PACIFIC BIOSCIENCES OF CALIFORNIA, INC.
Form 10-K
March 12, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

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

For the fiscal year ended December 31, 2014

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 (Address of principal executive offices) 94025 (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

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

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 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 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.

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
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

Aggregate market value of registrant's common stock held by non-affiliates of the registrant on June 30, 2014, based upon the closing price of Common Stock on such date as reported by NASDAQ Global Select Market, was approximately $315,556,000. 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 3, 2015: 74,516,357

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant's definitive Proxy Statement relating to its 2015 Annual Meeting of Stockholders to be held on May 20, 2015 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.

Pacific Biosciences of California, Inc.

Annual Report on Form 10-K

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 the beliefs and assumptions of the management of Pacific Biosciences of California, Inc. (the “Company,” “we,” “us,” or “our,”) 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, our statements regarding the sequencing advantages of SMRT® technology, current and future products, market opportunities, strategic plans, expectations regarding the conversion of backlog to revenue, expectations regarding our collaboration agreements including expected revenue and related milestone payments, manufacturing plans, research and development plans, product development, competition, expectations regarding unrecognized income tax benefits, expectations regarding the impact of an increase in market rates on the value of our financial instruments, the sufficiency of cash, cash equivalents and investments to fund 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,” “estimates,” “expects,” “intends,” “may,” “pla “potential,” “predicts,” “projects,” “seeks,” “should,” “target,” “will,” “would” or similar expressions and the negatives of thos 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 forward-looking statements. Also, forward-looking statements represent management’s beliefs and assumptions as of the date of this report. We assume no obligation to update 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.

ITEM 1. BUSINESS

Overview

We design, develop and manufacture the PacBio® RS II Sequencing System to help scientists resolve genetically complex problems. Based on our novel Single Molecule, Real-Time (SMRT®) technology, our products enable: de novo genome assembly to finish genomes in order to more fully identify, annotate and decipher genomic structures; full-length transcript analysis to improve annotations in reference genomes, characterize alternatively spliced isoforms and find novel genes; targeted sequencing to more comprehensively characterize genetic variations; and DNA base modification identification to help characterize epigenetic regulation and DNA damage. Our technology combines very high consensus accuracy and long read lengths with the ability to detect real-time kinetic information.

Our customers and our scientific collaborators have published a number of peer-reviewed articles in journals including Nature, Science, Cell, PNAS and The New England Journal of Medicine highlighting the power and applications of the SMRT platform in projects such as finishing genomes, structural variation discovery, isoform transcriptome characterization, rare mutation discovery and the identification of chemical modifications of DNA related to virulence and pathogenicity. Our research and development efforts are focused on seeking to further improve our existing products, including continuing chemistry and sample preparation improvements to increase throughput and expand our supported applications, and developing new products. By providing access to genetic information that was previously inaccessible, Pacific Biosciences enables scientists to confidently increase their understanding of biological 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.

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 modified bases, such as 5-hydroxymethylcytosine, or hmC, 8-oxoguanine and many others, play important physiological roles. For example, in bacteria, N6-methyladenine has been shown to play an important role in pathogenicity.

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 II 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 read length. 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 read length, the easier it is to assemble the genome.

First Generation Sequencing

First generation sequencing, often 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 read length that is approximately 700 bases on average, but may be extended to 1,000 bases. These are relatively long read lengths 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, also commonly referred to as “next generation sequencing”, 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 resulting copies are not uniformly representative of the original template DNA. In cases where the original template DNA contains regions of relatively high G-C content or relatively high A-T content, the PCR amplification process tends to under-represent these regions. As a result, these regions, which may contain entire genes, can be completely missed in the process.

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 read length 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 read length, variation in sequence equality with regard to representation bias and accuracy, 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 — Single Molecule, Real-Time Technology

We have developed our SMRT technology platform, which enables single molecule, real-time detection of biological processes. Based on our novel SMRT technology, we introduced the PacBio RS II System to address many of the limitations of the first and second generation technologies, by providing longer read lengths, elimination of amplification bias, increased flexibility, and reduced time to result. In addition, the PacBio RS II System, which includes the PacBio RS II instrument, consumables and software, enables the study of modified bases through its unique feature of detecting the kinetics of base incorporation during DNA synthesis.

Pacific Biosciences' SMRT Technology

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 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 real-time observation of the natural activity of the DNA polymerase, an enzyme 15 nanometers (nm) in diameter, we offer three key innovations:

•The SMRT Cell

•Phospholinked nucleotides

•The PacBio RS II instrument

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 causes the intensity of visible laser light, which has a wavelength of approximately 600nm, to decay exponentially in the ZMW. Therefore, shining a laser up into the ZMW selectively illuminates only the bottom portion of the ZMW. 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. When the labeled nucleotides diffuse into the bottom portion of the ZMWs, which contain the anchored DNA polymerases, their fluorescence can be monitored. 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 immobilization process randomly distributes polymerases into ZMWs across the SMRT Cell, resulting in approximately one-third of the ZMWs having a single template.

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 natural piece of DNA without evidence of labeling.

The PacBio RS II Instrument

The PacBio RS II instrument conducts, monitors, and analyzes single molecule biochemical reactions in real time. The instrument 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 assembles the different fragments from each ZMW based on common sequences.

SMRT Sequencing Advantages

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

· Longer read lengths

SMRT technology has been demonstrated to produce read lengths that are significantly longer than those of first and second generation sequencing technologies. Long read lengths are necessary to span repetitive regions to efficiently assemble genomes. Long read lengths are an important factor in enabling a comprehensive view of the genome, as they can reveal multiple types of genetic variation such as structural variants.

· High consensus accuracy

Users of SMRT technology can achieve very high consensus accuracy due to the attributes of SMRT sequencing, including long read lengths, lack of amplification bias, and lower systematic bias. Users of second generation sequencing technologies often cannot achieve comparable results due to their shorter read lengths and systematic bias.

· More uniformity and less systematic error

The sample preparation step for SMRT sequencing does not require amplification; when amplification is not used during sample preparation, the reads are not subject to amplification bias. Importantly, this allows for uniform identification of all bases present in a DNA sample and uniform coverage. As a result, SMRT sequencing can detect and identify regions and entire genes that may be missed by second generation sequencing technologies.

· Ability to observe and capture kinetic information

The ability to observe the activity of a DNA polymerase in real time enables the PacBio RS II 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 II 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. Other sequencing systems which rely on a sample preparation amplification step or limited by signal resolution are unable to directly measure this type of kinetic data.

· Flexibility

The PacBio RS II System has the ability to scale the throughput and cost of sequencing across a range of small to large projects. It can be used with a variety of sample types and can output a range of DNA lengths.

Our Products

We entered the market with our first commercial product, the PacBio RS and proprietary consumables, during the second quarter of 2011 and launched the higher performance PacBio RS II during the second quarter of 2013. The PacBio RS II System provides access to a wide range of applications. The system 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 PacBio RS II instrument's hardware.

The PacBio RS II Instrument

The PacBio RS II instrument 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 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. The Blade Center is the computational brain of the PacBio RS II instrument, responsible for processing

the sequencing data produced on the SMRT Cells. The PacBio RS II instrument has been designed to allow for performance improvements.

Consumables

Customers must purchase proprietary consumable products to run the PacBio RS II. Our consumable products include our proprietary SMRT Cells and reagent kits. One SMRT Cell is consumed per sequencing reaction on the PacBio RS II. Eight SMRT Cells are individually hermetically sealed and packaged together into a streamlined 8Pac format enabling researchers to choose the number of SMRT Cells they need per experiment.

We offer several reagent kits, each designed to address a specific step in the workflow. A template preparation kit is used to convert DNA into SMRTbell™ double-stranded DNA library formats and therefore includes typical molecular biology reagents, such as ligase, buffers and exonucleases. Our binding kits include our modified DNA polymerase, and are used to bind SMRTbell libraries to the polymerase in preparation for sequencing. Our sequencing kits contains reagents required for on-instrument, real-time sequencing, including the phospholinked nucleotides.

Product Enhancements

During 2014, we continued to significantly enhance the performance of the PacBio RS II System through a combination of sample preparation protocol enhancements, software releases, and the release of a new sequencing reagent chemistry. By providing an increasing number of longer reads per instrument run, the new chemistry enables users to assemble more genomes to a high quality. We have continually improved our software to expand the number of supported applications such as large genome assembly, sequencing of transcript isoforms produced from genes, and phasing of haplotypes in large amplicons. During 2015 we plan to further

improve our existing products, including chemistry and sample preparation improvements to increase throughput and expand our supported applications, and to develop new products.

Market for Our Products

Our customers use our products for sequencing genomes and transcriptomes across a wide range of organisms. Initially customers in research, government and commercial markets used the PacBio RS II to generate more complete assemblies of small and medium size genomes, such as bacteria and fungi, and for sequencing targeted regions of larger genomes such as humans and plants. As throughput and read lengths have increased, the complexity and size of genomes being resolved with SMRT sequencing has grown. Scientists now use SMRT sequencing to generate genome assemblies of humans, plants & animals, characterize transcriptomes through full-length isoform sequencing, and phase complex genomic regions like full-length HLA genes. We plan to continue increasing throughput and read lengths with future product enhancements, and to seek increased sales of our products in research and commercial markets such as human biomedical research, agriculture & biotechnology, microbiology & infectious disease, and immunogenomics.

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, may 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:

- Offer 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, high consensus accuracy, low bias, and kinetic information afford the scientific community a new tool to conduct research not possible with first and second generation sequencing instruments.

- Enhance product performance and introduce new products to increase market share.

The design of the PacBio RS II allows for significant performance improvements. Our flexible platform is designed to generate a recurring revenue stream through the sale of proprietary SMRT Cells and reagent kits. We plan to introduce additional product enhancements to further reduce DNA sequencing project cost and time to result while expanding application solutions. During 2014, we introduced a new sequencing chemistry, a variety of sample preparation improvements, and made significant enhancements to our software analysis toolkit. In addition, the software analysis tools have improved the ease of use of our products and have enabled our customers to take greater advantage of their SMRT sequencing data. We plan to continue introducing enhancements to our products over time and to develop new products.

· Leverage SMRT technology and community engagement to expand application capabilities and penetrate new markets.

We plan to leverage our customers' successes with our SMRT technology platform to expand its capabilities in applications our customers have identified as high-value because SMRT sequencing offers differentiated capabilities. Early applications identified by our customers include: de novo genome assembly, targeted sequencing of complex regions, isoform characterization, and epigenetic 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.

In 2013, we entered into a collaboration agreement with Roche to jointly develop products based on our SMRT technology for the human in vitro diagnostics market. In the long term, we believe that 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, develop sample preparation solutions, and drive adoption of our products in new application and market areas.

We work closely with our customers and collaborators to develop new applications and demonstrate SMRT sequencing capabilities on scientifically relevant projects. We partner 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 SMRT 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 also maintain the PacBio SampleNet site, a website on which we make available various methods developed internally and externally 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 personnel and field application scientists. The role of our sales personnel is to educate customers on the advantages of SMRT technology and the applications that our technology makes possible. The role of our field application scientists is to provide on-site training and scientific technical support to prospective and existing customers. Our field application scientists 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 field service engineers. These field service engineers are trained by experienced personnel to test, trouble-shoot, and service instruments installed at customer sites.

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 scientists. 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 research institutions, commercial laboratories, genome centers, clinical, government and academic institutions, genomics service providers, pharmaceutical companies and agricultural companies. In general, our customers will isolate, prepare and analyze genetic samples using the PacBio RS II System 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 companies may have DNA samples isolated from different strains of rice, corn or other crops. For year ended December 31, 2014, contractual revenue from Roche accounted for more than 10% of our total revenue. For each of the years ended December 31, 2013 and 2012, 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, and developing whole product solutions around these applications, we seek to drive the adoption of our products across a broader customer base and into numerous large-scale projects. In general, the broader adoption of new technologies by mainstream customers can take a number of years.

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 $26.2 million, or 43% of our total revenue, during fiscal 2014, compared to $14.6 million, or 52% of our total revenue, during fiscal 2013, compared to $14.6 million, or 56%, in fiscal 2012.

Backlog

As of December 31, 2014, our instrument backlog was approximately $8.4 million, compared to $7.4 million at December 31, 2013. 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 2015 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 some of the manufacturing and all of the final integration of our instruments in-house, while outsourcing most 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.

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 most critical 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 $48.2 million, $45.2 million and $47.6 million during 2014, 2013 and 2012, 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 read length 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 be advantageous.

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, 2014, we own or hold exclusive licenses to 163 issued U.S. patents, 108 pending U.S. patent applications, 66 granted foreign patents and 99 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 2033. We also have 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, one pending U.S. patent application, 14 granted foreign patents and one pending foreign patent application are licensed to us by the Cornell Research Foundation, which manages technology transfers on behalf of Cornell University, collectively referred to as Cornell. 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. 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.

In September 2013, we entered into a Development, Commercialization and License Agreement (the “Roche Agreement”) with Roche, pursuant to which we: (i) will develop diagnostic products for clinical use including sequencing systems and consumables based on our proprietary SMRT technology; (ii) granted to Roche an exclusive right to commercialize, and an exclusive license to sell, the developed diagnostic products for clinical use; and (iii)

will manufacture and supply certain products intended for clinical use as the exclusive supplier to Roche. We received a non-refundable up-front payment of $35.0 million in 2013 and a milestone payment of $10.0 million in 2014 pursuant to the Roche Agreement. Under the terms of the Roche Agreement, we may receive up to an additional $30.0 million based on the achievement of additional development milestones in future periods. The Roche Agreement has an initial term of thirteen years and provisions allowing Roche five-year renewals.

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. and Thermo Fisher Scientific Inc. 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. Increased competition may result in pricing pressures, which could harm our sales, profitability or market share.

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 read length, fast time to result and flexibility, as well as the breadth and depth of current and future products and applications.