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**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**  
Washington, DC 20549

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**FORM 8-K**

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**CURRENT REPORT**

**Pursuant to Section 13 or 15(d) of  
The Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported)**  
February 3, 2015

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**Pacific Biosciences of California, Inc.**

(Exact name of registrant as specified in its charter)

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**Delaware**  
(State or other jurisdiction  
of incorporation)

**001-34899**  
(Commission  
File Number)

**16-1590339**  
(IRS Employer  
Identification No.)

**1380 Willow Road**  
**Menlo Park, California 94025**  
(Address of principal executive offices, including zip code)

**(650) 521-8000**  
(Registrant's telephone number, including area code)

(Former name or former address, if changed since last report)

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Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
  - Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
  - Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
  - Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))
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#### **ITEM 1.01. ENTRY INTO A MATERIAL DEFINITIVE AGREEMENT**

On February 3, 2015, Pacific Biosciences of California, Inc. (the “Company”) entered into Amendment No. 2 (the “Amendment”) to Controlled Equity Offering<sup>SM</sup> Sales Agreement, dated October 5, 2012 as amended on November 8, 2013 (as amended by the Amendment, the “Agreement”), with Cantor Fitzgerald & Co., as sales agent (“Cantor”), pursuant to which the Company may offer and sell, from time to time, through Cantor, shares of the Company’s common stock, par value \$0.001 per share (the “Shares”); provided, however, that in no event shall the Company issue or sell through Cantor such number or dollar amount of Shares that would (a) exceed the number or dollar amount of shares of Common Stock registered on an effective Registration Statement on Form S-3 pursuant to which the offering is being made, (b) exceed the number of authorized but unissued shares of the Company’s common stock, (c) exceed the number or dollar amount of shares of the Company’s common stock permitted to be sold under a Registration Statement on Form S-3 (including General Instruction I.B.6 thereof, if applicable) or (d) exceed the number or dollar amount of shares of the Company’s common stock for which the Company has filed a prospectus supplement to register the Shares (the lesser of (a), (b), (c) and (d), the “Maximum Amount”). The Maximum Amount of Shares is currently up to an aggregate offering price of \$30.0 million. Such aggregate value of Shares is in addition to the shares sold under the original Agreement with Cantor dated October 5, 2012 and Amendment No. 1 to the Agreement, dated November 8, 2013. The Company intends to use the proceeds of this offering for general corporate purposes, including capital expenditures and working capital.

Under the Agreement, Cantor may sell the Shares by methods deemed to be an “at-the-market” offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended (the “Securities Act”), including sales made directly on The NASDAQ Global Select Market, on any other existing trading market for the Shares or to or through a market maker. In addition, under the Agreement, Cantor may sell the Shares by any other method permitted by law, including in privately negotiated transactions. Subject to the terms and conditions of the Agreement, Cantor will use commercially reasonable efforts, consistent with its normal trading and sales practices and applicable state and federal law, rules and regulations and the rules of The NASDAQ Global Select Market, to sell the Shares from time to time, based upon the Company’s instructions (including any price, time or size limits or other customary parameters or conditions the Company may impose).

The Company is not obligated to make any sales of the Shares under the Agreement. The offering of Shares pursuant to the Agreement will terminate upon the earlier of (a) the sale of all of the Shares subject to the Agreement or (b) the termination of the Agreement by Cantor or the Company.

The Company will pay Cantor a commission of 3.0% of the gross sales price per share sold and has agreed to provide Cantor with customary indemnification and contribution rights.

The Amendment is filed as Exhibit 10.1 to this Current Report on Form 8-K. The description of the Amendment does not purport to be complete and is qualified in its entirety by reference to the Amendment filed herewith as an exhibit to this Current Report on Form 8-K.

The Shares will be issued pursuant to the Company’s previously filed and effective Registration Statement on Form S-3 (File No. 333-199891), the base prospectus, dated November 21, 2014, filed as part of such Registration Statement, and the prospectus supplement, dated February 3, 2015, filed by the Company with the Securities and Exchange Commission.

This Current Report on Form 8-K shall not constitute an offer to sell or the solicitation of an offer to buy nor shall there be any sale of the Shares in any state in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state.

#### **ITEM 8.01. OTHER EVENTS**

On February 3, 2015, the Company announced its intention to issue and sell up to \$30,000,000 of shares of its common stock, par value \$0.001 per share, from time to time, through an “at-the-market” equity offering under which Cantor will act as sales agent.

The Company’s unaudited Consolidated Balance Sheets, Consolidated Statements of Operations and Comprehensive Loss and Consolidated Statements of Cash Flows are included as Exhibits 99.1 hereto and are incorporated herein by reference.

The Company has updated its disclosure regarding its Management’s Discussion and Analysis of Financial Condition and Results of Operations, Business and Risk Factors. The revised disclosure is filed herewith as Exhibit 99.2 and incorporated by reference.

The information set forth in this Item 8.01, as well as Exhibit 99.1 and 99.2 referenced therein, shall be deemed “filed” for purposes of the Securities Exchange Act of 1934, as amended, and shall be incorporated by reference into the Company’s filings under the Securities Act of 1933, as amended.

#### **ITEM 9.01. FINANCIAL STATEMENTS AND EXHIBITS.**

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(d) Exhibits.

- 5.1 Opinion of Wilson Sonsini Goodrich & Rosati, Professional Corporation.
  - 10.1 Amendment No. 2 dated February 3, 2015, to the Controlled Equity Offering<sup>SM</sup> Sales Agreement dated October 5, 2012, by and between Pacific Biosciences of California, Inc., and Cantor Fitzgerald & Co.
  - 23.1 Consent of Wilson Sonsini Goodrich & Rosati, Professional Corporation (included in Exhibit 5.1).
  - 99.1 Consolidated Balance Sheets (unaudited), Consolidated Statements of Operations and Comprehensive Loss (unaudited) and Consolidated Statements of Cash Flows (unaudited).
  
  - 99.2 Management's Discussion and Analysis of Financial Condition and Results of Operations, Business and Risk Factors.
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## EXHIBIT INDEX

<u>Exhibit No.</u>	<u>Description</u>
5.1	Opinion of Wilson Sonsini Goodrich & Rosati, Professional Corporation.
10.1	Amendment No. 2 dated February 3, 2015, to the Controlled Equity Offering <sup>SM</sup> Sales Agreement dated October 5, 2012, by and between Pacific Biosciences of California, Inc., and Cantor Fitzgerald & Co.
23.1	Consent of Wilson Sonsini Goodrich & Rosati, Professional Corporation (included in Exhibit 5.1).
99.1	Consolidated Balance Sheets (unaudited), Consolidated Statements of Operations and Comprehensive Loss (unaudited) and Consolidated Statements of Cash Flows (unaudited).
99.2	Management's Discussion and Analysis of Financial Condition and Results of Operations, Business and Risk Factors.

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February 3, 2015

Pacific Biosciences of California, Inc.  
1380 Willow Road  
Menlo Park, CA 94025

**Re: Registration Statement on Form S-3**

Ladies and Gentlemen:

We have acted as counsel to Pacific Biosciences of California, Inc., a Delaware corporation (the "**Company**"), in connection with preparation and filing of a Registration Statement on Form S-3 (File No. 333-199891) (the "**Registration Statement**") with the Securities and Exchange Commission (the "**Commission**") pursuant to the Securities Act of 1933, as amended (the "**Securities Act**"), and the Prospectus Supplement filed pursuant to Rule 424(b) under the Securities Act, dated February 3, 2015 (the "**Prospectus Supplement**"), relating to the sale by the Company of shares of its common stock, par value \$0.001 per share (the "**Common Stock**") having an aggregate offering price of up to \$30,000,000 (the "**Shares**").

The offering and sale of the Shares are being made pursuant to that certain Controlled Equity Offering Sales Agreement dated as of October 5, 2012, as amended by Amendment No. 1 dated as of November 8, 2013, as further amended by Amendment No. 2 dated as of February 3, 2015 (as amended, the "**Sales Agreement**"), by and between the Company and Cantor Fitzgerald & Co. ("**Cantor**").

We have examined copies of the Sales Agreement, the Registration Statement and the Prospectus Supplement. We have also examined instruments, documents and records which we deem relevant and necessary for the basis of our opinion hereinafter expressed. In such examination, we have assumed (i) the authenticity of original documents and the genuineness of all signatures, (ii) the conformity to the originals of all documents submitted to us as copies, and (iii) the truth, accuracy, and completeness of the information, representations and warranties contained in the records, documents, instruments and certificates we have reviewed.

Based on and subject to the foregoing, we are of the opinion that the Shares have been duly authorized by the Company, and when issued and delivered by the Company against payment therefor in accordance with the terms of the Sales Agreement, will be validly issued, fully paid and nonassessable.

We express no opinion as to the laws of any other jurisdiction other than the federal laws of the United States of America and the General Corporation Law of the State of Delaware.

We hereby consent to the use of this opinion as an exhibit to the Company's Current Report on Form 8-K, filed on or about February 3, 2015, for incorporation by reference into the Registration Statement. In giving our consent, we do not believe that we are "experts" within the meaning of such term as used in the Securities Act or the rules and regulations of the Commission issued thereunder with respect to any part of the Registration Statement, including this opinion as an exhibit.

Sincerely

WILSON SONSINI GOODRICH & ROSATI  
Professional Corporation

/s/ Wilson Sonsini Goodrich & Rosati,  
Professional Corporation

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PACIFIC BIOSCIENCES OF CALIFORNIA, INC.  
CONTROLLED EQUITY OFFERING<sup>SM</sup>

AMENDMENT NO. 2 TO  
SALES AGREEMENT

February 3, 2015

Cantor Fitzgerald & Co.  
499 Park Avenue  
New York, NY 10022

Ladies and Gentlemen:

Reference is made to the Sales Agreement, dated October 5, 2012, as amended by Amendment No. 1 dated November 8, 2013, including the Schedules thereto (collectively, the "Sales Agreement"), between Cantor Fitzgerald & Co. ("CF&Co") and Pacific Biosciences of California, Inc., a Delaware corporation (the "Company"), pursuant to which the Company may sell through CF&Co, as sales agent, shares of common stock, par value \$0.001 per share, of the Company. All capitalized terms used in this Amendment No. 2 to Sales Agreement between CF&Co and the Company (this "Amendment") and not otherwise defined herein shall have the respective meanings assigned to such terms in the Sales Agreement. CF&Co and the Company agree as follows:

A. Amendments to Sales Agreement. The Sales Agreement is amended as follows, effective as of the date hereof:

1. The first sentence of Section 1 of the Sales Agreement is hereby deleted and replaced in its entirety with the following:

"The Company agrees that, from time to time during the term of this Agreement, on the terms and subject to the conditions set forth herein, it may issue and sell through the Agent, shares of common stock (the "Placement Shares") of the Company, par value \$0.001 per share (the "Common Stock"); provided, however, that in no event shall the Company issue or sell through the Agent such number or dollar amount of Placement Shares that would (a) exceed the number or dollar amount of shares of Common Stock registered on the effective Registration Statement (defined below) pursuant to which the offering is being made, (b) exceed the number of authorized but unissued shares of Common Stock, (c) exceed the number or dollar amount of shares of Common Stock permitted to be sold under Form S-3 (including General Instruction I.B.6 thereof, if applicable) or (d) exceed the number or dollar amount of shares of Common Stock for which the Company has filed a Prospectus Supplement (defined below) (the lesser of (a), (b), (c) and (d), the "Maximum Amount").

2. The File No. for the Form S-3 set forth in the first sentence of the second paragraph of Section 1 of the Sales Agreement is hereby amended and restated in its entirety as "333-199891."

3. (i) Section 12(d) of the Sales Agreement is hereby deleted in its entirety and Section 12(e) is relabeled as Section 12(d); (ii) Newly labeled Section 12(d) of the Sales Agreement is hereby deleted and replaced in its entirety with the following: "This Agreement shall remain in full force and effect unless terminated pursuant to Sections 12(a), (b), or (c) above or otherwise by mutual agreement of the parties; provided, however, that any such termination by mutual agreement shall in all cases be deemed to provide that Section 8, Section 10, Section 11, Section 17 and Section 18 shall remain in full force and effect."; and (iii) Section 12(f) of the Sales Agreement is relabeled as Section 12(e).

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4. Schedule 1 is amended by adding the words “and February 3, 2015” immediately after “November 8, 2013.”

5. Schedule 3 shall be amended by adding under The Agent after “Josh Feldman (jfeldman@cantor.com)”:

“Sameer Vasudev (svasudev@cantor.com)”

6. The first sentence of the Form of Representation Date Certificate attached as Exhibit 7(l) is amended to add “and February 3, 2015” after “November 8, 2013.”

B. Prospectus Supplement. The Company shall file a 424(b) Prospectus Supplement reflecting this Amendment within two (2) Business Days of the date hereof.

C. No Other Amendments. Except as set forth in Part A above, all the terms and provisions of the Sales Agreement shall continue in full force and effect.

D. Counterparts. This Amendment may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Delivery of an executed Amendment by one party to the other may be made by facsimile or email transmission.

E. Governing Law. This Amendment shall be governed by, and construed in accordance with, the internal laws of the State of New York without regard to the principles of conflicts of laws.

**[Remainder of page intentionally left blank.]**

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If the foregoing correctly sets forth the understanding between us, please so indicate in the space provided below for that purpose.

Very truly yours,

**PACIFIC BIOSCIENCES OF CALIFORNIA, INC.**

By: /s/ Michael Hunkapiller

Name: Michael Hunkapiller

Title: President and Chief Executive Officer

ACCEPTED as of the date first above written:

**CANTOR FITZGERALD & CO.**

By: /s/ Jeffrey Lumby

Name: Jeffrey Lumby

Title: Senior Managing Director

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## PACIFIC BIOSCIENCES OF CALIFORNIA, INC.

Consolidated Balance Sheets  
(unaudited)

(in thousands, except per share amounts)	December 31,	
	2014	2013
<b>Assets</b>		
Current assets		
Cash and cash equivalents	\$ 36,449	\$ 26,362
Investments	64,899	86,166
Accounts receivable	3,406	2,746
Inventory, net	11,335	10,050
Prepaid expenses and other current assets	1,671	1,135
Total current assets	117,760	126,459
Property and equipment, net	6,601	9,236
Other long-term assets	162	490
Total assets	\$ 124,523	\$ 136,185
<b>Liabilities and Stockholders' Equity</b>		
Current liabilities		
Accounts payable	\$ 5,608	\$ 1,717
Accrued expenses	11,441	7,905
Deferred service revenue, current	6,121	4,046
Deferred contractual revenue, current	6,785	6,785
Other liabilities, current	1,534	2,102
Total current liabilities	31,489	22,555
Deferred service revenue, non-current	1,129	518
Deferred contractual revenue, non-current	19,735	26,519
Other liabilities, non-current	2,153	3,517
Notes payable	14,124	13,347
Financing derivative	944	549
Total liabilities	69,574	67,005
Commitments and contingencies		
Stockholders' equity		
Preferred Stock, \$0.001 par value:		
Authorized 50,000 shares; No shares issued or outstanding	—	—
Common Stock, \$0.001 par value:		
Authorized 1,000,000 shares; Issued and outstanding 73,927 and 66,275 shares at December 31, 2014 and 2013, respectively	74	66
Additional paid-in-capital	736,339	684,413
Accumulated other comprehensive income	9	14
Accumulated deficit	(681,473)	(615,313)
Total stockholders' equity	54,949	69,180
Total liabilities and stockholders' equity	\$ 124,523	\$ 136,185

PACIFIC BIOSCIENCES OF CALIFORNIA, INC.

Consolidated Statements of Operations and Comprehensive Loss  
(unaudited)

(in thousands, except per share amounts)	Years ended December 31,		
	2014	2013	2012
<b>Revenue:</b>			
Product revenue	\$ 35,299	\$ 20,039	\$ 20,089
Service and other revenue	8,511	6,446	5,894
Contractual revenue	16,784	1,696	—
Total revenue	60,594	28,181	25,983
<b>Cost of Revenue:</b>			
Cost of product revenue	29,626	15,706	18,796
Cost of service and other revenue	7,566	6,056	6,247
Total cost of revenue	37,192	21,762	25,043
Gross profit	23,402	6,419	940
<b>Operating Expense:</b>			
Research and development	48,230	45,217	47,623
Sales, general and administrative	38,026	38,745	47,655
Total operating expense	86,256	83,962	95,278
Operating loss	(62,854)	(77,543)	(94,338)
Interest expense	(2,828)	(2,478)	(274)
Other income (expense), net	(478)	728	147
Net loss	(66,160)	(79,293)	(94,465)
<b>Other comprehensive loss:</b>			
Unrealized loss on investments	(5)	(16)	(27)
Comprehensive loss	\$ (66,165)	\$ (79,309)	\$ (94,492)
<b>Net loss per share:</b>			
Basic and diluted net loss per share	\$ (0.94)	\$ (1.26)	\$ (1.69)
Shares used in computing basic and diluted net loss per share	70,475	62,784	55,733

**Consolidated Statements of Cash Flows**  
(unaudited)

(in thousands)	Years Ended December 31,		
	2014	2013	2012
<b>Cash flows from operating activities</b>			
Net loss	\$ (66,160)	\$ (79,293)	\$ (94,465)
Adjustments to reconcile net loss to net cash used in operating activities			
Depreciation and amortization	4,221	5,648	6,649
Amortization of debt discount and financing costs	793	595	—
Stock-based compensation	9,943	9,905	9,705
Other items	507	(352)	1,295
Changes in assets and liabilities			
Accounts receivable	(660)	76	1,735
Inventory	(1,285)	(60)	4,761
Prepaid expenses and other assets	(224)	840	50
Accounts payable	3,891	(1,271)	(1,754)
Accrued expenses	3,536	1,327	(1,333)
Deferred service revenue	2,686	386	(1,674)
Deferred contractual revenue	(6,784)	33,304	—
Other liabilities	(1,932)	(938)	(1,791)
Net cash used in operating activities	<u>(51,468)</u>	<u>(29,833)</u>	<u>(76,822)</u>
<b>Cash flows from investing activities</b>			
Purchase of property and equipment	(1,609)	(909)	(1,703)
Purchase of investments	(126,413)	(201,547)	(87,889)
Sales of investments	—	100	7,896
Maturities of investments	147,586	169,239	143,488
Net cash provided by (used in) investing activities	<u>19,564</u>	<u>(33,117)</u>	<u>61,792</u>
<b>Cash flows from financing activities</b>			
Proceeds from issuance of common stock from equity plans	3,968	3,079	2,705
Proceeds from issuance of common stock from at-the-market equity offering, net of issuance costs	38,023	19,927	—
Proceeds from issuance of debt agreement, net of issuance costs	—	19,766	—
Net cash provided by financing activities	<u>41,991</u>	<u>42,772</u>	<u>2,705</u>
Net increase (decrease) in cash and cash equivalents	10,087	(20,178)	(12,325)
Cash and cash equivalents at beginning of period	26,362	46,540	58,865
Cash and cash equivalents at end of period	<u>\$ 36,449</u>	<u>\$ 26,362</u>	<u>\$ 46,540</u>
<b>Supplemental disclosure of cash flow information</b>			
Interest paid	\$ 1,342	\$ 1,165	\$ —
<b>Supplemental disclosure of non-cash investing and financing activities</b>			
Inventory transferred to (from) property and equipment for internal use	—	(558)	1,164

**MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS****SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS**

Discussions under the captions "Management's Discussion and Analysis of Financial Condition and Results of Operations," "Business" and "Risk Factors," 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 Current Report on Form 8-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, 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 investment portfolio, 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," "plans," "potential," "predicts," "projects," "seeks," "should," "target," "will," "would" or similar expressions and the 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 forward-looking statements. Also, forward-looking statements represent management's beliefs and assumptions as of the date of this report. Except as required by law, 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.

**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.

**2014 Business Events and Trends**

**Bookings and Revenue Growth.** During the year ended December 31, 2014, we achieved stronger instrument sales and accepted orders for 40 instruments, compared to 25 during 2013, ending 2014 with 15 in backlog. We attribute the stronger bookings largely to increased customer awareness of the expanding applications for SMRT Sequencing, and the improved reliability and performance of our instruments. We generally expect installation of new instruments to occur one to two quarters after they are booked. Revenue during 2014 was \$60.6 million dollars, up 115% over revenue of \$28.2 million recognized during the year ended December 31, 2013. The revenue increase year-over-year stemmed from substantial increases in all categories, including sales of instruments, consumables, service and other revenue, and a \$15.1 million increase in contractual revenue. Revenue can fluctuate on a quarterly basis, which in some cases may be attributable to seasonal fluctuations.

**Product Enhancements.** During 2014, we continued to significantly enhance the performance of the PacBio RS II System, which includes the PacBio RS II instrument, consumables and software, 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 sequencing reagent 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.

**Diagnostic Collaboration with Roche.** During the third quarter of 2013 we entered into a Development, Commercialization and License Agreement (the "Roche Agreement") with F. Hoffman-La Roche Ltd ("Roche"), whereby we received a nonrefundable up-front payment of \$35 million. The Roche Agreement also provides for our ability to receive additional payments totaling up to \$40 million, subject to our achievement of certain milestones. During 2014, we recognized ongoing revenue of \$6.8 million from the up-front payment and also achieved our first milestone under the Roche Agreement, for which we received \$10 million during the third quarter of 2014, leaving a remaining \$30 million in potential milestone payments. We expect to earn another \$10 million in milestone revenue during 2015; however, achievement of future milestones is not assured. During 2015, we also expect to continue recognizing revenue from the up-front payment.

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**Cash Position.** For the year ended December 31, 2014, our balance of cash, cash equivalents and investments totaled \$101.3 million, reflecting a decrease of \$11.2 million from the prior year, primarily reflecting our net loss of \$66.2 million, less \$14.2 million non-cash expenses for stock compensation expense and depreciation. During 2014, we also raised \$38.0 million through the sale of common stock under our “at-the-market” offering. We plan to raise additional capital in the future. To the extent we raise additional funds through the issuance of equity, such issuance will result in dilution to our stockholders. Our cash position is dependent on our revenue, including timing of contractual revenue as well as any additional funds raised.

## Results of Operations

### Comparison of the Years Ended December 31, 2014 and 2013

	Year Ended December 31,		\$ Change	% Change
	2014	2013		
Revenue:	(in thousands, except percentages)			
Product revenue	\$ 35,299	\$ 20,039	\$ 15,260	76%
Service and other revenue	8,511	6,446	2,065	32%
Contractual revenue	16,784	1,696	15,088	890%
Total revenue	60,594	28,181	32,413	115%
Cost of Revenue:				
Cost of product revenue	29,626	15,706	13,920	89%
Cost of service and other revenue	7,566	6,056	1,510	25%
Total cost of revenue	37,192	21,762	15,430	71%
Gross profit	23,402	6,419	16,983	265%
Operating Expense:				
Research and development	48,230	45,217	3,013	7%
Sales, general and administrative	38,026	38,745	(719)	(2%)
Total operating expense	86,256	83,962	2,294	3%
Operating loss	(62,854)	(77,543)	14,689	19%
Interest expense	(2,828)	(2,478)	(350)	(14%)
Other income, net	(478)	728	(1,206)	(166%)
Net loss	\$ (66,160)	\$ (79,293)	\$ 13,133	17%

### Revenue

Revenue for the year ended December 31, 2014 totaled \$60.6 million compared to \$28.2 million for the year ended December 31, 2013. The revenue increased in all categories, including sales of instruments, consumables, service and other revenue, and contract revenue from the Roche Agreement.

	Year Ended December 31,		\$ Change	% Change
	2014	2013		
Revenue:	(in thousands, except percentages)			
Instrument revenue	\$ 22,125	\$ 11,521	\$ 10,604	92%
Consumable revenue	13,174	8,518	4,656	55%
Total product revenue	35,299	20,039	15,260	76%
Service and other revenue	8,511	6,446	2,065	32%
Contractual revenue	16,784	1,696	15,088	890%
Total revenue	\$ 60,594	\$ 28,181	32,413	115%

Product revenue for the year ended December 31, 2014 consisted of \$22.1 million from sales of our instruments and instrument upgrades and \$13.2 million from sales of consumables, compared to \$11.5 million from sales of our instruments and \$8.5 million from sales of consumables in the year ended December 31, 2013. Instrument revenue for the years ended December 31, 2014 and 2013 reflects revenue derived from the delivery of 38 and 17 instruments during the periods, respectively. The increase in consumable sales reflects our larger installed instrument base and higher sales of consumables per instrument within the installed base.

Service and other revenue for the year ended December 31, 2014 primarily consisted of service revenue of \$8.4 million compared to service revenue of \$6.2 million for the year ended December 31, 2013. Service revenue was, and continues to be, derived from product maintenance agreements sold on our installed instruments. The increase in service revenue from 2013 to 2014 was primarily attributable to a larger installed instrument base in 2014.

Contractual revenue for the year ended December 31, 2014 consists of a full year of quarterly amortization of \$1.7 million and our achievement of a development milestone for which we received \$10.0 million from Roche. During 2013, contractual revenue included \$1.7 million, representing one quarter of amortization. As of December 31, 2014, \$26.5 million remains deferred and will be amortized as revenue over the remaining estimated obligation period. The amortization period is based upon management's expectations of delivering pursuant to the Roche Agreement and is subject to change based on multiple factors including progress towards deliverables under the contract.

#### *Gross Profit*

Gross profit for the year ended December 31, 2014 totaled \$23.4 million, resulting in a gross margin of 38.6%, compared to a \$6.4 million gross profit for the year ended December 31, 2013 and a gross margin of 22.8%. The increase for both gross margin and gross profit is primarily due to the increase in contractual revenue, specifically the \$10.0 million relating to the achievement of a development milestone and an increase in contractual revenue amortization of \$5.1 million during 2014.

Cost of product revenue of \$29.6 million for the year ended December 31, 2014 reflects the costs primarily relating to the sale of 38 instruments and consumables shipped during the period while cost of product revenue of \$15.7 million for the year ended December 31, 2013 reflects the costs primarily relating to the sale of 17 instruments and consumables shipped during the period. The increase of \$13.9 million in cost of product revenue for the year ended December 31, 2014 compared to the year ended December 31, 2013 was primarily due to the higher quantity of instruments and consumables shipped during the year ended December 31, 2014.

Cost of service and other revenue for the year ended December 31, 2014 increased to \$7.6 million compared to \$6.1 million for the year ended December 31, 2013. The increase in cost of service and other revenue reflected higher service costs for personnel, materials and support infrastructure necessary to support the rising installed base of our instruments.

Gross margin for 2015 is expected to remain variable depending on the revenue mix, including in particular, the amount of contractual revenue.

#### *Research and Development Expense*

For the year ended December 31, 2014, research and development expenses increased \$3.0 million, or 7%, compared to the year ended December 31, 2013. The increase in research and development expense was primarily attributed to an increase of \$2.4 million in personnel-related expense including stock-based compensation, and higher external product development expenses. Research and development expense includes stock-based compensation of \$3.8 million and \$4.1 million during the years ended December 31, 2014 and 2013, respectively. We expect our research and development expenses to increase in 2015.

#### *Sales, General and Administrative Expense*

Selling, general and administrative expenses for the year ended December 31, 2014 remained relatively flat compared to the year ended December 31, 2013. Selling, general and administrative expenses include stock-based compensation of \$5.4 million and \$5.3 million during the years ended December 31, 2014 and 2013, respectively. We expect our selling, general and administrative expenses to increase in 2015.

#### *Interest Expense*

Interest expense for the year ended December 31, 2014 remained relatively flat compared to the year ended December 31, 2013. Interest expense related primarily to the debt facility entered into during the year ended December 31, 2013

#### *Other Income (Expense), Net*

Other income (expense), net consists primarily of interest income earned on cash and investments, accretion of discounts and amortization of premiums related to investments, net gains or losses on foreign currency transactions, net gains or losses resulting from changes in the estimated fair value of the financing derivative and foreign income taxes.

## **Liquidity and Capital Resources**

### ***Liquidity***

Since our inception we have financed our operations primarily through the issuance of common stock and convertible preferred stock, in addition to our debt facility. Cash and investments at December 31, 2014 totaled \$101.3 million, compared to \$112.5 million at December 31, 2013. For the year ended December 31, 2014, we received \$38.0 million, net, through the sale of common stock under our "at-the-market" offering. Excluding proceeds from the "at-the-market" offering of \$38.0 million, cash and investments decreased by \$49.2 million compared to December 31, 2013, primarily reflecting \$51.5 million of cash used in operating activities and \$1.6 million of fixed asset purchases, partially offset by \$4.0 million of proceeds received from equity sales through our employee equity plans.

We believe that existing cash, cash equivalents and investments will be sufficient to fund our projected operating requirements for at least 12 months; however, we plan to raise additional capital in the future. These expectations are based on our current operating and financing plans, which are subject to change. Factors that may affect our capital needs include, but are not limited to, slower than expected adoption of our products resulting in lower sales of our products and services; future acquisitions; our ability to maintain new collaboration and customer

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arrangements; the progress of our research and development programs; initiation or expansion of research programs and collaborations; the costs involved in preparing, filing, prosecuting, defending and enforcing intellectual property rights; the purchase of patent licenses; and other factors.

To the extent we raise additional funds through the sale of equity or convertible debt securities, the issuance of such securities will result in dilution to our stockholders. There can be no assurance that such funds will be available on favorable terms, or at all. If adequate funds are not available, we may be required to curtail operations significantly or to obtain funds by entering into collaboration agreements on unattractive terms. Our inability to raise capital could have a material adverse effect on our business, financial condition and results of operations.

The following table summarizes our cash flows activities for the periods indicated.

	Year Ended December 31,		
	2014	2013	2012
	(in thousands)		
Net cash provided by (used in):			
Operating activities	\$ (51,468)	\$ (29,833)	\$ (76,822)
Investing activities	19,564	(33,117)	61,792
Financing activities	41,991	42,772	2,705

#### *Operating Activities*

Our primary uses of cash in operating activities are for the manufacturing and sale of PacBio RS II instruments and consumables, development of ongoing product enhancements and future products, and support functions related to our selling, general and administrative activities. The net cash used for the years ended December 31, 2014, 2013 and 2012 primarily reflects the net loss for those periods, partially offset by non-cash operating expenses including depreciation, stock-based compensation, and changes in working capital.

Cash used in operating activities of \$51.5 million in 2014 reflected a net loss of \$66.2 million, partially offset by non-cash stock-based compensation of \$9.9 million and depreciation and amortization of \$4.2 million. The change in net operating assets and liabilities was primarily due to an increase of \$3.9 million in accounts payable, an increase of \$3.5 million in accrued expenses, partially offset by \$6.8 million in deferred contractual revenue during 2014.

Cash used in operating activities of \$29.8 million in 2013 reflected a net loss of \$79.3 million, partially offset by non-cash stock-based compensation of \$9.9 million and depreciation and amortization of \$5.6 million. The change in net operating assets and liabilities was primarily due to an increase of \$33.3 million of deferred development revenue associated with the Roche agreement, and (ii) the fluctuation among prepaid expenses and other assets, accounts payable, accrued expenses, and other liabilities due to the timing of payments during 2013.

Cash used in operating activities of \$76.8 million in 2012 reflected a net loss of \$94.5 million, a non-cash stock-based compensation of \$9.7 million and depreciation and amortization of \$6.6 million. Changes in working capital were due primarily to (i) inventory decreasing as a result of a decrease in the amount of instruments awaiting customer acceptance as compared to the prior year (ii) accounts receivable and deferred revenue decreasing due to the timing of instrument sales, and (iii) prepaid expenses and other assets, accounts payable, accrued expenses and other current liabilities fluctuated primarily due to the timing of vendor, litigation related, and employee compensation payments during 2012.

#### *Investing Activities*

Our investing activities consist primarily of capital expenditures and investment purchases and maturities.

In 2014, net cash provided by investing activities was \$19.6 million, comprised of net maturities of investments of \$21.2 million, partially offset by purchases of property and equipment of \$1.6 million.

In 2013, net cash used in investing activities was \$33.1 million, comprised of net purchases of investments of \$32.2 million and \$0.9 million of purchases of property and equipment.

In 2012, net cash provided by investing activities was \$61.8 million, comprised of net sales and maturities of investments of \$63.5 million, partially offset by \$1.7 million of purchases of property and equipment.

#### *Financing Activities*

In 2014, cash provided by financing activities was \$42.0 million, resulting from net proceeds of \$38.0 million from our common stock "at-the-market" offering and \$4.0 million from the issuance of common stock through our equity compensation plans. We are not obligated to make sales under our "at-the-market" offering.

In 2013, cash provided by financing activities was \$42.8 million, comprised of net proceeds of \$19.8 million from our debt facility, net proceeds of \$19.9 million from our common stock "at-the-market" offering, and \$3.1 million from the issuance of our common stock through the sale of shares under our ESPP and stock option exercises.



In 2012, cash provided by financing activities was \$2.7 million, resulting from the issuance of our common stock through the sale of shares under our ESPP and stock option exercises.

### Capital Resources

In November 2014, we filed a shelf registration statement on Form S-3 with the SEC pursuant to which we may, from time to time, sell up to an aggregate of \$150 million of our common stock, warrants or debt securities. On November 21, 2014, the registration statement was declared effective by the SEC, which will allow us to access the capital markets for the three-year period following the effective date.

### Debt facility and warrant agreement

Under the terms of our February 2013 debt agreement with Deerfield (the “Facility Agreement”), we received \$20.5 million and we issued promissory notes in the aggregate principal amount of \$20.5 million (the “Notes”). The Notes bear simple interest at a rate of 8.75% per annum, payable quarterly in arrears commencing on April 1, 2013 and on the first business day of each January, April, July and October thereafter. We received net proceeds of \$20.0 million, representing \$20.5 million of gross proceeds, less a \$500,000 facility fee, before deducting other expenses of the transaction.

The Facility Agreement also contains various representations and warranties, and affirmative and negative covenants, customary for financings of this type, including restrictions on our ability to incur additional indebtedness or liens on our assets, except as permitted under the Facility Agreement. In addition, we are required to maintain consolidated cash and cash equivalents on the last day of each calendar quarter of not less than \$2.0 million. As security for our repayment of our obligations under the Facility Agreement, we granted a security interest in substantially all of our property and interests in property.

### Common stock “at-the-market” offering

On October 5, 2012, we entered into a sales agreement pursuant to which we may offer and sell, from time to time, shares of our common stock having an aggregate offering price of up to \$30.0 million through an “at-the-market” offering. On November 8, 2013, the sales agreement was amended to increase the shares of our common stock that may be sold pursuant to the sales agreement by an additional aggregate offering price of \$30.0 million. On February 3, 2015, the sales agreement was amended again in order to increase the shares of our common stock that may be sold pursuant to the sales agreement. We may currently sell under the agreement shares of our common stock having an aggregate offering price of up to \$30.0 million. Such aggregate value of shares of our common stock is in addition to the shares sold under the original sales agreement, dated October 5, 2012, and the first amendment to such sales agreement, dated November 8, 2013. We pay a commission equal to 3% of the gross proceeds from the sale of shares of our common stock under the sales agreement. We intend to use the net proceeds from this offering for general corporate purposes, including capital expenditures and working capital. We may also use a portion of the net proceeds from this offering to acquire or invest in complementary businesses, technologies, product candidates or other intellectual property. We are not obligated to make any sales of shares of our common stock under the sales agreement. As of December 31, 2014, we have sold a total of 14.1 million shares of our common stock at an average price of \$4.27 through our “at-the-market” offering.

At the election of the holders representing a majority of the aggregate principal amount of the outstanding Notes issued pursuant to the Facility Agreement, the holders may elect to receive 25% of the net proceeds from any financing that includes an equity component, including without limitation, sales pursuant to our “at-the-market” offering. This right is subject to certain exceptions set forth in the Facility Agreement, including that the right will not apply until we have issued 15.0 million shares of our common stock following the date of the Facility Agreement. To the extent we raise additional capital in the future through the sale of common stock under our “at the market” offering, we may be obligated, at the election of the holders of the Notes, to pay 25% of the net proceeds from any such financing activities as payment of the Notes.

### Contractual Obligations, Commitments and Contingencies

The following table provides summary information concerning our future contractual obligations as of December 31, 2014.

	Payments due by period (in thousands)			
	Total	less than 1 year	1-3 years	More than 3 years
Purchase commitments and obligations	\$ 13,648	\$ 13,648	\$ —	\$ —
Operating lease obligations (1)	4,079	3,984	95	—
Facility financing obligation	668	668	—	—
Debt (2)	28,978	1,794	9,225	17,959
<b>Total contractual obligations</b>	<b>\$ 47,373</b>	<b>\$ 20,094</b>	<b>\$ 9,320</b>	<b>\$ 17,959</b>

(1) Maintenance, insurance, taxes and contingent rent obligations are excluded. Our current lease obligations for our headquarters in Menlo Park expire at the end of 2015.

(2) Under the terms of the Debt, we received \$20.5 million in funding. The amounts in the table above include interest and principal repayments on the debt.

### *Purchase commitments and obligations*

These amounts include an estimate of all open purchase orders and contractual obligations in the ordinary course of business, including commitments with contract manufacturers and suppliers, for which we have not received the goods or services. A majority of these purchase obligations are due within a year. Although open purchase orders are considered enforceable and legally binding, the terms generally allow us the option to cancel, reschedule, and adjust our requirements based on our business needs prior to the delivery of goods or performance of services.

### *Facility Financing Obligation*

In December 2009 we entered into a build-to-suit lease agreement for a manufacturing and office facility where we are considered the owner of the project under GAAP. When we are considered the owner of a project, we record the shell of the facility at its fair value at the date construction commences with a corresponding facility financing obligation. Accordingly, we recorded \$3.0 million of building and leasehold improvement assets and a corresponding liability to facility financing obligation.

The table above reflects only payment obligations that are fixed and determinable. Milestone payments and royalty payments under our license agreements are not included in the table above because we cannot, at this time, determine when or if the events triggering the commencement of payment obligations will become potentially payable.

### *License Agreements*

Payments related to licensing and other arrangements not included in the contractual obligations table include amounts related to cancelable license agreements with third parties for certain patent rights and technology. Under the terms of these agreements, we may be obligated to pay royalties based on revenue from the sales of licensed products, or minimum royalties, whichever is greater, and license maintenance fees. The future license maintenance fees and minimum royalty payments under the license agreements are not deemed to be material.

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## 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 complimentary 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, N<sup>6</sup>-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.

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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 Bioscience’ 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.

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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

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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:

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- **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.

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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

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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.

### **Employees**

As of December 31, 2014, we had 344 full-time employees. Of these employees, 134 were in research and development, 62 were in operations, 101 were in marketing, sales, service and support, and 47 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 website is located at [www.pacb.com](http://www.pacb.com). The information posted on our website is not incorporated into this Current Report on Form 8-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 website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC.

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## RISK FACTORS

*You should consider carefully the risks and uncertainties described below, 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 have limited experience as a commercial company.***

Our first commercial product launched in 2011 and we have limited sales to date 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 current and future 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;
- develop and commercialize new products or achieve an acceptable return, on our research and development efforts and expenses;
- comply with 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 existing or future products;
- scale our manufacturing activities to meet potential demand at a reasonable cost;
- avoid infringement and misappropriation of third-party intellectual property;
- obtain licenses to third-party intellectual property on commercially reasonable terms;
- obtain valid and enforceable patents that give us a competitive advantage;
- protect our proprietary technology; 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 continue to incur substantial losses and negative cash flow from operations 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.***

We cannot be sure that our current or future products will gain acceptance in the marketplace at levels sufficient to support our costs. Our success depends, in part, on our ability to expand the market for genetic analysis to include new applications that are not practicable with other current technologies. To accomplish this, we must successfully commercialize, and continue development of, our proprietary Single Molecule, Real-Time (SMRT) technology for use in a variety of life science and other applications. There can be no assurance that we will be successful in securing additional customers for our products. Furthermore, we cannot guarantee that our products 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 and/or our sales and distribution partners may fail to achieve or sustain market acceptance of our current or future products by academic, government and clinical laboratories and pharmaceutical, diagnostic, biotechnology and agriculture companies, among others, across the full range of our intended life science and other 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 further grow our customer base, our future sales and revenue would be materially harmed and our business may not succeed.

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***Our development and commercialization of future products, including those related to our arrangement with Roche, may not result in the benefits we anticipate, and could have a material adverse effect on our business, financial condition and results of operations.***

We entered into an agreement with F. Hoffman-La Roche Ltd. (“Roche”), pursuant to which we are developing and expect to manufacture diagnostic products for clinical use, including sequencing systems and consumables based on our proprietary SMRT technology (the “Roche Agreement”), and we are engaged in research and development efforts, which, if successful, may result in the introduction of new products in the future. Our research and development efforts are complex and require us to incur substantial expenses. We may not be able to develop and commercialize new products or achieve an acceptable return, if any, on our research and development efforts and expenses. There can also be no assurance that we will be able to develop and manufacture future products as provided by the terms of the Roche Agreement or that Roche will be able to commercialize and sell the developed diagnostic products. We may also be unable to meet the additional development milestones required for additional payments from Roche. We could also be involved in disputes with Roche, which could lead to delays in or termination of our development and manufacture of diagnostic products and result in time-consuming and expensive litigation or arbitration. In addition, any such dispute could diminish Roche’s commitment to us and reduce the resources they devote to commercializing the developed diagnostic products. If Roche terminates or breaches the Roche Agreement, or otherwise acquires, develops and/or commercializes alternative or competing products, the successful commercialization of our diagnostic products for clinical use would be materially and adversely affected.

If we are not able to realize the benefits we anticipate from the development and commercialization of future products, including the expected benefits from the Roche Agreement, it could have a material adverse effect on our business, financial condition and results of operations. In addition, the introduction of future products may lead to our limiting or ceasing development of further enhancements to our existing products, as we focus our resources on the new products, and could result in reduced marketplace acceptance and loss of sales of our existing products, materially adversely affecting our revenue and operating results. New products may also have quality or other defects, especially in the early stages of introduction. If we do not successfully manage product transitions, our business, reputation and financial condition may be materially adversely harmed.

***Rapidly changing technology in life sciences and diagnostics could make the products we are developing obsolete unless we continue to develop and commercialize new and improved products and pursue new market opportunities.***

Our industry is characterized by rapid and significant technological changes, frequent new product introductions and enhancements and evolving industry standards. Our future success will depend on our ability to continually improve our products, to develop and introduce new products that address the evolving needs of our customers on a timely and cost-effective basis and to pursue new market opportunities. These new market opportunities may be outside the scope of our proven expertise or in areas where the market demand is unproven, and new products and services developed by us may not gain market acceptance. Our inability to develop and introduce new products and to gain market acceptance of new products could harm our future operating results. Unanticipated difficulties or delays in replacing existing products with new products or in commercializing improved or new products in sufficient quantities to meet customer demand could diminish future demand for our products and harm our future operating results.

***Increased market adoption of our products by customers may depend on the availability of sample preparation and informatics tools, some of which may be developed by third parties.***

Our commercial success may depend in part upon the development of sample preparation and software and informatics tools by third parties for use with our products. We cannot guarantee that third parties will develop tools that our customers or potential customers will find useful with our products. A lack of additional available complementary sample preparation and informatics tools may impede the adoption of our products and may adversely impact our business.

***We operate in a highly competitive industry and if we are not able to compete effectively, our business and operating results will likely be harmed.***

Some of our current competitors, including Illumina, Inc. and Thermo Fisher Scientific Inc., as well as other potential competitors, have greater name recognition, more substantial intellectual property portfolios, longer operating histories, significantly greater financial, technical, research and/or other resources, more substantial experience in new product development, larger and more established manufacturing capabilities and marketing, sales and support functions, and/or more established distribution channels to deliver products to customers than we do. These competitors may be able to respond more quickly and effectively than we can to new or changing opportunities, technologies, standards or customer requirements. In light of these advantages, even if our technology is more effective than the products or service offerings of our competitors, current or potential customers might purchase competitive products and services instead of our products. Increased competition may result in pricing pressures, which could harm our sales, profitability or market share. Our failure to further enhance our existing products and to introduce new products to compete effectively could materially and adversely affect our business, financial condition or results of operations.

***We may be unable to successfully increase sales of our products.***

Our ability to achieve profitability depends on our ability to attract customers for our current and future products, and we may be unable to effectively market our products. To perform sales, marketing, distribution and customer support functions successfully, we face a number of risks, including:

- our ability to attract, retain and manage the sales, marketing and service personnel necessary to expand market acceptance for our technologies;
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- the time and cost of maintaining and growing a specialized sales, marketing and service force for a particular application, which may be difficult to justify in light of the revenue generated; and
- our sales, marketing and service force may be unable to execute successful commercial activities.

We have enlisted and may continue to enlist third parties to assist with sales, distribution and customer support. There is no guarantee that we will be successful in attracting desirable sales and distribution partners or that we will be able to enter into arrangements with such partners on terms favorable to us. If our sales and marketing efforts, or those of any of our third-party sales and distribution partners, are not successful, our technologies and products may not gain market acceptance, which could materially impact our business operations.

***We rely on other companies for the manufacture of certain components and sub-assemblies and intend to outsource additional sub-assemblies in the future. We may not be able to successfully scale the manufacturing process necessary to build and test multiple products on a full commercial basis, which could materially harm our business.***

Our products are complex and involve a large number of unique components, many of which require precision manufacturing. The nature of the products requires customized components that are currently available only from a limited number of sources, and in some cases, single sources. We have chosen to source certain critical components from a single source, including suppliers for our SMRT Cells, reagents and instruments. If we are required to purchase these components from an alternative source, it could take several months or longer to qualify the alternative sources. If we are unable to secure a sufficient supply of these product components on a timely basis, our operations and manufacturing will be adversely affected, we could be unable to meet customer demand and our business and results of operations may be adversely affected.

The operations of our third-party manufacturing partners and suppliers could be disrupted by conditions unrelated to our business or operations or that are beyond our control. If our manufacturing partners or suppliers are unable or fail to fulfill their obligations to us for any reason, we may not be able to manufacture our products and satisfy customer demand or our obligations under sales agreements in a timely manner, and our business could be harmed as a result. Our current manufacturing process is characterized by long lead times between the ordering and delivery of our products. If we have ordered insufficient components to manufacture our products on a timely basis to meet customer demand, our sales and our gross margin may be adversely affected and our business could be materially harmed. If we are unable to reduce our manufacturing costs and establish and maintain reliable high volume manufacturing suppliers as we scale our operations, our business could be materially harmed.

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

In order to successfully derive revenue from our products, we need to supply our customers with products that meet their specifications, quality requirements and expectations. Our customers have previously experienced variability in the performance of our instruments and SMRT Cells. There is no assurance that we will be able to manufacture our products so that they consistently achieve the product specifications and quality that our customers expect, including those products and specifications that may be developed pursuant to the Roche Agreement. There is also no assurance that we will be able to increase manufacturing yields and decrease costs, or that we will be successful in forecasting customer demand or manufacturing and supply costs. Furthermore, we may not be able to increase manufacturing to meet anticipated demand. An inability to manufacture products that consistently meet specifications, in necessary quantities and at commercially acceptable costs, will have a negative material impact on our business.

***We intend to raise additional financing to fund our existing operations. Equity and debt securities we issue may have rights senior to common stockholders.***

We intend to raise additional funds through public or private debt or equity financing. Additional funds may not be available on terms acceptable to us or at all, particularly in light of restrictions under our debt agreement. We have incurred and may further incur additional debt. Debt holders have rights senior to common stockholders to make claims on our assets and the terms of our existing debt agreement restrict certain activities, including our ability to pay dividends on our common stock.

***Our indebtedness could adversely affect our financial condition and prevent us from fulfilling our obligations.***

Our net losses since inception and our expectation of incurring substantial losses and negative cash flow for the foreseeable future, combined with our existing indebtedness, could:

- make it more difficult for us to satisfy our obligations, including under the debt agreement;
  - increase our vulnerability to general adverse economic and industry conditions;
  - limit our ability to fund future working capital, capital expenditures, research and development and other business opportunities;
  - require us to dedicate a substantial portion of our cash flow from operations to service payments on our indebtedness;
  - increase the volatility of the price of our common stock;
  - limit our flexibility to react to changes in our business and the industry in which we operate;
  - place us at a competitive disadvantage to our competitors that have less or no indebtedness; and
  - limit, along with the financial and other restrictive covenants in our indebtedness, among other things, our ability to borrow additional funds.
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***Our existing debt contains covenants which may adversely impact our business and our failure to comply with such covenants could cause our outstanding indebtedness to become immediately payable.***

Our existing debt contains various affirmative and negative covenants, including restrictions on our and our subsidiaries' ability to incur additional indebtedness or liens on our assets. These covenants impose significant operating and financial restrictions on us, including restrictions on our ability to take certain actions that may be in our best interests.

A breach of any of the covenants contained in our debt could result in an event of default. If an event of default exists, debt holders could elect to declare all amounts outstanding under the debt to be immediately due and payable. If we are unable to repay our indebtedness when due and payable, debt holders could proceed against the collateral granted to them to secure such indebtedness. We have pledged substantially all of our property and interests in property, including our intellectual property, as collateral under our existing debt. If the debt holders accelerate the repayment of our indebtedness, we may not have sufficient funds to make such repayment, which could have a material adverse effect on our liquidity and ability to conduct our business.

In addition, at the election of the holders representing a majority of the aggregate principal amount of the outstanding notes issued pursuant to our existing debt agreement, the holders may elect to receive 25% of the net proceeds from any financing that includes an equity component, including without limitation, the sale or issuance of our common stock, options, warrants or other securities convertible or exchangeable for shares of our common stock, as payment of the notes. This right is subject to certain exceptions set forth in our existing debt agreement, including that the right will not apply until we have issued 15.0 million shares of our common stock following the date of our existing debt agreement. To the extent we raise additional capital in the future through the sale of common stock under our "at the market" offering or through other financing activities, we may be obligated, at the election of the holders of the notes, to pay 25% of the net proceeds from any such financing activities as payment of the notes.

***Our products are highly complex and have recurring support requirements.***

In light of the highly complex technology involved in our products, there can be no assurance that we will be able to continue providing adequate support for our products. Our customers have in the past experienced reliability issues with our products. If our products have reliability or other quality issues or require unexpected levels of support in the future, 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 generally deliver our sequencing instruments with one year of service included in the purchase price and offer additional years of service for an additional fee. If our service and support costs increase, our business and operations may be adversely affected.

***Our products could have unknown defects or errors, which may give rise to claims against us or divert application of our resources from other purposes.***

Products using our SMRT technology are complex and may develop or contain undetected defects or errors. We cannot provide assurance that material performance problems will not arise. Despite testing, defects or errors may arise in our products, which could result in a failure to achieve increased market acceptance, diversion of development resources, injury to our reputation and increased warranty, service and maintenance costs. We generally ship our sequencing instruments with one year of service included in the purchase price with an option to purchase one or more additional years of service. We also provide a warranty for our consumables, which is generally limited to replacing, or at our option, giving credit for, any consumable with defects in material or workmanship. Defects or errors in our products may also discourage customers from purchasing our products. The costs incurred in correcting any defects or errors may be substantial and could adversely affect our operating margins. In addition, such defects or errors could lead to the filing of product liability claims against us or against third parties who we may have an obligation to indemnify against such claims, which could be costly and time-consuming to defend and result in substantial damages. Although we have product liability insurance, any product liability insurance that we have or procure in the future may not protect our business from the financial impact of a product liability claim. Moreover, we may not be able to obtain adequate insurance coverage on acceptable terms. Any insurance that we have or obtain will be subject to deductibles and coverage limits. A product liability claim could have a serious adverse effect on our business, financial condition and results of operations.

***We depend on the continuing efforts of our senior management team and other key personnel. If we lose members of our senior management team or other key personnel or are unable to successfully retain, recruit and train qualified scientists, engineering and other personnel, our ability to develop our products could be harmed, and we may be unable to achieve our goals.***

Our future success depends upon the continuing services of members of our senior management team and scientific and engineering personnel. In particular, our scientists and engineers are critical to our future technological and product innovations and we will need to hire additional qualified personnel. Our industry, particularly in the San Francisco Bay Area, is characterized by high demand and intense competition for talent, and the turnover rate can be high. We compete for qualified management and scientific personnel with other life science companies, academic institutions and research institutions, particularly those focusing on genomics. Our employees could leave our company with little or no prior notice and would be free to work for a competitor. If one or more of our senior executives or other key personnel were unable or unwilling to continue in their present positions, we may not be able to replace them easily or at all, and other senior management may be required to divert attention from other aspects of the business. In addition, we do not have "key person" life insurance policies covering any member of our management team or other key personnel. The loss of any of these individuals or any inability to attract or retain qualified personnel, including scientists, engineers and others, could prevent us from pursuing collaborations and adversely affect our product development and introductions, business growth prospects, results of operations and financial condition.

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***A significant portion of our potential sales depends on customers' spending budgets that may be subject to significant and unexpected variation which could have a negative effect on the demand for our products.***

Our instrument sales represent significant capital purchases for our customers. Potential customers for our current or future products include academic and government institutions, genome centers, medical research institutions, clinical laboratories, pharmaceutical, agricultural, biotechnology, diagnostic and chemical companies. Their spending budgets can have a significant effect on the demand for our products. Spending budgets are based on a wide variety of factors, including the allocation of available resources to make purchases, funding from government sources which is highly uncertain, the spending priorities among various types of research equipment and policies regarding capital expenditures during economically uncertain periods. Any decrease in capital spending or change in spending priorities of our customers and potential customers could significantly reduce the demand for our products. Any delay or reduction in purchases by potential customers or our inability to forecast fluctuations in demand could harm our future operating results.

***We may not be able to convert our orders in backlog into revenue.***

Our backlog represents product orders from our customers that we have confirmed and for which we have not yet recognized revenue. We may not receive revenue from these orders, and the order backlog we report may not be indicative of our future revenue.

Many events can cause an order to be delayed or not completed at all, some of which may be out of our control. If we delay fulfilling customer orders, those customers may seek to cancel their orders with us. In addition, customers may otherwise seek to cancel or delay their orders even if we are prepared to fulfill them. If our orders in backlog do not result in sales, our operating results may suffer.

***Delivery of our products could be delayed or disrupted by factors beyond our control, and we could lose customers as a result.***

We rely on third-party carriers for the timely delivery of our products. As a result, we are subject to carrier disruptions and increased costs that are beyond our control. Any failure to deliver products to our customers in a safe and timely manner may damage our reputation and brand and could cause us to lose customers. If our relationship with any of these third-party carriers is terminated or impaired or if any of these third parties are unable to deliver our products, the delivery and acceptance of our products by our customers may be delayed, which could harm our business and financial results. The failure to deliver our products in a safe and timely manner may harm our relationship with our customers, increase our costs and otherwise disrupt our operations.

***We are, and may become, subject to governmental regulations that may impose burdens on our operations, and the markets for our products may be narrowed.***

We are subject, both directly and indirectly, to the adverse impact of government regulation of our operations and markets. For example, export of our instruments may be subject to strict regulatory control in a number of jurisdictions. The failure to satisfy export control criteria or to obtain necessary clearances could delay or prevent shipment of products, which could adversely affect our revenue and profitability. Moreover, the life sciences industry, which is expected to be one of the primary markets for our technology, has historically been heavily regulated. There are, for example, laws in several jurisdictions restricting research in genetic engineering, which may narrow our markets. Given the evolving nature of this industry, legislative bodies or regulatory authorities may adopt additional regulations that may adversely affect our market opportunities. Additionally, if ethical and other concerns surrounding the use of genetic information, diagnostics or therapies become widespread, there may be less demand for our products. Our business is also directly affected by a wide variety of government regulations applicable to business enterprises generally and to companies operating in the life science industry in particular. Failure to comply with government regulations or obtain or maintain necessary permits and licenses could result in a variety of fines or other censures or an interruption in our business operations which may have a negative impact on our ability to generate revenue and could increase the cost of operating our business.

***Our products could in the future be subject to regulation by the U.S. Food and Drug Administration or other domestic and international regulatory agencies, which could increase our costs and delay our commercialization efforts, thereby materially and adversely affecting our business and results of operations.***

Our products are not currently subject to U.S. Food and Drug Administration, or FDA, clearance or approval since they are not intended for use in the diagnosis or treatment of disease. However, in the future, certain of our products or related applications could be subject to FDA regulation, or the FDA's regulatory jurisdiction could be expanded to include our products. Even where a product is exempted from FDA clearance or approval, the FDA may impose restrictions as to the types of customers to which we or our partners can market and sell our products. Such regulation and restrictions may materially and adversely affect our business, financial condition and results of operations.

Many countries have laws and regulations that could affect our products. The number and scope of these requirements are increasing. Unlike many of our competitors, this is an area where we do not have expertise. We, or our other third-party sales and distribution partners, may not be able to obtain regulatory approvals in such countries or may incur significant costs in obtaining or maintaining our foreign regulatory approvals. In addition, the export by us of certain of our products, which have not yet been cleared for domestic commercial distribution, may be subject to FDA or other export restrictions.

***Doing business internationally creates operational and financial risks for our business.***

Conducting and launching operations on an international scale requires close coordination of activities across multiple jurisdictions and time zones and consumes significant management resources. If we fail to coordinate and manage these activities effectively, our business, financial condition or results of operations could be adversely affected. International operations entail a variety of risks, including challenges in staffing and managing foreign operations, tariffs and other trade barriers, unexpected changes in legislative or regulatory requirements of foreign countries into which we sell our products, difficulties in obtaining export licenses or in overcoming other trade barriers and restrictions

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resulting in delivery delays and significant taxes or other burdens of complying with a variety of foreign laws. In conducting our international operations, we will be subject to U.S. laws relating to our international activities, as well as foreign laws relating to our activities in other countries. Failure to comply with these laws may subject us to financial and other penalties in the U.S. and foreign countries that could impact our operations or financial condition.

Changes in the value of the relevant currencies may affect the cost of certain items required in our operations. Changes in currency exchange rates may also affect the relative prices at which we are able to sell products in the same market. Our revenue from international customers may be negatively impacted as increases in the U.S. dollar relative to our international customers' local currencies could make our products more expensive, impacting our ability to compete. Our costs of materials from international suppliers may increase as the value of the U.S. dollar decreases relative to their local currency. Foreign policies and actions regarding currency valuation could result in actions by the United States and other countries to offset the effects of such fluctuations. Such actions may adversely impact our financial condition and results of operations.

***If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired, which would adversely affect our business and our stock price.***

Ensuring that we have adequate internal financial and accounting controls and procedures in place to produce accurate financial statements on a timely basis is a costly and time-consuming effort that needs to be re-evaluated frequently. We may in the future discover areas of our internal financial and accounting controls and procedures that need improvement. Operating as a public company requires sufficient resources within the accounting and finance functions in order to produce timely financial information, ensure the level of segregation of duties, and maintain adequate internal control over financial reporting customary for a U.S. public company.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting to provide reasonable assurance regarding the reliability of our financial reporting and the preparation of financial statements for external purposes in accordance with U.S. generally accepted accounting principles. Our management does not expect that our internal control over financial reporting will prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud, if any, within our company will have been detected.

Pursuant to Section 404 of the Sarbanes-Oxley Act, we perform periodic evaluations of our internal control over financial reporting. While we have in the past performed this evaluation and concluded that our internal control over financial reporting was operating effectively, there can be no assurance that in the future material weaknesses or significant deficiencies will not exist or otherwise be discovered. In addition, if we are unable to produce accurate financial statements on a timely basis, investors could lose confidence in the reliability of our financial statements, which could cause the market price of our common stock to decline and make it more difficult for us to finance our operations and growth.

***Our ability to use net operating losses to offset future taxable income may be subject to substantial limitations.***

Under Section 382 of the Internal Revenue Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating losses, or NOLs, to offset future taxable income. We believe that we have had one or more ownership changes, as a result of which our existing NOLs are currently subject to limitation. Future changes in our stock ownership could result in additional ownership changes under Section 382. We may not be able to utilize a material portion of our NOLs, even if we attain profitability.

***Our sales cycle is unpredictable and lengthy, which makes it difficult to forecast revenue and may increase the magnitude of quarterly fluctuations in our operating results.***

The sales cycle for our sequencing instruments is lengthy because they are a major capital item and generally require the approval of our customers' senior management. This may contribute to substantial fluctuations in our quarterly operating results, particularly during the periods in which our sales volume is low. Because of these fluctuations, it is likely that in some future quarters our operating results will fall below the expectations of securities analysts or investors. If that happens, the market price of our stock would likely decrease. Past fluctuations in our quarterly operating results have resulted in decreases in our stock price. Such fluctuations also mean that investors may not be able to rely upon our operating results in any particular period as an indication of future performance.

***Our operations involve the use of hazardous materials, and we must comply with environmental, health and safety laws, which can be expensive and may adversely affect our business, operating results and financial condition.***

Our research and development and manufacturing activities involve the use of hazardous materials, including chemicals and biological materials, and some of our products include hazardous materials. Accordingly, we are subject to federal, state, local and foreign laws, regulations and permits relating to environmental, health and safety matters, including, among others, those governing the use, storage, handling, exposure to and disposal of hazardous materials and wastes, the health and safety of our employees, and the shipment, labeling, collection, recycling, treatment and disposal of products containing hazardous materials. Liability under environmental laws and regulations can be joint and several and without regard to fault or negligence. For example, under certain circumstances and under certain environmental laws, we could be held liable for costs relating to contamination at our or our predecessors' past or present facilities and at third-party waste disposal sites. We could also be held liable for damages arising out of human exposure to hazardous materials. There can be no assurance that violations of environmental, health and safety laws will not occur as a result of human error, accident, equipment failure or other causes. The failure to comply with past, present or future laws could result in the imposition of substantial fines and penalties, remediation costs, property damage and personal injury claims, investigations, the suspension of production or product sales, loss of permits or a cessation of operations.

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Any of these events could harm our business, operating results and financial condition. We also expect that our operations will be affected by new environmental, health and safety laws and regulations on an ongoing basis, or more stringent enforcement of existing laws and regulations. New laws or changes to existing laws may result in additional costs and may increase penalties associated with violations or require us to change the content of our products or how we manufacture them, which could have a material adverse effect on our business, operating results and financial condition.

***Our facilities in California are located near known earthquake faults, and the occurrence of an earthquake or other catastrophic disaster could cause damage to our facilities and equipment, which could require us to cease or curtail operations.***

Our facilities in the San Francisco Bay Area are located near known earthquake fault zones and are vulnerable to damage from earthquakes. We are also vulnerable to damage from other types of disasters, including fire, floods, power loss, communications failures and similar events. If any disaster were to occur, our ability to operate our business at our facilities would be seriously, or potentially completely, impaired. In addition, the nature of our activities could cause significant delays in our research programs and commercial activities and make it difficult for us to recover from a disaster. The insurance we maintain may not be adequate to cover our losses resulting from disasters or other business interruptions. Accordingly, an earthquake or other disaster could materially and adversely harm our ability to conduct business.

***Ethical, legal, privacy and social concerns surrounding the use of genetic information could reduce demand for our technology.***

Our products may be used to provide genetic information about humans, agricultural crops and other living organisms. The information obtained from our products could be used in a variety of applications which may have underlying ethical, legal, privacy and social concerns, including the genetic engineering or modification of agricultural products or testing for genetic predisposition for certain medical conditions. Governmental authorities could, for safety, social or other purposes, call for limits on or regulation of the use of genetic testing. Such concerns or governmental restrictions could limit the use of our products, which could have a material adverse effect on our business, financial condition and results of operations.

***Disruption of critical information technology systems or material breaches in the security of our systems could harm our business, customer relations and financial condition.***

Information technology ("IT") helps us operate efficiently, interface with customers, maintain financial accuracy and efficiency and accurately produce our financial statements. IT systems are used extensively in virtually all aspects of our business, including sales forecast, order fulfillment and billing, customer service, logistics, and management of data from running samples on our products. Our success depends, in part, on the continued and uninterrupted performance of our IT systems. IT systems may be vulnerable to damage from a variety of sources, including telecommunications or network failures, power loss, natural disasters, human acts, computer viruses, computer denial-of-service attacks, unauthorized access to customer or employee data or company trade secrets, and other attempts to harm our systems. Certain of our systems are not redundant, and our disaster recovery planning is not sufficient for every eventuality. Despite any precautions we may take, such problems could result in, among other consequences, disruption of our operations, which could harm our reputation and financial results.

If we do not allocate and effectively manage the resources necessary to build and sustain the proper IT infrastructure, we could be subject to transaction errors, processing inefficiencies, the loss of customers, business disruptions or the loss of or damage to intellectual property through security breach. If our data management systems do not effectively collect, store, process and report relevant data for the operation of our business, whether due to equipment malfunction or constraints, software deficiencies or human error, our ability to effectively plan, forecast and execute our business plan and comply with applicable laws and regulations will be impaired, perhaps materially. Any such impairment could materially and adversely affect our reputation, financial condition, results of operations, cash flows and the timeliness with which we report our internal and external operating results.

***Security breaches and other disruptions could compromise our information and expose us to liability, which would cause our business and reputation to suffer.***

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, our proprietary business information and that of our customers, suppliers and business partners, and personally identifiable information of our customers and employees, in our data centers and on our networks. The secure processing, maintenance and transmission of this information is critical to our operations. Despite our security measures, our IT infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance, faulty password management or other disruptions. Third parties may attempt to fraudulently induce employees or other persons into disclosing user names, passwords or other sensitive information, which may in turn be used to access our IT systems. Any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, disruption of our operations and damage to our reputation, which could adversely affect our business, revenues and competitive position.

***Regulations related to conflict minerals will cause us to incur additional expenses and could limit the supply and increase the costs of certain materials used in the manufacture of our products.***

We are subject to requirements under the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, or the Dodd-Frank Act, that require us to conduct diligence, and report whether or not our products contain conflict minerals. The implementation of these requirements could adversely affect the sourcing, availability and pricing of the materials used in the manufacture of components used in our products. Furthermore, the complex nature of our products requires components and materials that may be available only from a limited number of sources and, in some cases, from only a single source. We have incurred, and will continue to incur, additional costs to comply with the disclosure requirements, including costs related to conducting diligence procedures to determine the sources of conflict minerals that may

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be used or necessary to the production of our products and, if applicable, potential changes to components, processes or sources of supply as a consequence of such verification activities. We may face reputational harm if we determine that certain of our instruments contain minerals not determined to be conflict free or if we are unable to alter our processes or sources of supply to avoid using such materials. Reputational harm could adversely affect our business, financial condition or results of operations.

### ***Risks Related to Our Intellectual Property***

#### ***Failure to secure patent or other intellectual property protection for our products and improvements to our products may reduce our ability to maintain any technological or competitive advantage over our competitors and potential competitors.***

Our ability to protect and enforce our intellectual property rights is uncertain and depends on complex legal and factual questions. Our ability to establish or maintain a technological or competitive advantage over our competitors may be diminished because of these uncertainties. For example:

- we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications or issued patents;
- we or our licensors might not have been the first to file patent applications for these inventions;
- it is possible that neither our pending patent applications nor the pending patent applications of our licensors will result in issued patents;
- our patents or the patents of our licensors may not be of sufficient scope to prevent others from practicing our technologies, developing competing products, designing around our patented technologies or independently developing similar or alternative technologies;
- our and our licensors' patent applications or patents have been, are and may in the future be, subject to interference, opposition or similar administrative proceedings, which could result in those patent applications failing to issue as patents, those patents being held invalid or the scope of those patents being substantially reduced;
- we or our partners may not adequately protect our trade secrets;
- we may not develop additional proprietary technologies that are patentable; or
- the patents of others may limit our freedom to operate and prevent us from commercializing our technology in accordance with our plans.

The occurrence of any of these events could impair our ability to operate without infringing upon the proprietary rights of others or prevent us from establishing or maintaining a competitive advantage over our competitors.

#### ***Variability in intellectual property laws may adversely affect our intellectual property position.***

Intellectual property laws, and patent laws and regulations in particular, have been subject to significant variability either through administrative or legislative changes to such laws or regulations or changes or differences in judicial interpretation, and it is expected that such variability will continue to occur. Additionally, intellectual property laws and regulations differ among countries. Variations in the patent laws and regulations or in interpretations of patent laws and regulations in the United States and other countries may diminish the value of our intellectual property and may change the impact of third-party intellectual property on us. Accordingly, we cannot predict the scope of patents that may be granted to us, the extent to which we will be able to enforce our patents against third parties or the extent to which third parties may be able to enforce their patents against us.

#### ***Some of the intellectual property that is important to our business is owned by other companies or institutions and licensed to us, and changes to the rights we have licensed may adversely impact our business.***

We license from third parties some of the intellectual property that is important to our business. If we fail to meet our obligations under these licenses, these third parties could terminate the licenses. If the third parties who license intellectual property to us fail to maintain the intellectual property that we have licensed, or lose rights to that intellectual property, the rights we have licensed may be reduced or eliminated, which could subject us to claims of intellectual property infringement. Termination of these licenses or reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms, or could subject us to claims of intellectual property infringement in litigation or other administrative proceedings that could result in damage awards against us and injunctions that could prohibit us from selling our products. In addition, some of our licenses from third parties limit the field in which we can use the licensed technology. Therefore, in order for us to use such licensed technology in potential future applications that are outside the licensed field of use, we may be required to negotiate new licenses with our licensors or expand our rights under our existing licenses. We cannot assure you that we will be able to obtain such licenses or expanded rights on reasonable terms or at all. In addition, we have limited rights to participate in the prosecution and enforcement of the patents and patent applications that we have licensed. As a result, we cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. Further, because of the rapid pace of technological change in our industry, we may need to rely on key technologies developed or licensed by third parties, and we may not be able to obtain licenses and technologies from these third parties at all or on reasonable terms. The occurrence of these events may have a material adverse effect on our business, financial condition or results of operations.

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***The measures that we use to protect the security of our intellectual property and other proprietary rights may not be adequate, which could result in the loss of legal protection for, and thereby diminish the value of, such intellectual property and other rights.***

In addition to patents, we also rely upon trademarks, trade secrets, copyrights and unfair competition laws, as well as license agreements and other contractual provisions, to protect our intellectual property and other proprietary rights. Despite these measures, any of our intellectual property rights could be challenged, invalidated, circumvented or misappropriated. In addition, we attempt to protect our intellectual property and proprietary information by requiring our employees and consultants to enter into confidentiality and assignment of inventions agreements, and by entering into confidentiality agreements with our third-party development, manufacturing, sales and distribution partners, who may also acquire, develop and/or commercialize alternative or competing products or provide services to our competitors. For example, Roche has certain access to our trade secrets and other proprietary information pursuant to the Roche Agreement, subject to the confidentiality provisions thereof; however, Roche has also developed and commercializes its 454 Life Sciences sequencing systems and is developing alternative and potentially competing sequencing products through its recent acquisition of Genia Technologies. There can be no assurance, however, that such measures will provide adequate protection for our intellectual property and proprietary information. These agreements may be breached, and we may not have adequate remedies for any such breach. In addition, our trade secrets and other proprietary information may be disclosed to others, or others may gain access to or disclose our trade secrets and other proprietary information. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time consuming, and the outcome is unpredictable. Additionally, others may independently develop proprietary information and techniques that are substantially equivalent to ours. The occurrence of these events may have a material adverse effect on our business, financial condition or results of operations.

***Our intellectual property may be subject to challenges in the United States or foreign jurisdictions that could adversely affect our intellectual property position.***

Our pending, issued and granted U.S. and foreign patents and patent applications have been, are and may in the future be, subject to challenges by third parties asserting prior invention by others or invalidity on various grounds, through proceedings, such as interferences, reexamination or opposition proceedings. Addressing these challenges to our intellectual property has previously been, and any future challenges can be, costly and distract management's attention and resources. For example, we previously incurred significant legal expenses to litigate and settle a complaint seeking review of a patent interference decision of the U.S. Patent and Trademark Office. Additionally, as a result of these challenges, our patents or pending patent applications may be determined to be unpatentable to us, invalidated or unenforceable in whole or in part. Accordingly, adverse rulings from the relevant patent offices in these proceedings may negatively impact the scope of our intellectual property protection for our products and technology and may adversely affect our business.

***Some of our technology is subject to "march-in" rights by the U.S. government.***

Some of our patented technology was developed with U.S. federal government funding. When new technologies are developed with U.S. government funding, the government obtains certain rights in any resulting patents, including a nonexclusive license authorizing the government to use the invention for non-commercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise "march-in" rights to use or allow third parties to use our patented technology. The government can exercise its march-in rights if it determines that action is necessary because 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. In addition, our rights in such inventions are subject to government license rights and foreign manufacturing restrictions.

***We may become involved in legal proceedings to enforce our intellectual property rights.***

Our intellectual property rights involve complex factual, scientific and legal questions. We operate in an industry characterized by significant intellectual property litigation. Even though we may believe that we have a valid patent on a particular technology, other companies may have from time to time taken, and may in the future take, actions that we believe violate our patent rights. Legal actions to enforce these patent rights can be expensive and may involve the diversion of significant management time and resources. Our enforcement actions may not be successful, could give rise to legal claims against us and could result in some of our intellectual property rights being determined to be invalid or not enforceable.

***We could in the future be subject to legal proceedings with third parties who may claim that our products infringe or misappropriate their intellectual property rights.***

Our products are based on complex, rapidly developing technologies. We may not be aware of issued or previously filed patent applications belonging to third parties that mature into issued patents that cover some aspect of our products or their use. In addition, because patent litigation is complex and the outcome inherently uncertain, our belief that our products do not infringe third-party patents of which we are aware or that such third-party patents are invalid and unenforceable may be determined to be incorrect. As a result, third parties have claimed, and may in the future claim, that we infringe their patent rights and have filed, and may in the future file, lawsuits or engage in other proceedings against us to enforce their patent rights. In addition, as we enter new markets, our competitors and other third parties may claim that our products infringe their intellectual property rights as part of a business strategy to impede our successful entry into those markets. Patent litigation between competitors in our industry is common. Additionally, we have certain obligations to many of our customers to indemnify and defend them against claims by third parties that our products or their use infringe any intellectual property of these third parties. In defending ourselves against any of these claims, we have in the past incurred, and could in the future incur, substantial costs, and the attention of our management and technical personnel could be diverted. For example, we previously incurred significant legal expenses to litigate and settle a complaint alleging patent infringement. Even if we have an agreement to indemnify us against such costs, the indemnifying party may be unable to uphold its contractual obligations. To avoid or settle legal claims, it may be necessary or desirable in the future to obtain

licenses relating to one or more products or relating to current or future technologies, which could negatively affect our gross margins. We may not be able to obtain these licenses on commercially reasonable terms, or at all. We may be unable to modify our products so that they do not infringe the intellectual property rights of third parties. In some situations the results of litigation or settlement of claims may require that we cease allegedly infringing activities which could prevent us from selling some or all of our products. The occurrence of these events may have a material adverse effect on our business, financial condition or results of operations.

In addition, in the course of our business we may from time to time have access or be alleged to have access to confidential or proprietary information of others, which though not patented, may be protected as trade secrets. Others could bring claims against us asserting that we improperly used their confidential or proprietary information, or misappropriated their technologies and incorporated those technologies into our products. A determination that we illegally used the confidential or proprietary information or misappropriated technologies of others in our products could result in our having to pay substantial damage awards or be prevented from selling some or all of our products, which could adversely affect our business.

***We have not yet registered some of our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business.***

Some of our trademark applications may not be allowed for registration, and our registered trademarks may not be maintained or enforced. In addition, in the U.S. Patent and Trademark Office and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings.

***Our use of “open source” software could adversely affect our ability to sell our products and subject us to possible litigation.***

A portion of our products or technologies developed and/or distributed by us incorporate “open source” software, and we may incorporate open source software into other products or technologies in the future. Some open source software licenses require that we disclose the source code for any modifications to such open source software that we make and distribute to one or more third parties, and that we license the source code for such modifications to third parties, including our competitors, at no cost. We monitor the use of open source software in our products to avoid uses in a manner that would require us to disclose or grant licenses under our source code that we wish to maintain as proprietary, however there can be no assurance that such efforts have been or will be successful. In some circumstances, distribution of our software that includes or is linked with open source software could require that we disclose and license some or all of our proprietary source code in that software, which could include permitting the use of such software and source code at no cost to the user. Open source license terms are often ambiguous, and there is little legal precedent governing the interpretation of these licenses. Successful claims made by the licensors of open source software that we have violated the terms of these licenses could result in unanticipated obligations including being subject to significant damages, being enjoined from distributing products that incorporate open source software, and being required to make available our proprietary source code pursuant to an open source license, which could substantially help our competitors develop products that are similar to or better than ours and otherwise adversely affect our business.

#### ***Risks Related to Owning Our Common Stock***

***The price of our common stock has been, is, and may continue to be, highly volatile, and you may be unable to sell your shares at or above the price you paid to acquire them.***

The market price of our common stock is highly volatile, and we expect it to continue to be volatile for the foreseeable future in response to many risk factors listed in this section, and others beyond our control, including:

- actual or anticipated fluctuations in our financial condition and operating results;
  - announcements of technological innovations by us or our competitors;
  - announcements by our customers, partners or suppliers relating directly or indirectly to our products, services or technologies;
  - overall conditions in our industry and market;
  - addition or loss of significant customers;
  - changes in laws or regulations applicable to our products;
  - actual or anticipated changes in our growth rate relative to our competitors;
  - announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, capital commitments or achievement of significant milestones;
  - additions or departures of key personnel;
  - competition from existing products or new products that may emerge;
  - issuance of new or updated research or reports by securities analysts;
  - fluctuations in the valuation of companies perceived by investors to be comparable to us;
  - disputes or other developments related to proprietary rights, including patents, litigation matters and our ability to obtain intellectual property protection for our technologies;
  - announcement or expectation of additional financing efforts;
  - sales of our common stock by us or our stockholders;
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- share price and volume fluctuations attributable to inconsistent trading volume levels of our shares;
- reports, guidance and ratings issued by securities or industry analysts; and
- general economic and market conditions.

If any of the forgoing occurs, it would cause our share price or trading volume to decline. Stock markets in general and the market for companies in our industry in particular have experienced price and volume fluctuations that have affected and continue to affect the market prices of equity securities of many companies. These fluctuations often have been unrelated or disproportionate to the operating performance of those companies. These broad market and industry fluctuations, as well as general economic, political and market conditions such as recessions, interest rate changes or international currency fluctuations, may negatively impact the market price of our common stock. You may not realize any return on your investment in us and may lose some or all of your investment. In the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We have been a party to this type of litigation in the recent past and may be the target of this type of litigation again in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

***Future sales of our common stock could cause our share price to fall.***

We maintain a shelf registration statement on Form S-3 with the SEC pursuant to which we may, from time to time, sell up to an aggregate of \$150 million of our common stock, warrants or debt securities. We have in the past, and may in the future, establish "at-the-market" offerings pursuant to which we may offer and sell shares of our common stock. Any sales of securities under the registration statement will result in dilution of our stockholders and could cause our share price to fall.

In addition, the holders of a significant number of shares of our common stock are entitled to rights with respect to registration of such shares under the Securities Act pursuant to an investor rights agreement between such holders and us. If such holders, by exercising their registration rights, sell a large number of shares, they could adversely affect the market price for our common stock. If we file a registration statement for the purpose of selling additional shares to raise capital and are required to include shares held by these holders pursuant to the exercise of their registration rights, our ability to raise capital may be impaired. Such holders have waived their registration rights with respect to the sale of shares of our common stock pursuant to the registration statements on Form S-3.

***Concentration of ownership by our principal stockholders may result in control by such stockholders of the composition of our board of directors.***

Our existing significant stockholders, executive officers, directors and their affiliates beneficially own a significant number of our outstanding shares of common stock. As a result, these stockholders will be able to exercise a significant level of control over all matters requiring stockholder approval, including the election of directors. This control could have the effect of delaying or preventing a change of control of our company or changes in management and will make the approval of certain transactions difficult or impossible without the support of these stockholders.

***Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management and limit the market price of our common stock.***

Provisions in our certificate of incorporation and bylaws, as amended and restated, may have the effect of delaying or preventing a change of control or changes in our management. Our amended and restated certificate of incorporation and bylaws include provisions that:

- authorize our board of directors to issue, without further action by the stockholders, up to 50,000,000 shares of undesignated preferred stock and up to approximately 1,000,000,000 shares of authorized but unissued shares of common stock;
- require that any action to be taken by our stockholders be effected at a duly called annual or special meeting and not by written consent;
- specify that special meetings of our stockholders can be called only by our board of directors, the Chairman of the Board, the Chief Executive Officer or the President;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- establish that our board of directors is divided into three classes, Class I, Class II and Class III, with each class serving staggered terms;
- provide that our directors may be removed only for cause; and
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum.

These provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

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***Our development agreement with Roche may deter or reduce the number of potential acquirers thus reducing or placing negative pressure on our stock price.***

The Roche Agreement could make an acquisition of our company, which may be beneficial to our stockholders, less likely, whether or not we realize the expected benefits from the Roche Agreement. For example, the exclusive rights and licenses granted to Roche pursuant to the Roche Agreement, or our development, manufacturing and supply obligations pursuant to the Roche Agreement, may make an acquisition of our company less appealing to third parties that compete with Roche.

***Our large number of authorized but unissued shares of common stock may potentially dilute your stockholdings.***

We have a significant number of authorized but unissued shares of common stock. Our board of directors may issue shares of common stock from this authorized but unissued pool from time to time without stockholder approval, resulting in the dilution of our existing stockholders.

***We do not intend to pay dividends for the foreseeable future.***

We have never declared or paid any cash dividends on our common stock and do not intend to pay any cash dividends in the foreseeable future. In addition, the terms of our existing debt agreement restrict our ability to pay dividends on our common stock. We anticipate that we will retain all of our future earnings for use in the operation of our business and for general corporate purposes. Any determination to pay dividends in the future will be at the discretion of our board of directors. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any future gains on their investments.

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