PACIFIC BIOSCIENCES OF CALIFORNIA, INC.
Form 10-K
March 15, 2013
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2012

Or

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number 001-34899

Pacific Biosciences of California, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**16-1590339**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
1380 Willow Road	
Menlo Park, CA 94025	**94025**
(Address of principal executive offices)	**(Zip Code)**

(Registrant s telephone number, including area code)

(650) 521-8000

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.001 per share	**The NASDAQ Stock Market LLC**

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known, seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer x
Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ¨ No x

Aggregate market value of registrant s common stock held by non-affiliates of the registrant on June 30, 2012, based upon the closing price of Common Stock on such date as reported by NASDAQ Global Select Market, was approximately $89,575,000. Shares of voting stock held by each officer and director have been excluded in that such persons may be deemed to be affiliates. This assumption regarding affiliate status is not necessarily a conclusive determination for other purposes.

Number of shares outstanding of the issuer s common stock as of March 7, 2013: 57,497,327

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant s definitive Proxy Statement relating to its 2013 Annual Meeting of Stockholders to be held on May 23, 2013 are incorporated by reference into Part III of this Form 10-K where indicated. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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Pacific Biosciences of California, Inc.

Annual Report on Form 10-K

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SPECIAL NOTE REGARDING FORWARD LOOKING STATEMENTS

Discussions under the captions Business, Risk Factors, and Management s Discussion and Analysis of Financial Condition and Results of Operations contain or may contain forward-looking statements that are based on our management s beliefs and assumptions and on information currently available to our management. The statements contained in this Annual Report on Form 10-K that are not purely historical are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act), and include, but are not limited to, statements regarding the sequencing advantages of our SMRT technology, our market opportunity, our strategic plans, our expectation regarding the conversion of backlog to revenue, our manufacturing plans, our research and development plans, our competition, our intent regarding dividends, our expectation regarding our unrecognized income tax benefits, the sufficiency of our cash, cash equivalents and investments to fund our projected operating requirements, and the effects of recent accounting pronouncements on our financial statements. Such statements may be signified by terms such as anticipates, believes, could, seeks, estimates, expects, intends, may, plans, potential, predicts, projects, should, will, would or negatives of those terms. Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed under the heading Risk Factors in this report and in other documents we file with the Securities and Exchange Commission (SEC). Given these risks and uncertainties, you should not place undue reliance on these forward-looking statements. Also, forward-looking statements represent our management s beliefs and assumptions only as of the date of this report. Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

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PART I

ITEM 1. BUSINESS

Overview

We develop, manufacture and market an integrated platform for high resolution genetic analysis. We have developed a technology to study the synthesis, composition, structure, and regulation of DNA. Combining advances in nanofabrication, biochemistry, molecular biology, surface chemistry and optics, we created a technology platform using our proprietary single molecule, real-time, or SMRT, technology. Our SMRT technology uses the natural processing power of enzymes, combined with specially designed reagents and detection systems, to record individual biochemical events as they occur. The ability to observe single molecule events in real time provides the scientific community with an advanced tool for investigating basic biochemical processes such as DNA synthesis. Our SMRT technology has the potential to advance scientific understanding by providing a window into biological processes that has not previously been open.

Our initial focus is on the DNA sequencing market where we have developed and introduced a third generation sequencing platform, the PacBio *RS* High Resolution Genetic Analyzer, using our proprietary SMRT technology. The PacBio *RS* maintains many of the key attributes of first and second generation sequencing technologies while solving many of their inherent limitations, including short readlengths, limited flexibility, long time to result, complex sample preparation and risk of amplification bias. Our system provides long readlengths, flexibility in experimental design, fast time to result, and ease of use. The PacBio *RS* consists of an instrument platform that uses our proprietary consumables, which are currently comprised of our SMRT Cells and several chemical reagent kits used to prepare and sequence DNA samples. Our system is designed to be integrated into existing laboratory workflows and information systems.

Pacific Biosciences of California, Inc., formerly Nanofluidics, Inc. was incorporated in the State of Delaware in 2000. Our executive offices are located at 1380 Willow Road, Menlo Park, California 94025, and our telephone number is (650) 521-8000.

The Underlying Science

Genetic inheritance in living systems is conveyed through a naturally occurring information storage system known as deoxyribonucleic acid, or DNA. DNA stores information in linear chains of the chemical bases adenine, cytosine, guanine and thymine, represented by the symbols, A, C, G and T. Inside living cells, these chains usually exist in pairs bound together in a double helix by complementary bases, with A of one strand always binding to a T of the other strand and C always binding to G.

In humans, there are approximately three billion DNA base-pairs in the molecular blueprint of life, called the genome. These three billion bases are divided into 23 chromosomes ranging in size from 50 million to 250 million bases. Normally, there are two complete copies of the genome contained in each cell, one of maternal origin and the other of paternal origin. When cells divide, the genomes are replicated by an enzyme called DNA polymerase, which visits each base in the sequence, creating a complementary copy of each chromosome using building blocks called nucleotides. Contained within these chromosomes are approximately 23,000 smaller regions, called genes, each one containing the recipe for a protein or group of related proteins. The natural process of protein production takes place in steps. In a simplified model, the first step is transcription, a process in which an enzyme called RNA polymerase uses DNA as a template to synthesize new strands of messenger RNA, or mRNA. The mRNAs are then translated into proteins by ribosomes. The resulting proteins go on to play crucial roles in cellular structure and function and thus the operation of biological systems.

Numerous scientific approaches have evolved to adapt to the emerging awareness of the magnitude of complexity embedded in biological systems. The field of genomics developed to study the interactions among components in the genome and the massive quantities of associated data. Subsequently, proteomics, transcriptomics and a number of other related fields emerged.

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Advances in biology over the next decade are expected to be shaped by a more detailed understanding of the fundamental complexity of biological systems. These systems vary among individuals in previously unrecognized ways and are influenced by factors including time, molecular interactions, and cell type.

Importantly for the future of genomics, the first few whole-genome sequencing studies of disease have shown that rare mutations play a critical role in human disease. These mutations would not have been detected in earlier studies because too few people, or perhaps only one person, carry the specific mutation. In addition, it is now understood that structural changes to the genome in which whole sections are deleted, inverted, copied or moved may be responsible for a significant fraction of variation among individuals. The scope of these structural changes challenges the very idea of a reference genome.

Recent discoveries have highlighted additional complexities in the building blocks of DNA and RNA, including the presence of modified bases. It has long been known that in humans and many other multicellular organisms, the cytosine bases can be chemically modified through the addition of a methyl group in a process called methylation. These chemical modifications have been shown to play a role in embryonic development, have important impacts on diseases such as cancer and can even affect the characteristics of offspring for multiple generations. More recently, it has been discovered that other bases, such as hydroxymethylcytosine, or hmC, 8-Oxoguanine and many others, play important physiological roles. In bacteria, 6-methyladenine has been shown to play an important role in pathogenicity

In a recently published study in *Nature Biotechnology* of the Shiga-toxin-producing *E. coli* strain that caused a serious outbreak in northern Germany in 2011 which killed approximately fifty people and sickened over 1,000 others, researchers had previously sequenced the genome of the same strain; however, the data had not explained the high virulence of the strain. By analyzing the outbreak strain sequence for 6-methyladenine residues using the PacBio *RS*, researchers discovered a series of methylase-like enzymes that targeted specific sequences throughout the genome as they made their chemical changes. Follow-up studies of a particular methylase suggest that it alters the expression of gene pathways related to horizontal gene transfer an important property that could be linked to virulence.

Another source of complexity derives from the processing of RNA molecules after being transcribed from the genome. The majority of all genes code for different forms of a protein that can be made depending on the structure of the RNA molecule, referred to as splice variants. A detailed understanding of both the expression pattern and regulation of these variants is believed to play an important role in a number of critical biological processes.

Recent advances in our understanding of biological complexity have highlighted the need for advanced tools such as the PacBio *RS* to study DNA, RNA and proteins. In the field of DNA sequencing incremental technological advances have provided novel insights into the structure and function of the genome. Despite these advances, researchers have not been able to fully characterize the human genome and the genomes of other living organisms because of inherent limitations in these tools.

Evolution of Sequencing

In order to understand the limitations of current DNA sequencing technologies, it is important to understand the sequencing process. This consists of three phases: sample preparation, physical sequencing, and analysis. The first step of sample preparation is to either break the target genome into multiple small fragments, or depending on the amount of sample DNA available, amplify the target region using a variety of molecular methods. In the physical sequencing phase, the individual bases in each fragment are identified in order, creating individual reads. The number of individual bases identified contiguously is defined as readlength. In the analysis phase, bioinformatics software is used to align overlapping reads, which allows the original genome to be assembled into contiguous sequence. The longer the readlength, the easier it is to assemble the genome.

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First Generation Sequencing

First generation sequencing, also referred to as Sanger sequencing, was originally developed by Frederick Sanger in 1977. With this technology, during sample preparation, scientists first make different sized fragments of DNA each starting from the same location. Each fragment ends with a particular base that is labeled with one of four fluorescent dyes corresponding to that particular base. Then all of the fragments are distributed in order of their length by driving them through a gel. Information regarding the last base is used to determine the original sequence. Under standard conditions, this method results in a readlength that is approximately 700 bases on average, but may be extended to 1,000 bases. These are relatively long readlengths compared with many other sequencing methods. However, first generation sequencing is limited by the small amounts of data that can be processed per unit of time, referred to as throughput.

Second Generation Sequencing

Commercial second generation DNA sequencing tools emerged in 2005 in response to the low throughput of first generation methods. To address this problem, second generation sequencing tools achieve much higher throughput by sequencing a large number of DNA molecules in parallel. In order to generate this large number of DNA molecules, a copying method called PCR amplification is required. In addition to adding time and complexity to the sample preparation process, the amplification process can introduce errors known as amplification bias. The effect of this bias is that the resulting copies are not uniformly representative of the original template DNA.

In most second generation tools, tens of thousands of identical strands are anchored to a given location to be read in a process consisting of successive flushing and scanning operations. The flush and scan sequencing process involves sequentially flushing in reagents, such as labeled nucleotides, incorporating nucleotides into the DNA strands, stopping the incorporation reaction, washing out the excess reagent, scanning to identify the incorporated base and finally treating that base so that the strand is ready for the next flush and scan cycle. This cycle is repeated until the reaction is no longer viable.

Due to the large number of flushing, scanning and washing cycles required, the time to result for second generation methods is generally long, often taking days. This repetitive process also limits the average readlength produced by most second generation systems under standard sequencing conditions to approximately 35 to 400 bases. The array of DNA anchor locations can have a high density of DNA fragments, leading to extremely high overall throughput and a resultant low cost per identified base when the machine is run at high capacity. However, the disadvantages of second generation sequencing include short readlength, complex sample preparation, the need for amplification, long time to result, the need for many samples to justify machine operation and significant data storage and interpretation requirements.

First and second generation sequencing technologies have led to a number of scientific advances. However, given the inherent limitations of these technologies, researchers still have not been able to unravel the complexity of genomes.

Pacific Biosciences Solution The Third Generation of Sequencing Technology

We have developed a technology platform that enables single molecule, real-time, or SMRT, detection of biological processes. Based on our SMRT technology platform, we have introduced a third generation DNA sequencing system, the PacBio *RS*, that addresses many of the limitations of the first and second generation technologies, by providing longer readlengths, increased flexibility, reduced time to result, simplified sample preparation and elimination of amplification bias. In addition, the PacBio *RS* enables the study of modified bases through its unique feature of detecting the kinetics of base incorporation during DNA synthesis.

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Pacific Biosciences SMRT Technology

Our SMRT technology enables the observation of DNA synthesis as it occurs in real time by harnessing the natural process of DNA replication, which in nature is a highly efficient and accurate process actuated by the DNA polymerase. The DNA polymerase attaches itself to a strand of DNA to be replicated, examines the individual base at the point it is attached, and then determines which of four building blocks, or nucleotides, is required to complement that individual base. After determining which nucleotide is required, the polymerase incorporates that nucleotide into the growing strand that is being produced. After incorporation, the enzyme advances to the next base to be replicated and the process is repeated.

To overcome the challenges inherent in observing the natural activity of the DNA polymerase, an enzyme that is 15 nanometers (nm) in diameter running in real time, we introduced three key innovations:

The SMRT Cell

Phospholinked nucleotides

The PacBio *RS*

The SMRT Cell

One of the fundamental challenges with observing a single DNA polymerase molecule working in real time is the ability to detect the incorporation of a single nucleotide, taken from a large pool of potential nucleotides, during DNA synthesis. To resolve this problem, we utilize our nanoscale innovation, the zero-mode waveguide, or ZMW.

A ZMW is a hole, tens of nanometers in diameter. The small size of the ZMW prevents visible laser light, which has a wavelength of approximately 600nm, from passing entirely through the ZMW. Rather than passing through, the light decays as it enters the ZMW. Therefore, by shining a laser into the ZMW, only the bottom 30nm of the ZMW becomes illuminated. DNA polymerases are anchored to the bottom of the glass surface of the ZMWs using a proprietary technique. Nucleotides, each type labeled with a different colored fluorophore, are then flooded above an array of ZMWs at the required concentration. As no laser light penetrates up through the holes to excite the fluorescent labels, the labeled nucleotides above the ZMWs do not fluoresce. Only when they diffuse into the bottom 30nm of the ZMW do they fluoresce. When the correct nucleotide is detected by the polymerase, it is incorporated into the growing DNA strand in a process that takes milliseconds in contrast to simple diffusion which takes microseconds. This difference in time results in higher signal intensity for incorporated versus unincorporated nucleotides, which creates a high signal-to-noise ratio. Thus, the ZMW has the ability to detect a single incorporation event against the background of fluorescently labeled nucleotides at biologically relevant concentrations. Our DNA sequencing is performed on proprietary SMRT Cells, each having an array of approximately 150,000 ZMWs. Each ZMW is capable of containing a DNA polymerase molecule bound to a single DNA template. Currently, our system can monitor 75,000 ZMWs simultaneously. The system can be set up to monitor the first set of 75,000 ZMWs on a SMRT Cell, then immediately shift to monitoring the second set of 75,000 ZMWs on the same SMRT Cell. As a result, the SMRT Cell enables the potential detection of approximately 150,000 single molecule sequencing reactions. Currently, our immobilization process randomly distributes polymerases into ZMWs across the SMRT Cell, resulting in approximately one-third of the ZMWs being available for use. We plan on introducing an enhancement to our system in 2013 that would enable the system to monitor the 150,000 ZMWs simultaneously.

Phospholinked Nucleotides

Our proprietary phospholinked nucleotides have a fluorescent dye attached to the phosphate chain of the nucleotide rather than to the base. As a natural step in the synthesis process, the phosphate chain is cleaved when the nucleotide is incorporated into the DNA strand. Thus, upon incorporation of a phospholinked nucleotide, the DNA polymerase naturally frees the dye molecule from the nucleotide when it cleaves the phosphate chain. Upon cleaving, the label quickly diffuses away, leaving a completely natural piece of DNA with no evidence of labeling remaining.

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The PacBio RS

The PacBio *RS* is an instrument that conducts, monitors, and analyzes single molecule biochemical reactions in real time. The PacBio *RS* uses a high numerical aperture objective lens and four single-photon sensitive cameras to collect the light pulses emitted by fluorescent reagents allowing the observation of biological processes. An optimized set of algorithms is used to translate the information that is captured by the optics system. Using the recorded information, light pulses are converted into either an A, C, G or T base call with associated quality metrics. Once sequencing is started, the real-time data is delivered to the system s primary analysis pipeline, which outputs base identity and quality values, or QVs. To generate a consensus sequence from the data, an assembly process aligns the different fragments from each ZMW based on common sequences.

SMRT Sequencing Advantages

Sequencing based on our SMRT technology offers the following key benefits:

Single molecule, real-time analysis. The ability to observe single molecules in real time combined with long readlength allows our system to observe structural and cell type variation that present challenges for existing short-read technologies. Unlike many other sequencing platforms, minimal amounts of reagent and sample preparation are required and there are no time-consuming flushing, scanning and washing steps.

Longer readlengths. Our SMRT technology has been demonstrated to produce a distribution of readlengths of 4,500 base pairs on average, with 5% of reads over 12,000 base pairs, which facilitates mapping and assembly. Longer readlengths require the sequencing of fewer overlapping segments, referred to as coverage, to efficiently assemble the underlying genomic structure. Long readlengths are an important factor in enabling a comprehensive view of the genome, as they can reveal multiple types of genetic variation, such as large-scale rearrangements observed in cancer. Long readlengths are also highly enabling for *de novo* assembly of genomes, where reference genomes do not exist or are not used for the assembly.

Faster time to result. With the PacBio *RS*, sample preparation to sequencing results can take less than one day. A typical sequencing run can require as little as 30 to 120 minutes of instrument time, with target polymerase speeds of two to three bases per second, compared to other technologies which can take multiple days to produce results. This fast time to result may have important implications for applications where speed is of critical importance such as infectious disease monitoring and molecular pathology.

Less systematic error. The sample preparation step for SMRT sequencing does not require amplification and therefore the reads are not subject to amplification bias. In addition, the read errors from SMRT sequencing are largely random, and therefore they can be more easily resolved by aligning and comparing multiple overlapping reads. Second generation sequencing technologies generally have more systematic read errors, and are more difficult to resolve because identical errors are more likely to be present in each overlapping read. As a result, we believe that SMRT sequencing can enable a more complete assembly of genomes and higher consensus accuracy with less coverage than other available sequencing technologies.

Ease of use. Our system is designed to be easy to use and adopt because it is compatible with existing lab workflows and informatics infrastructures. Our SMRTbell sample preparation protocol is designed to be simple and fast. The PacBio *RS* is equipped with a touchscreen interface that requires minimal user intervention. The data format has been designed to be compatible with standard informatics systems. We believe that these attributes allow for easy training at customer sites.

Flexibility and granularity. The PacBio *RS* system offers multiple protocols, including standard and circular consensus sequencing, enabling the user to optimize performance based on the needs for a particular project. It can be used with a variety of sample types and can output a range of DNA lengths. The system also has the ability to scale the throughput and cost of sequencing across a range of small and large projects.

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Ability to observe and capture kinetic information. The ability to observe the activity of a DNA polymerase in real time enables the PacBio *RS* to collect, measure and assess the dynamics and timing of nucleotides being added to a growing DNA strand, referred to as kinetics. It is well established in the scientific community that chemical modification of DNA such as the addition of a methyl group, known as methylation, can alter the biological activity of the affected nucleotide. The PacBio *RS* detects changes in kinetics automatically by capturing and recording changes in the duration of, and distances between, each of the fluorescent pulses during a typical sequencing analysis. Integrated software can then translate these kinetic signatures into uniquely characterized modified bases such as 6mA, 4mC and 5mC in bacteria. First and second generation sequencing systems are unable to accurately record this type of kinetic data because the flush and scan sequencing process disrupts the timing of the natural incorporation process.

Our Products

We have entered the market with our first product, the PacBio *RS*, a third generation sequencing instrument that provides real-time information at the single molecule level. The initial application for the system is DNA sequencing, and the architectural design of the system may enable a broader range of applications over time. The instrument is designed for expandable capability to permit performance improvements and new applications to be delivered through chemistry and software enhancements without necessitating changes to the hardware.

Our sequencing system includes the PacBio *RS* instrument platform that uses our proprietary consumables, including our SMRT Cells and reagent kits, providing a complete solution to the customer.

The PacBio RS

The PacBio *RS* is an instrument that conducts, monitors and analyzes biochemical sequencing reactions. The instrument is an integrated unit that includes high performance optics, automated liquid handling, a touchscreen control interface, a computational Blade Center and software. The instrument s high performance optics monitor the thousands of ZMWs in real time. The automated liquid handling system performs reagent mixing and prepares SMRT Cells. The instrument s touchscreen control interface, the *RS* Touch, is the user s primary control center to design and monitor experiments as they occur in real time. The Blade Center is the computational brain of the PacBio *RS,* responsible for processing the sequencing data being produced on the SMRT Cells. The PacBio *RS* has been designed to allow for performance improvements without replacement of the instrument hardware.

Consumables

To run our PacBio *RS*, our customers must purchase our proprietary consumable products. Our consumable products include our proprietary SMRT Cells and reagent kits. One SMRT Cell is consumed per sequencing reaction on the PacBio *RS*. Eight SMRT Cells are individually hermetically sealed and packaged together into a streamlined 8Pac format. This enables a researcher to use one or more SMRT Cells per run.

We offer several reagent kits, each designed to address a specific step in the workflow. The Template Preparation Kit is used to convert DNA into our SMRTbell double-stranded DNA library format and therefore includes typical molecular biology reagents, such as ligase, buffers and exonucleases. The Binding Kit, which includes our modified DNA polymerase, is then used to bind this library to the polymerase in preparation for sequencing. The Sequencing Kit contains the reagents required for on-instrument, real-time sequencing, including the phospholinked nucleotides. Each sample can be sequenced in a single SMRT Cell or across many SMRT Cells depending on the needs of the project. As a result, the price per reaction is dependent on the experiment design.

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Product Enhancements

During 2012, we introduced a number of product enhancements that improved the performance and reliability of our products. In the first quarter of 2012, we launched our C2 product release, which doubled readlengths to approximately 3,000 bases on average, with 5 percent of those reads above 8,000 bases, increased throughput, defined as mappable data per SMRT cell, reduced input sample requirements, and significantly improved system reliability. During the second quarter, we launched new software which provided customers with the ability to detect base modifications using the kinetic information captured by the PacBio RS system. During the third quarter, we introduced the Automated MagBead Station, which simplifies sample preparation, and enables customers to generate more consistent, high-quality data from lower quality starting samples. The MagBead Station can also further reduce the amount of input sample required. Since the beginning of the year, we have introduced product and method improvements that have cut the sample input required to sequence with the PacBio RS system by approximately 90%. During the fourth quarter, we introduced a follow-on software release that included automated tools for detecting and characterizing methylated bases in bacteria, which enables the study of bacterial methylomes on a large scale. We also introduced our XL chemistry and software release in the fourth quarter, which further increased the readlength and throughput capabilities of our system. With this most recent chemistry and software, our customers can now generate readlengths of 4,500 bases on average, with 5 percent of those reads above 12,000 bases. Finally, during the fourth quarter, we made available an early version of new secondary analysis software on our DevNet site, which enables customers to assemble genomes with 99.999% accuracy at 20x coverage using only standard, PacBio long reads.

Market for Our Products

Our customers use our products for sequencing the genomes of a wide range of organisms. With its current throughput capability, the PacBio *RS* is well-suited for sequencing smaller genomes, such as bacteria, and for sequencing targeted regions of larger genomes such as humans and plants. Over the past year, we have increased the throughput of the PacBio *RS* through product enhancements, which we believe will expand the targeted applications for our products. We plan on continuing to increase throughput with future product enhancements.

There are a number of emerging markets for sequencing-based tests, including molecular diagnostics, which represent significant potential opportunities for our products. The development of these markets is subject to variability driven by ongoing changes in the competitive landscape, evolving regulatory requirements, government funding of research and development activities, and macroeconomic conditions. Introductions of new technologies and products, while positive to the overall development of these markets, when evaluated relative to uncertainties surrounding government budgets and economic stress in certain regions of the world, result in greater competition for the limited financial resources available. As we continue to expand into these emerging markets, the development of our business will be impacted by the variability of the factors affecting the growth of these markets.

Pacific Biosciences Strategy

We plan to execute the following strategy:

Contribute to the future of biological analysis by offering differentiated products based on our proprietary SMRT technology. Our SMRT technology provides a window into biological processes that has not previously been available. The combination of our products and underlying SMRT technology s ability to deliver long read lengths, complete assemblies, and short time to result afford the scientific community a new tool to conduct research not possible with first and second generation sequencing instruments.

Focus initially on a small number of sequencing applications in which our SMRT technology provides unique capability. While we believe our third generation sequencing technology will address many of the limitations in current sequencing technologies and enable a wide range of experiments and

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applications, we plan to drive adoption of our technology by focusing initially on applications that our customers have identified as high-value applications for SMRT sequencing. Among the early applications identified by our customers are *de novo* Genome Assembly, Targeted Sequencing and Base Modification Analysis. We plan to develop whole product solutions around these applications, making it easier for customers who are not typically early adopters of new technology to take advantage of SMRT sequencing.

Continually enhance product performance to increase market share. The design of the PacBio *RS* allows for significant performance improvements without replacement of the instrument hardware. Our flexible platform is designed to generate a recurring revenue stream through the sale of proprietary SMRT Cells and reagent kits. Our research and development efforts are focused on product enhancements to reduce DNA sequencing cost and time as well as expand capabilities. During 2012, we introduced our C2 and XL chemistry enhancements, our automated MagBead loader, software analysis tools for enhanced assembly, and secondary analysis tools for detecting and characterizing base modifications. Compared with our initial product launch in 2011, these product enhancements have enabled an approximate 4x improvement in readlength, an approximate 5x improvement in mappable data per SMRT Cell, and reduced input sample required by 90%. In addition, we have demonstrated the capability of achieving consensus accuracy of Q50 (99.999%) with 20x fold coverage, and automated the detection and characterization of base modifications in bacteria. We also significantly improved the reliability of our products so that the instrument uptime of the PacBio *RS* is comparable to that of some of the more mature life science tools. We plan to continue introducing enhancements to our products over time.

Leverage platform to develop and launch additional applications. We plan to leverage our SMRT technology platform to develop new applications such as sequencing larger and more complex genomes and expanding the ability to detect and characterize base modifications. In the long term, our SMRT technology may also be adapted for RNA transcription monitoring, direct RNA sequencing, protein translation and ligand binding. We believe these applications can create substantial new markets for our technology.

Create a global community of users to enhance informatics capabilities and drive adoption of our products. We have worked closely with members of the informatics community to develop and define standards for working with single molecule, real-time sequence data. We maintain the PacBio DevNet site, a website on which we make available various software tools and information about our SMRT sequencing technology to support academic informatics developers, life scientists and independent software vendors interested in creating tools to work with our third generation sequencing data. This gives the user flexibility to perform further analysis of the sequencing data through third-party software or share data with collaborators. To maximize the flexibility and functionality for all users, all of our secondary analysis algorithms are made available under an open source license. We have also launched the PacBio SampleNet site, a website on which we make available various tools for simplifying and enhancing sample preparation protocols.

Marketing, Sales, Service and Support

We market our products through a direct sales force in North America and Europe and primarily through distributors in Asia. Our sales strategy involves the use of a combination of sales managers, sales representatives and field application specialists. The role of our sales managers and sales representatives is to educate customers on the advantages of SMRT technology and the applications that our technology makes possible. The role of our field application specialists is to provide on-site training and scientific technical support to prospective and existing customers. Our field application specialists are technical experts, often with advanced degrees, and generally have extensive experience in academic research and core sequencing lab experience.

Service for our instruments is performed by our field service engineers. Our field service engineers are trained by experienced personnel to test, trouble-shoot, and service instruments installed at customer sites.

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In addition, we maintain an applications lab team in Menlo Park, California composed of scientific experts who can transfer knowledge from the research and development team to the field application specialists. The applications lab team also runs foundational scientific collaborations and proof of principle studies, which help demonstrate the value of our product offering to prospective customers.

Customers

Our customers include genome centers, clinical, government and academic institutions, genomics service providers and agricultural companies. In general, our customers will isolate, prepare and analyze genetic samples using the PacBio *RS* in their own research labs to address their specific applications and scientific questions. For example, customers in academic research institutions may have bacteria, animal, or human DNA samples isolated from various sources while agricultural biology, or AgBio, companies may have DNA samples isolated from different strains of rice, corn or other crops. For each of the years ended December 31, 2012, 2011 and 2010, no single end customer accounted for more than 10% of our total revenue.

We believe that the majority of our current customers are early adopters of sequencing technology. By focusing our efforts on high-value applications, we plan to drive the adoption of our products across a broader customer base and into large-scale projects. In general, the broader adoption of new technologies by mainstream customers can take a number of years, and there can be no assurance that we will be successful in gaining broader adoption.

We currently sell our products to a number of customers outside the United States, including customers in other areas of North America, Europe, and Asia. Revenue from customers outside the United States totaled $14.6 million, or 56% of our total revenue, during fiscal 2012, compared to $6.3 million, or 19%, in fiscal 2011, and there were no sales to customers outside the United States in fiscal 2010 (see also Note 12. Segment and Geographic Information in the Notes to Consolidated Financial Statements of this Form 10-K). The Company s assets are primarily located in the United States of America. Please see the risk factor titled Doing business internationally creates operational and financial risks for our business in Part I, Item 1A in this Form 10-K for a discussion of the risks we face with respect to our foreign operations.

Our business is subject to seasonal fluctuations. Although we have a limited history of selling our products, similar to other companies in our industry, we have experienced a reduction in sales during our fiscal third quarter, which are the three months ending September 30 each year, when many customers, particularly those in Europe, take extended vacations.

Backlog

As of December 31, 2012, our system revenue backlog was approximately $2.9 million, compared to $11.0 million at December 31, 2011. We define backlog as purchase orders or signed contracts from our customers which we believe are firm and for which we have not yet recognized revenue. We expect to convert this backlog to revenue during the first half of 2013 subject to customers who may otherwise seek to cancel or delay their orders even if we are prepared to fulfill them.

Manufacturing

Our principal manufacturing facilities are located at our headquarters in Menlo Park, California. We currently perform most of the manufacture of our instruments in-house, while outsourcing certain sub-assemblies to third-party manufacturers. With respect to the manufacture of SMRT Cells, we subcontract wafer fabrication and processing to semiconductor processing facilities, but conduct critical surface treatment processes internally. In addition, we currently manufacture critical reagents in-house, including our phospholinked nucleotides and our DNA polymerase.

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We purchase both custom and off-the-shelf components from a large number of suppliers and subject them to significant quality specifications. We periodically conduct quality audits of suppliers and have established a supplier certification program. We purchase components through purchase orders. Some of the components required in our products are currently either sole sourced or single sourced.

Research and Development

Our SMRT technology requires the blending of a number of unique disciplines, namely nanofabrication, physics, photonics, optics, molecular biology, engineering, signal processing, high performance computing, and bioinformatics. Our research and development team is a blend of these disciplines creating a single, cross-functional operational unit. We have also established productive working relationships with technology industry leaders, as well as leading academic centers, to augment and complement our internal research and development efforts. Research and development expense incurred was $47.6 million, $76.1 million and $111.8 million during 2012, 2011 and 2010, respectively.

We plan to continue investment in research and development to enhance the performance and expand the application of our current products, and introduce additional products based on our SMRT technology. Our goals include further improvements in sequencing readlength and mappable data per SMRT Cell, chemistry and software enhancements for expanding base modification analysis, and enhancements in sample preparation and bioinformatics tools that take advantage of the capabilities of our products. In addition, our engineering teams will continue their focus on increasing instrument component and system reliability, reducing costs, and implementing additional system flexibility and versatility through the enhancement of existing products and development of new products.

Intellectual Property

Developing and maintaining a strong intellectual property position is an important element of our business. We have sought patent protection for our SMRT technology, and may seek patent protection for improvements and ancillary technology conceived in developing our SMRT technology if we believe such protection will give us an advantage over competitors or potential competitors.

Our current patent portfolio, including patents exclusively licensed to us, is directed to various technologies, including SMRT nucleic acid sequencing and other methods for analyzing biological samples, ZMW arrays, surface treatments for such ZMW arrays, phospholinked nucleotides and other reagents for use in nucleic acid sequencing, optical components and systems, processes for identifying nucleotides within nucleic acid sequences and processes for analysis and comparison of nucleic acid sequence data. Some of the patents and applications that we own, as well as some of the patents and applications that we have licensed from other parties, are subject to U.S. government march-in rights, whereby the U.S. government may disregard our exclusive patent rights on its own behalf or on behalf of third parties by imposing licenses in certain circumstances, such as if we fail to achieve practical application of the U.S. government funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, U.S. government funded inventions must be reported to the government and U.S. government funding must be disclosed in any resulting patent applications.

As of December 31, 2012, we own or hold exclusive licenses to 103 issued U.S. patents, 108 pending U.S. patent applications, 58 granted foreign patents and 112 pending foreign patent applications, including foreign counterparts of U.S. patent and patent applications. The full term of the issued U.S. patents will expire between 2016 and 2031. We also have exclusive and non-exclusive patent licenses with various third parties to supplement our own large and robust patent portfolio.

Of these patents and patent applications, 22 issued U.S. patents, three pending U.S. patent applications, 19 granted foreign patent and four pending foreign patent applications are licensed to us by the Cornell Research

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Foundation, which manages technology transfers on behalf of Cornell University, collectively referred to as Cornell. These patents and patent applications are directed to the core SMRT sequencing methods and systems and other analysis methods, and to ZMW arrays used in our current and planned products. The license agreement provides us with the exclusive right to make, use, sell, offer for sale, lease, import, export or otherwise dispose of products covered by the licensed patents in all fields of use. In exchange, we are obligated to make certain royalty payments to Cornell, including a minimum annual royalty payment, and meet certain reporting and other requirements to Cornell. We are also obligated to reimburse Cornell for the costs of prosecuting the patents and patent applications that are subject to the license. The research leading to the licensed technology was funded by the U.S. government and therefore our license from Cornell is subject to U.S. government march-in rights. Cornell may terminate its agreement with us if we are in default of our payment or reporting obligations, are in material breach of the agreement, or fail to fulfill our diligence obligations with respect to commercializing products using the licensed technology.

We have also entered into a license agreement with Indiana University Research and Technology Corporation, or IURTC, for U.S. Patent No. 6,399,335, which relates to nucleoside triphosphates that include a labeling group attached through the terminal phosphate group in the triphosphate chain. Under the terms of this license agreement, we have exclusive rights to make, have made, sell, offer to sell, have sold, use, import and have imported, products that practice the invention claimed in the patent in certain sequencing-related fields. In exchange, we are obligated to make certain royalty and milestone payments to IURTC, and to meet certain reporting requirements to IURTC. We are also obligated to reimburse IURTC for the costs of prosecuting the patents and patent applications that are subject to the license. The research leading to the licensed technology was funded by the U.S. government and therefore our license from IURTC is subject to U.S. government march-in rights. IURTC may terminate its agreement with us if we are in default of our payment or record keeping obligations, are in material breach of the agreement, or fail to fulfill our diligence obligations with respect to commercializing products using the licensed technology.

In addition, we have entered into a license agreement with Stanford University, or Stanford, for U.S. Patent No. 7,297,532, referred to as the 532 patent, which relates to immobilized ribosomes for use in analysis of ribosomal activity. Under the terms of this license agreement, we have exclusive rights to make, have made, use, import, offer to sell and sell products that would practice the invention claimed in the patent in certain fields of use until June 8, 2018, after which the license will become non-exclusive until the 532 patent expires. In exchange, we are obligated to make certain royalty and license maintenance payments to Stanford, and to meet certain reporting and other obligations to Stanford. We are also obligated to reimburse Stanford for all patenting expenses associated with the 532 patent, including maintenance fees and costs associated with any interference or reexamination matters. The research leading to the 532 patent was funded by the U.S. government and therefore our license from Stanford is subject to U.S. government march-in rights. Stanford may terminate its agreement with us if we are in default of our payment or reporting obligations, are in breach of any provision of the agreement, or fail to fulfill our diligence obligations with respect to commercializing products relating to the 532 patent.

We have also entered into a license agreement with GE Healthcare Bio-Sciences Corp, or GE Healthcare, for several U.S. and foreign patents and pending patent applications related to labeled nucleoside polyphosphate compounds. Under the terms of the license, we have the non-exclusive right to make, have made, import, use, distribute, offer to sell and sell products that practice the inventions claimed in the patents. In exchange, we are obligated to make certain royalty and other payments to GE Healthcare. GE Healthcare may terminate its agreement with us if, among other things, we are in breach of the agreement.

In June 2010, we entered into a collaboration agreement with Gen-Probe Incorporated, or Gen-Probe, regarding the research and development of instruments integrating our SMRT technologies and Gen-Probe s sample preparation technologies for use in clinical diagnostics. The agreement expired by its own terms on December 15, 2012. Certain provisions of the agreement survive its expiration, including those relating to the disposition of any intellectual property developed or created in the course of the collaboration and those providing each party with

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preferred access to certain products of the other party when commercially available. However, we do not anticipate that these surviving provisions will have a material impact on our business or intellectual property position.

Where patent protection is difficult to obtain or difficult to enforce for a particular technological development or the technological development derives greater value from being maintained as confidential information, we seek to protect such information as a trade secret.

Competition

Given the market opportunity, there are a significant number of competing companies offering DNA sequencing equipment or consumables. These include Illumina Inc., Life Technologies Corporation and Roche Applied Science. These companies currently have greater financial, technical, research and/or other resources than we do. They also have larger and more established manufacturing capabilities and marketing, sales and support functions. We expect the competition to intensify within this market as there are also several companies in the process of developing new technologies, products and services, such as Oxford Nanopore Technologies Ltd.

In order for us to successfully compete against these companies, we will need to demonstrate that our products deliver superior performance and value as a result of our key differentiators, including single molecule, real-time resolution, long readlength, fast time to result and flexibility, as well as the breadth and depth of current and future applications.

Employees

As of December 31, 2012, we had 342 full-time employees. Of these employees, 125 were in research and development, 67 were in operations, 104 were in marketing, sales, service and support, and 46 were in general and administration. With the exception of our field-based sales and service teams, substantially all of our employees are located at our headquarters in Menlo Park, California. None of our employees are represented by labor unions or are covered by a collective bargaining agreement with respect to their employment. We have not experienced any work stoppages, and we consider our relationship with our employees to be good.

Available Information

Our web site is located at www.pacificbiosciences.com. The information posted on our web site is not incorporated into this Annual Report on Form 10-K. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge through the Investors section of our web site as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC.

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ITEM 1A. RISK FACTORS

You should consider carefully the risks and uncertainties described below, together with all of the other information in this Annual Report on Form 10-K, which could materially affect our business, financial condition, results of operations and prospects. The risks described below are not the only risks facing us. Risks and uncertainties not currently known to us or that we currently deem to be immaterial also may materially affect our business, financial condition, results of operations and prospects.

Risks Related to Our Business

We are an early stage commercial company.

During 2011 we launched our first commercial product and as such, we have limited historical financial data upon which to base our projected revenue, planned operating expense or upon which to evaluate us and our commercial prospects. Based on our limited experience in developing and marketing new products, we may not be able to effectively:

drive adoption of our products;

attract and retain customers for our products;

provide appropriate levels of customer training and support for our products;

implement an effective marketing strategy to promote awareness of our products;

focus our research and development efforts in areas that generate returns on these efforts;

comply with evolving regulatory requirements applicable to our products;

anticipate and adapt to changes in our market;

maintain and develop strategic relationships with vendors and manufacturers to acquire necessary materials for the production of our products;

scale our manufacturing activities to meet potential demand at a reasonable cost;

avoid infringement and misappropriation of third-party intellectual property;

obtain licenses on commercially reasonable terms to third-party intellectual property;

obtain valid and enforceable patents that give us a competitive advantage;

protect our proprietary technology;

protect our products from any equipment or software-related system failures; and

attract, retain and motivate qualified personnel.

In addition, a high percentage of our expenses is and will continue to be fixed. Accordingly, if we do not generate revenue as and when anticipated, our losses may be greater than expected and our operating results will suffer.

We have incurred losses to date, and we expect to continue to incur significant losses as we develop our business and may never achieve profitability.

We have incurred net losses since inception and we cannot be certain if or when we will produce sufficient revenue from our operations to support our costs. Even if profitability is achieved, we may not be able to sustain profitability. We expect to incur substantial losses and negative cash flow for the foreseeable future.

If our products fail to achieve and sustain sufficient market acceptance, we will not generate expected revenue and our business may not succeed.

Although we have now commercialized the PacBio *RS* and started recognizing revenue from our products, we cannot be sure that they will gain acceptance in the marketplace at levels sufficient to support our costs. Our

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success depends, in part, on our ability to expand the market for genetic analysis to include new applications that are not practical with other current technologies. To accomplish this, we must successfully commercialize, and continue development of, our SMRT technology for use in a variety of life science applications. There can be no assurance that we will be successful in securing additional customers for our products, in particular, our first product which is focused on DNA sequencing. Furthermore, we cannot guarantee that the design of our products, including the initial and subsequent specifications and any enhancements or improvements to those specifications, will be satisfactory to potential customers in the markets we seek to reach. These markets are dynamic, and there can be no assurance that they will develop as quickly as we expect or that they will reach their full potential. As a result, we may be required to refocus our marketing efforts, and we may have to make changes to the specifications of our products to enhance our ability to enter particular markets more quickly. Even if we are able to implement our technology successfully, we may fail to achieve or sustain market acceptance of our products by academic and government research laboratories and pharmaceutical, biotechnology and agriculture companies, among others, across the full range of our intended life science applications. If the market for our products grows more slowly than anticipated, if competitors develop better or more cost-effective products or if we are unable to develop a significant customer base, our future sales and revenue would be materially harmed and our business may not succeed. For example, in September 2011, we implemented a reduction in our workforce due in part to our infrastructure being staffed to support a faster adoption rate for our products. If the adoption rate for our products continues to be slow or does not grow, our business may be adversely affected.

Our products are highly complex, with significant support requirements.

In light of the highly complex technology involved in our products, there can be no assurance that we will be able to successfully provide adequate support for our products. Our customers have experienced reliability issues with our PacBio *RS* instruments that we believe are consistent with the introduction of similar new, highly complex products. While we believe that our customers, particularly those who were early adopters of other new DNA sequencing technologies in the past, understand that such issues can be common with novel, highly complex products like the PacBio *RS*, if our products continue to have reliability or other quality issues or require unexpected levels of support, the market acceptance and utilization of our products may not grow to levels sufficient to support our costs and our reputation and business could be harmed. We deliver our PacBio *RS* instruments with one year of service included in the purchase price with an option to purchase one or more additional years of service. Since launching our PacBio *RS* instrument during 2011, we have incurred significant service and support costs. If service and support costs increase, our business and operations may be adversely affected.

We may not be able to produce instruments that consistently achieve the specifications and quality that our customers expect.

We have established performance standards for our commercial products that we may not consistently achieve using our current design and manufacturing processes. If we do not consistently achieve the specifications and quality that our customers expect, customer demand may be negatively affected. Customers may refuse to accept our products in a timely manner or at all, which would adversely affect our revenue. Any inability to meet performance standards may materially impact the commercial viability of our products and harm our business.

We may be unable to consistently manufacture our consumable kits, including SMRT Cells, to the specifications required by our customers or in quantities necessary to meet demand at an acceptable cost.