATP invested in these 42 projects, the public realized at least $1.90 in benefits (see Table 7-2). If benefits had been calculated for other projects, the measures in Tables 7-1 and 7-2 would likely have increased.

7.2 IMPACT OF ATP ON THE BIOTECHNOLOGY INDUSTRY

ATP's Tools for DNA Diagnostics program was created as a public-private partnership to ensure that the program would address both technology and market needs. ATP funding invigorated market interest in a growing sector and contributed to the emergence of an industry.

Representatives from Affymetrix and the former Molecular Dynamics believe that the success of the JV and ATP's support was "a shining light" that encouraged other firms "to go for it" and develop and market technologies for what was becoming the pharmacogenomics and genomics marketplace. In addition, Affymetrix's ATP-supported software research spawned an "ecosystem of companies" that serves the IT needs of an industry.

Table 7-2. Lower-Bound Public Performance Measures—All Tools for DNA Diagnostics Projects

Public benefits of 3 projects (2005 $ millions)	402.3
Public costs of 42 projects (2005 $ millions)	–164.2
Net public benefits (2005 $ millions)	238.2
NPV of net benefits (2005 $ millions)[a]	119.7
Benefit-to-cost ratio	1.9
Internal rate of return	28%

[a]To compute NPV, net public benefits were discounted to 1995 using a 7% annual discount rate.

Source: RTI estimates.

In the case of that project, the dollar value and scope of the ATP award, followed by the success of the two companies and the technologies they developed, validated what Affymetrix and Molecular Dynamics were doing, in the eyes of the scientific community. This validation in turn helped focus venture capital and investor attention on the emerging biotechnology industry. That project's $31.5 million award was larger than most venture capital placements and did not bring the constraints that are usually seen with a near-term focus on commercialization.

When the Tools for DNA Diagnostics focused program was launched in 1994, the biotech sector was still in its infancy. Up to that point, the industry was dominated by large laboratory instrumentation and medical device manufacturers. Small start-up companies often relied on angel financing, partnerships with large pharmaceutical companies, or personal (often called bootstrap) financing. As one participant noted, even if a biotech company had external financing, an additional $1 or $2 million provides researchers with greater freedom to pursue scientific discovery.

Some of these technologies might not have even survived at all without ATP. The founders and principal investigators at MT, Orchid, CuraGen, Nanogen, and Third Wave all expressed the importance of the ATP funding in supporting very small companies in a new industry. A good number of ATP-supported start-ups in this field were founded by former academics with ideas and technical acumen, but little access to capital. At such an early development stage, many start-ups fail.

In general, venture capital financing may be available once a firm has met its first few milestones and its technology is nearing commercialization. Venture capitalists will bring business acumen and focus to the funded organization, emphasizing bringing the technology to market. Venture capitalists trade risk for a high expected return and will bring in specialists and highly qualified management personnel to mitigate risks.

The challenge for innovators is that venture capitalists often require that firms have already met their first few technology milestones, yet many innovators deplete their funds before they achieve such milestones. Furthermore, venture capitalists may bring focus, but typically at the expense of scientific discovery.

The market failure exists in the technology development stages between conceptualization and prototype development. ATP's long-term focus permits organizations to address scientific barriers, contribute to science, and pursue high-risk ventures.

One industry expert believes that the technologies that will revolutionize health care between 2009 and 2020 were pioneered in the 1990s. Incubation time—the period between conceptualization and mainstream adoption—is long for biotechnologies in health care. ATP's support of core research and technology development helped provide a foundation for technologies that may have incubation times of 15 years or more.

Many of the leaders in the molecular diagnostics field were ATP awardees that were afforded the opportunity to further invest in their technology because of the support they received. As one interviewee noted, the list of ATP awardees covers several of the major players in molecular diagnostics (see Table 7-3). Consequently, ATP awardees believe that investors were more likely to invest in their businesses because their technology was far more developed and robust than it would have otherwise been. Or, as in the case of Molecular Dynamics, ATP funds permit public companies to pursue high-risk projects that would not be undertaken otherwise.

ATP's Tools for DNA Diagnostics technology development program moved concepts into practical technologies, enabling advances in public health. The projects profiled in this report provided the tools to move medical science significantly closer to personalized medicine.

ATP accelerated the introduction and increased the power of diagnostic technologies that the research community has come to rely on everyday. Ultimately, the principal beneficiaries of these technologies are the patients who will receive more timely, better quality, and more effective care because their doctors, clinicians, and researchers have exponentially more powerful DNA diagnostic tools at their disposal.

The information generated—a sequenced genome, an expression profile of a diseased tissue sample, or an early warning of a gene that may make a patient more likely to contract an illness—have social impacts that are invaluable. Personalized medicine is still a work in progress, but ATP's early investment in its core technologies accelerated its introduction, bringing the day of its introduction forward in time.

Table 7-3. ATP Awardees—Tools for DNA Diagnostics Projects

3-Dimensional Pharmaceuticals, Inc.	Gene Check, Inc.	Nanogen, Inc.
Aclara BioSciences, Inc.	Gene Network Sciences, Inc.	Orchid BioSciences, Inc.
Affymetrix, Inc.	Genosensor Consortium	PharmaSeq, Inc
Amersham Biosciences Corp.	HandyLab, Inc.	Qualicon
Applied Biosystems, Inc.	Incyte Corporation	Rheogene LLC
Ardais Corporation	JDS Uniphase	Sangamo BioSciences, Inc.
Bio-Rad Laboratories	Large Scale Proteomics Corporation	Sarnoff Corporation
Caliper Life Sciences	Medical Analysis Systems, Inc.	Sequenom, Inc.
Callida Genomics, Inc. (formerly Hyseq Inc.)	Moldyn, Inc.	Third Wave Technologies, Inc.
Clinical Micro Sensors, Inc.	Molecular Dynamics, Inc.	Vysis, Inc.
CuraGen Corporation	Motorola, Inc.	Xtrana, Inc.

Note: This list of companies includes companies with projects that were competitively funded as part of the Tools for DNA Diagnostics focused program as well as projects awarded during ATP's general competitions. Some companies were awarded multiple projects, and some were joint ventures for which only the lead organization was included in this table. Thus, this list is not exhaustive.

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Appendix A: ATP's 42 Tools for DNA Diagnostics Projects

Table A-1. ATP's 42 Tools for DNA Diagnostics Projects

Project Number	Project Title	Lead Organization	State	Single or Joint Award	Start Date	End Date	Total ATP $	Total Industry Cost Share $
1992-01-0044	Genosensor Technology Development	Genosensor Consortium, c/o Houston Advanced Research Center	Texas	J	08/18/93	07/31/98	$9,233,968	$9,234,055
1993-01-0113	Hyperthermophilic Microorganisms in Molecular Biology and Biotechnology	Amersham Biosciences (formerly United States Biochemical Corp.)	New Jersey	S	02/15/94	02/14/97	$1,557,689	$838,902
1994-01-0137	Enhanced Molecular Dynamics Simulation Technology for Biotechnology Applications	Moldyn, Inc.	Massachusetts	S	02/15/95	02/14/98	$1,988,000	$1,341,000
1994-01-0284	Standardization of 2-D Protein Analysis Using Manufacturable Gel Media	Large Scale Proteomics Corporation (formerly Large Scale Biology Corporation)	Maryland	S	01/16/95	01/15/98	$1,902,000	$1,445,000
1994-05-0004	Compact Blue Laser for Diagnostics	JDS Uniphase (formerly Uniphase Laser Division)	California	J	01/01/95	12/31/97	$1,450,000	$1,453,000
1994-05-0006	Development of Rapid DNA Medical Diagnostics	Sequenom (formerly Gene Trace Systems Inc.)	California	S	01/01/95	12/31/97	$1,997,000	$699,000

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Table A-1. ATP's 42 Tools for DNA Diagnostics Projects (continued)

Project Number	Project Title	Lead Organization	State	Single or Joint Award	Start Date	End Date	Total ATP $	Total Industry Cost Share $
1994-05-0012	Development of a Generic Technology for the Targeted Detection and Cleavage of DNA and RNA	Third Wave Technologies, Inc.	Wisconsin	S	01/01/95	12/31/96	$1,998,000	$771,000
1994-05-0016	Miniature Integrated Nucleic Acid Diagnostic (MIND(TM)) Development	Affymetrix, Inc.	California	J	02/01/95	01/31/00	$31,478,000	$31,487,000
1994-05-0017	Molecular Cytogenetics Using the GeneScope: An Ultrafast, Multicolor System for Automated FISH Analysis	Bio-Rad Laboratories	California	S	03/01/95	02/28/98	$2,000,000	$1,648,000
1994-05-0018	SBH Format 3 Megabase Diagnostics Instrumentation	Callida Genomics, Inc. (formerly Hyseq Inc.)	California	S	01/01/95	12/31/97	$2,000,000	$1,498,000
1994-05-0019	DNA Diagnostic Systems Based on Novel Chem-jet Techniques	Incyte Genomics (formerly Combion, Inc./Incyte Pharm. Inc.)	California	S	02/01/95	01/31/98	$1,790,000	$987,000
1994-05-0021	Development and Commercial Application of Genosensor Based Comparative Genome Hybridization	Vysis, Inc.	Illinois	S	03/01/95	02/28/98	$2,000,000	$1,514,000
1994-05-0027	Integrated Microfabricated DNA Analysis Device for Diagnosis of Complex Genetic Disorders	CuraGen Corporation	Connecticut	J	02/01/95	01/31/98	$2,267,000	$2,899,000

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Table A-1. ATP's 42 Tools for DNA Diagnostics Projects (continued)

Project Number	Project Title	Lead Organization	State	Single or Joint Award	Start Date	End Date	Total ATP $	Total Industry Cost Share $
1994-05-0029	MicroLab: A High-Throughput, Low-Cost Approach to DNA Diagnostics by Array Hybridization	Sarnoff Corporation	New Jersey	S	02/01/95	01/31/98	$2,000,000	$6,208,000
1994-05-0033	Automated DNA Amplification and Fragment Size Analysis	Qualicon (formerly DuPont, FQMS Group)	Delaware	S	01/01/95	12/31/97	$2,000,000	$1,175,000
1994-05-0034	Integrated Microfabricated Devices for DNA Typing	Orchid BioSciences (formerly Molecular Tool, Inc., Alpha Center)	New Jersey	S	02/15/95	02/14/98	$1,962,000	$494,000
1995-01-0098	RNA Binding Protein Technology for Identification of Novel Therapeutics	Message Pharmaceuticals, Inc. (formerly Bearsden Bio/Symphony Pharmaceuticals)	Pennsylvania	S	08/01/95	07/31/98	$1,707,420	$576,432
1995-01-0177	Crystallization and Structural Determination of G-Coupled Protein Receptors	3-Dimensional Pharmaceuticals, Inc.(formerly 3-Dimensional Pharmaceuticals Inc.)	Pennsylvania	S	08/15/95	08/14/98	$1,998,126	$1,670,663
1995-08-0006	Real-Time Micro-PCR Analysis System	PE-Biosystems (formerly Perkin-Elmer)	California	J	09/01/95	04/30/99	$7,281,494	$7,377,975
1995-08-0009	An Integrated Microelectronic DNA Diagnostic System	Nanogen, Inc.	California	S	08/01/95	12/31/97	$2,000,000	$1,500,000

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Table A-1. ATP's 42 Tools for DNA Diagnostics Projects (continued)

Project Number	Project Title	Lead Organization	State	Single or Joint Award	Start Date	End Date	Total ATP $	Total Industry Cost Share $
1995-08-0012	Development of Bar Code Diagnostics for DNA Diagnostics	Vysis, Inc.	Illinois	S	08/01/95	07/31/98	$2,000,000	$2,273,812
1995-08-0015	Self-Contained Cartridge Integrating Nucleic Acid Extraction, Specific Target Amplification, and "Dip Stick" Immediate Detection	Xtrana, Inc. (formerly Molecular Innovations, Inc./ Immun. Associates of Dnvr)	Colorado	S	08/01/95	07/31/98	$1,580,548	$90,000
1995-08-0016	Generation and Development of Novel Nucleic Acid Binding Proteins and Their Use as DNA Diagnostics	Sangamo BioSciences	California	S	08/01/95	07/31/98	$2,000,000	$456,250
1995-08-0017	DNA Diagnostics Using Self-Detected Target-Cycling Reaction (SD-TCR)	Medical Analysis Systems (formerly NAVIX, Inc.)	California	S	09/01/95	02/28/98	$2,000,000	$1,116,344
1995-08-0023	Arrayed Primer Extension (APEX): The Next Generation DNA Analysis System for Sequencing in DNA Diagnosis	Amersham Biosciences Corp. (formerly USB/Amersham Pharmacia Biotech, Inc.)	New Jersey	J	09/15/95	09/14/00	$5,785,406	$5,812,303
1996-01-0141	Programmable Nanoscale Engines for Molecular Separation	CuraGen Corporation	Connecticut	S	04/01/97	03/31/99	$2,000,000	$1,430,820
1996-01-0172	A Portable Genetic Analysis System	Nanogen, Inc.	California	S	05/01/97	09/30/99	$2,000,000	$1,935,255

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Table A-1. ATP's 42 Tools for DNA Diagnostics Projects (continued)

Project Number	Project Title	Lead Organization	State	Single or Joint Award	Start Date	End Date	Total ATP $	Total Industry Cost Share $
1996-01-0315	Development of Novel DNA Binding Proteins as Antiviral Therapeutics	Sangamo BioSciences, Inc.	California	S	05/01/97	04/30/00	$2,000,000	$680,000
1997-01-0135	Simple, Generic, and Low-Cost Genetic-Based Tools for Disease Detection, Monitoring, and Intervention	Third Wave Technologies, Inc.	Wisconsin	S	10/01/97	09/30/99	$2,000,000	$2,093,399
1997-01-0226	Measurement Technology for Quantitation of the Complete Human Proteome	Large Scale Proteomics Corporation (formerly Large Scale Biology Corporation)	Maryland	S	10/01/97	03/31/00	$1,995,256	$1,017,600
1998-08-0003	DNA Diagnostics for the Point of Care Using Electronic Nucleic Acid Detection	Clinical Micro Sensors, Division of Motorola, Inc.	California	S	12/01/98	11/30/01	$1,908,567	$1,883,534
1998-08-0007	Reference Laboratory LabChip DNA Diagnostics System	Caliper Technologies Corporation	California	S	01/01/99	12/31/01	$1,999,998	$2,146,745
1998-08-0014	Polymerase Signaling Assay for DNA Variation Detection on Universal Processor Arrays	Orchid BioSciences, Inc.	New Jersey	S	01/01/99	12/31/01	$1,954,313	$1,012,373
1998-08-0020	Multiplex DNA Diagnostic Assay Based on Microtransponders	PharmaSeq, Inc	New Jersey	S	11/01/98	07/31/01	$1,978,000	$540,000
1998-08-0029	Multiplexed Sample Preparation Microsystem for DNA Diagnostics	Aclara BioSciences, Inc.	California	S	12/01/98	05/31/01	$1,998,826	$1,599,061

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Table A-1. ATP's 42 Tools for DNA Diagnostics Projects (continued)

Project Number	Project Title	Lead Organization	State	Single or Joint Award	Start Date	End Date	Total ATP $	Total Industry Cost Share $
1998-08-0031	Integrated, Micro-Sample Preparation System for Genetic Analysis	PE Corporation (formerly Applied Biosystems/PE-Biosystems)	California	J	01/01/99	09/12/02	$9,563,632	$10,966,329
1999-01-1104	Microfluidics Device for Diagnosis of Nosocomial Agents (MeDiNA)	Motorola, Inc.	Arizona	J	11/01/99	10/31/02	$4,392,000	$4,583,426
2001-3B-4620	Engineering Systems for Site Specific Alteration of Mammalian Genomes	Rheogene LLC	Pennsylvania	S	01/01/02	07/31/05	$2,000,000	$1,358,382
2002-1I-4983	A Medical Informatics Data Model, Software Development Toolkit and Applications to Enable the Use of Clinical Information in Genomic-based Pharmaceutical Research	Ardais Corporation	Massachusetts	S	11/01/02	10/31/05	$1,957,425	$1,628,391
2002-1I-5063	Cost-Effective Detection of Efficacious and Non-Toxic Drug Targets via Breakthrough in Silico Methods	Gene Network Sciences, Inc.	New York	S	11/01/02	10/31/05	$2,000,000	$1,349,763
2002-2B-5475	Portable DNA Analysis Device Using Real-Time PCR and On-Chip Electrochemical Detection	HandyLab, Inc.	Michigan	S	07/01/03	06/30/05	$2,000,000	$500,000
2002-3B-5860	High Throughput, Low Cost SNP Genotyping for Diagnostics and Genome Scanning	Gene Check, Inc.	Colorado	S	10/01/03	09/30/06	$1,762,178	$153,290

About the Authors

Alan O'Connor is an economist in RTI's Technology, Energy, and the Environment program. He has 10 years' experience in technology program evaluation, case study and business analysis, trends assessment, survey research, and benefit-cost modeling. In recent years, he has led cross-functional teams that have investigated technological change and standardization issues in the biotechnology sector, electronic data exchange in heavy industries, and investments in infratechnologies. His clients include ATP, NIST, EPA, and DHHS.

Brent Rowe is a senior analyst in RTI's in Technology, Energy, and the Environment program. He has experience in technology and industry assessments, statistical analysis, and survey development and administration. He has evaluated innovative technologies, such as Internet Protocol Version 6 (IPv6), and developed economic impact models of specific regulatory policy alternatives. His topical experience includes the Internet, telecommunications, biotechnology and semiconductor industries, and he has contributed to studies for DHS, NIST, NTIA, and the North Carolina Utilities Commission.

Michael Gallaher is the director of RTI's Technology, Energy, and the Environment program and has over 10 years of experience leading projects for NIST, EPA, and other federal agencies modeling the economic impact of new technologies. Dr. Gallaher specializes in developing baseline/counterfactual scenarios from which incremental costs and benefits can be measured and has conducted both retrospective and prospective technology assessments. Most of the projects he has led have involved modeling the adoption of new technologies and assessing the barriers to adoption. Dr. Gallaher has led over 30 economic impact assessments for agencies such as NIST, EPA, NSF, and NTIA.

Joel Sevinsky is a research biochemist in RTI's Proteomics Research Program. He has experience in proteomics, genomics, molecular biology, microbiology, and bioinformatics. Dr. Sevinsky specializes in methods development for shotgun proteomics. His current research includes strategies for high-throughput searching of metagenomic sequences for genome annotation and metabolic labelling methods for protein turnover profiling of entire proteomes.

Dallas Wood is a research associate in RTI's Center for Regulatory Economics and Policy Research. He has experience in industry analysis, technology program evaluation, statistical analysis, survey administration, and regional economic impact analysis. He uses his statistical training to analyze and interpret data after it has been collected. Mr. Wood has worked on research projects for NIST, EPA, DHS, NTIA, and several private-sector clients.

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The Advanced Technology Program (ATP) is a partnership between government and private industry to conduct high-risk research to develop enabling technologies that promise significant commercial payoffs and widespread benefits for the economy. ATP provides a mechanism for industry to extend its technological reach and push the envelope beyond what it otherwise would attempt.

Promising future technologies are the domain of ATP:

- Enabling or platform technologies essential to development of future new products, processes, or services across diverse application areas
- Technologies where challenging technical issues stand in the way of success
- Technologies that involve complex "systems" problems requiring a collaborative effort by multiple organizations
- Technologies that will remain undeveloped, or proceed too slowly to be competitive in global markets, in the absence of ATP support

ATP funds technical research, but does not fund product development— that is the responsibility of the company participants. ATP is industry driven, and is grounded in real-world needs. Company participants conceive, propose, co-fund, and execute all of the projects cost-shared by ATP. Most projects also include participation by universities and other nonprofit organizations.

Each project has specific goals, funding allocations, and completion dates established at the outset. All projects are selected in rigorous competitions that use peer review to identify those that score highest on technical and economic criteria. Single-company projects can have duration up to three years; joint venture projects involving two or more companies can have duration up to five years.

Small firms on single-company projects cover at least all indirect costs associated with the project. Large firms on single-company projects cover at least 60 percent of total project costs. Participants in joint venture projects cover at least half of total project costs. Companies of all sizes participate in ATP-funded projects. To date, nearly two out of three ATP project awards have gone to individual small businesses or to joint ventures led by a small business.

Contact ATP for more information:

- On the Internet: www.atp.nist.gov
- By e-mail: atp@nist.gov
- By phone: 1-800-ATP-FUND (1-800-287-3863)
- By writing: Advanced Technology Program, National Institute of Standards and Technology, 100 Bureau Drive, Stop 4701, Gaithersburg, MD 20899-4701