PACBIO INVESTOR DAY

November 15, 2022

Agenda

7:00 am	**Breakfast / Revio + Onso demos**
8:15 am	**Welcome, agenda, safe harbor** *Todd Friedman, Director Investor Relations*
8:20 am	**Accelerating innovation in genomics** *Christian Henry, President + Chief Executive Officer*
8:50 am	**Unleashing HiFi, long-read sequencing at scale** *David Miller, VP Product Marketing*
9:15 am	**Delivering an extraordinary level of short-read accuracy + PacBio's roadmap** *Mark Van Oene, Chief Operating Officer*
9:35 am	**Unlocking the multi-billion-dollar revenue opportunity** *Dr. Jennifer Stone, VP Segment Marketing*
10:15 am	**Q&A #1 + Break** *Christian, Mark, David, Jennifer*
11:00 am	**Fueling the commercial engine** *Jeff Eidel, Chief Commercial Officer*
11:15 am	**Building exceptional quality at scale** *Mike Goloubef, SVP Manufacturing*
11:25 am	**Driving a sustainable P&L** *Susan Kim, Chief Financial Officer*
11:40 am	**Q&A #2** *Christian, Jeff, Mike, Susan*
12:10 pm	**Lunch + Break**
12:30 pm	**Shifting paradigms – lunch session** *Jonas Korlach, Chief Scientific Officer*
12:55 pm	**Closing remarks** *Christian Henry, President + Chief Executive Officer*
1:00 pm	**Adjourn**

Forward-looking statements

All statements in this presentation (and any accompanying oral presentation) that are not historical of fact are "forward-looking statements" within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, and the U.S. Private Securities Litigation Reform Act of 1995, including statements relating to future operating results, including revenue, margins, guidance, goals and operating plans; expectations with respect to development and commercialization timeframes; future availability, uses, accuracy, sensitivity, advantages, compatibility, pricing, specifications, quality or performance of, or benefits or expected benefits of using, PacBio products or technologies, including the Revio and Onso systems; throughput, scalability, affordability, coverage, run times, data, density, type and cost per genome, pricing, consumable requirements, number of genomes that can be sequenced per year; the use of NVIDIA GPUs and AI-enabled compute in the Revio system and related improvements in yield and accuracy; schedule flexibility and downtime; expected delivery timeframes; expectations regarding competition in the short-and long-read sequencing technologies markets; market sizes, market growth and market opportunities, as well as our ability to capture market share; expected use applications; expectations with respect to collaborations and partnerships, and other future events. Readers are cautioned not to place undue reliance on these forward-looking statements and any such forward-looking statements are qualified in their entirety by reference to the following cautionary statements. All forward-looking statements speak only as of the date of this presentation and are based on current expectations and involve a number of assumptions, risks and uncertainties that could cause the actual results to differ materially from such forward-looking statements, including, among others, challenges inherent in developing, manufacturing, launching, marketing and selling new products, and achieving anticipated new sales; challenges related to the testing, validation and commercialization of our products, including the fact that Revio and Onso are entering beta testing, are not yet commercially available, and remains subject to additional development and validation; potential product performance and quality issues and potential delays in development and delivery timelines; assumptions, risks and uncertainties related to the ability to attract new customers and retain and grow sales from existing customers; rapidly changing technologies and extensive competition in genomic sequencing that could make the products PacBio is developing obsolete or non-competitive; supply chain risks; customers and prospective customers curtailing or suspending activities utilizing our products; the impact of U.S. export restrictions on the shipment of PacBio products to certain countries; third-party claims alleging infringement of patents and proprietary rights or seeking to invalidate PacBio's patents or proprietary rights; and risks associated with macroeconomic and geopolitical conditions. Readers are strongly encouraged to read the full cautionary statements contained in the Company's filings with the Securities and Exchange Commission, including the risks set forth in the Company's Forms 8-K, 10-K, and 10-Q. The Company disclaims any obligation to update or revise any forward-looking statements, except as required by law.

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PacBio

Accelerating innovation in genomics

Christian Henry | President & Chief Executive Officer

November 15, 2022

Objectives for today

1. Outline our strategy for addressing the multi-billion-dollar revenue opportunity
2. Introduce latest sequencing technology that is poised to disrupt the market
3. Show that we have the right team and scale to deliver
4. Demonstrate our ability to create a long-term sustainable and profitable business

Five themes to take away from today's meeting

- Our long-term strategy is intended to drive growth, profitability, and shareholder value
- We believe our differentiated products and technologies will enable us to further penetrate the market, reach more customers, and drive our growth
- We address a large sequencing market and have a significant growth opportunity
- We have the leadership team and go-to-market infrastructure to win
- We believe we can achieve positive cash flow within forecast horizon

Our financial targets

Grow revenues 40-50% CAGR through 2026, or >$500M

Improve gross margins[1] to 55-60%+ by 2026

Achieve positive cash flow during 2026

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[1]Non-GAAP

How our technology will advance biology

We have the technology to address these today

…oncologists could provide a reference-grade genome for every oncology patient?

…researchers built a cell atlas representing all isoforms — enabling a new paradigm in gene expression?

…you could sequence 1 billion 1kb reads?

…you could get five "omes" in 1 run with 1 technology — genome, epigenome, chromatin, transcriptome, metagenome?

Mission

Enabling the promise of genomics to better human health

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Values

Be curious

Take action

Delight our customers

Execution matters

Work together

Who is PacBio?

2000
Founded

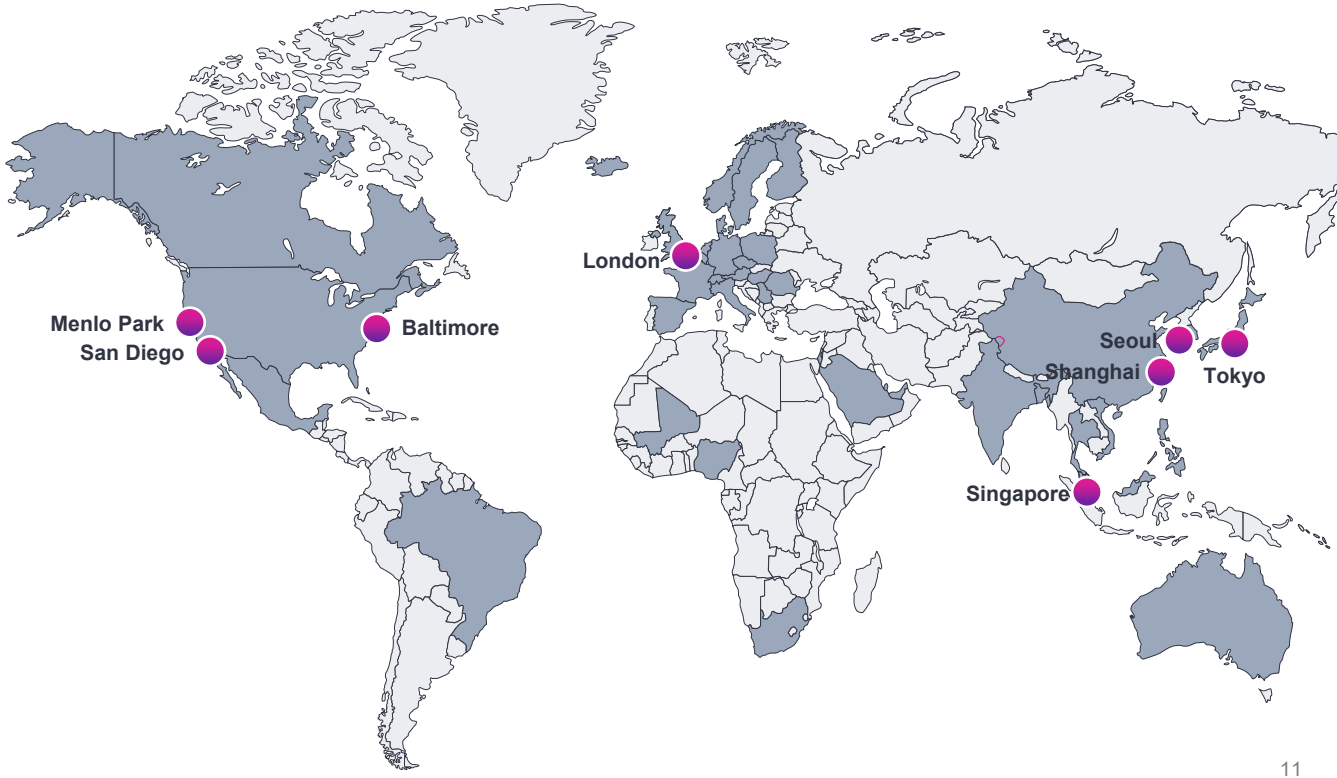
PACB
Publicly traded on NASDAQ since 2010

390+ exclusive issued US patents held[1]
representing continued innovation

770+ employees[2]
~225 Commercial
~420 Research + Ops

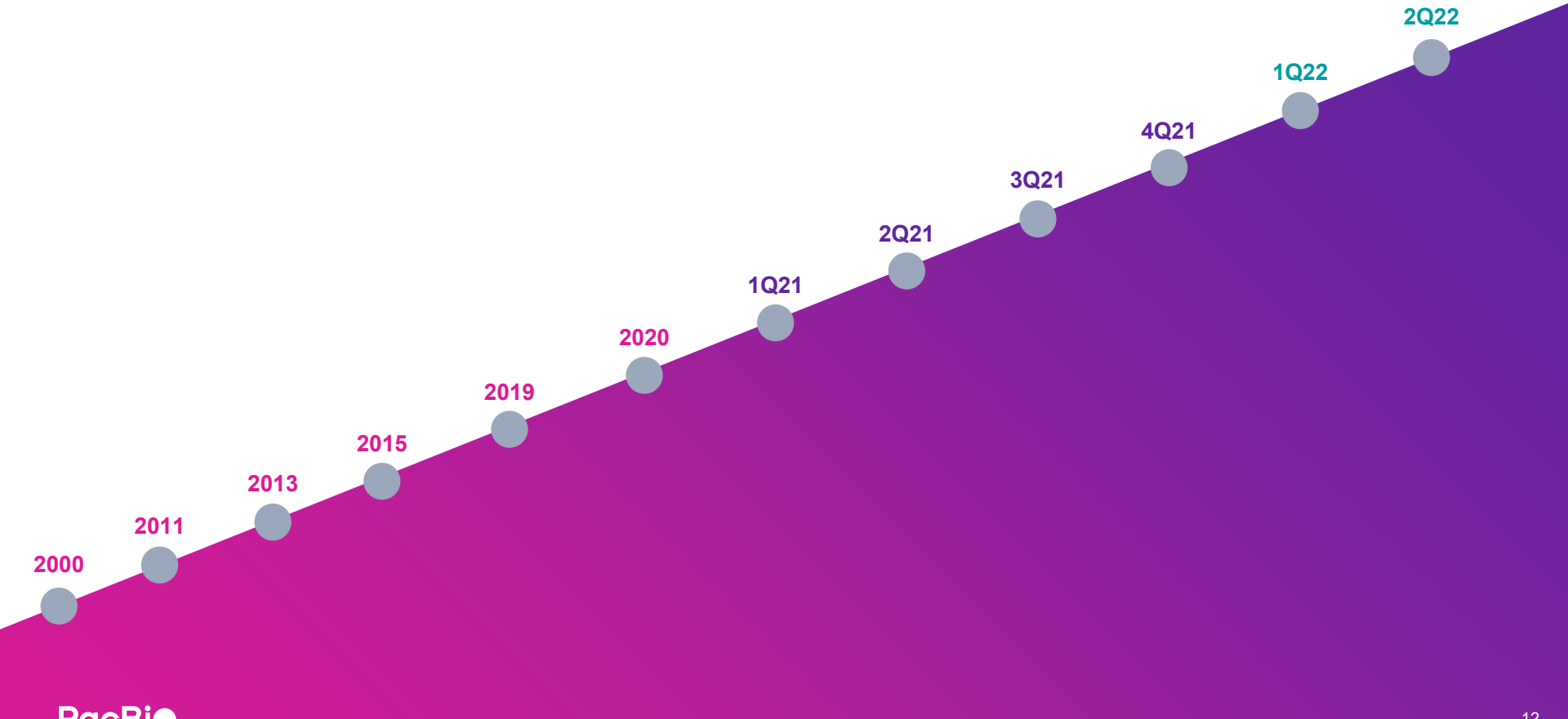
8 Global offices

~40 Countries with instrument installations



[1]As of 12/31/21
[2]As of 9/30/22

PacBio timeline + key milestones



PacBio timeline + key milestones

2000

Company founded

2011

RS I
75k ZMW

2013

RS II
150k ZMW

2015

Sequel
1M ZMW

2019

HiFi sequencing disrupts sequencing paradigm

Sequel II
8M ZMW

2020

Christian Henry named CEO

Sequel IIe
HiFi on instrument

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PacBio timeline + key milestones

2020

1Q21

$900M SoftBank investment

SoftBank

2Q21

HiFi yield improvements

T2T publication HiFi enables first complete human genome sequence

3Q21

OMNIOME

Acquired Omniome for differentiated, short-read SBB technology

circulomics

Acquired Circulomics to extend our capabilities in extraction + sample prep

4Q21

Launched HiFiViral, first kitted solution

1Q22

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PacBio timeline + key milestones

2Q21

3Q21

4Q21

1Q22

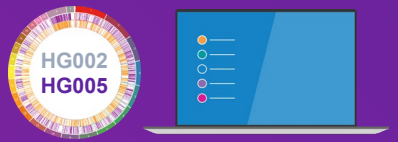
HiFi improvements in efficiency + usability

2Q22

Methylation calling on instrument

High-throughput sample setup

Gene editing QC workflow



4Q22

Revio launch

Onso beta

Strategic drivers

Human applications will drive market growth

Over the next decade, multiple *'omics* approaches will demonstrate clinical utility

Leveraging multiple technologies will enable PacBio to resolve more biological questions

A global, scaled business model is required to be competitive and maximize opportunity

Both differentiated technology and competitive economics are required to win

Strategic drivers

Human health applications will drive market growth

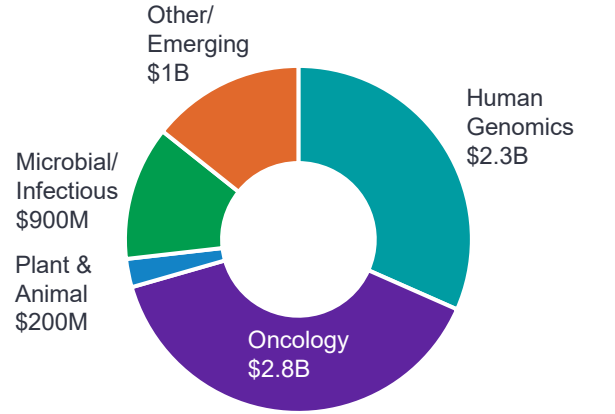
Sequencing market growth propelled by investment in human health-related segments

Expect 18% CAGR 2022–26[1]

2022

~$7B

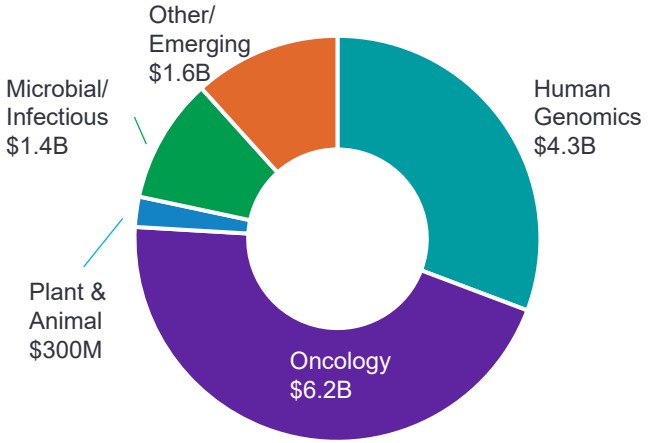
Estimated next gen sequencing market size in 2022



2026

~$14B

Estimated next gen sequencing market size in 2026

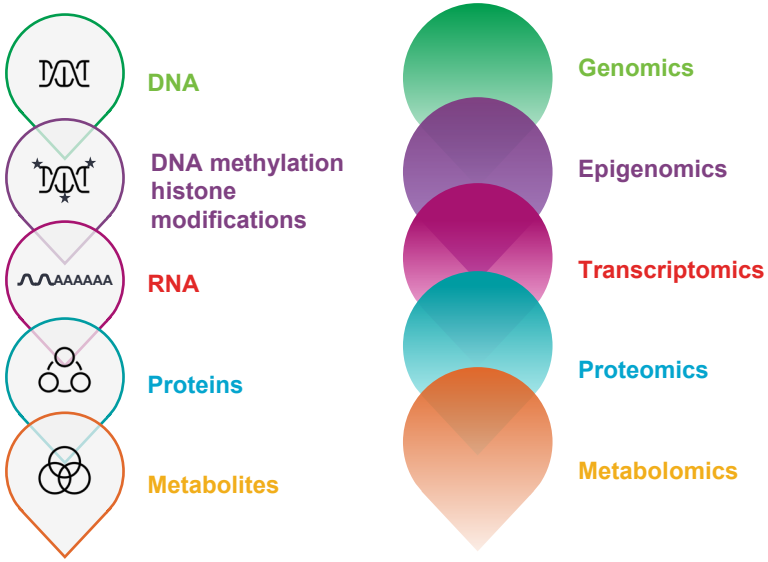


[1]Market sizes based in Decibio NGS manufacturers report 2021, peer company disclosures, and internal estimates

Strategic drivers

Over the next decade, clinicians will leverage insights from multiple '*omics* approaches

Integration of multiomics data



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Strategic drivers

Creating a “multiomics” portfolio

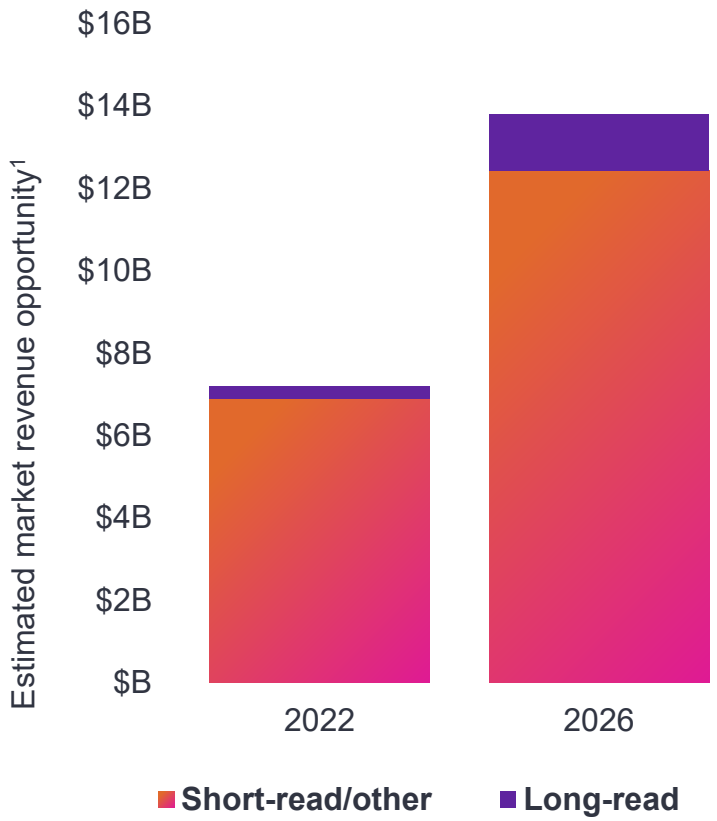
Multi-product offerings in each technology stack, dependent on the scale + applications of the user

Strategic drivers

Leveraging multiple technologies enables us to serve the entire sequencing market with highly differentiated products

Estimated long-read market growth >40% CAGR through 2026 with revenues >$1B

Short-read/other sequencing market estimated to grow mid-teens % CAGR through 2026 with revenues >$12B



[1]Based on internal estimates and external consensus estimates in addition to market sizes based in Decibio NGS manufacturers report 2021, peer company disclosures

Strategic drivers

A global, scaled business model is required to be competitive and maximize opportunity

8 Global locations

770+ Employees

~225 Commercial

~420 Research + Ops

As of 9/30/22

Strategic drivers

Differentiated technology and competitive economics are required to win

Revio™

1,300
Up to 1,300 HiFi human genomes/year

1–4
SMRT Cells in parallel

15×
Annual throughput vs Sequel IIe

Onso™

≥90%
Bases Q40+ (>99.99% accuracy)

400–500M
Reads

200 + 300
Cycle kits

Expected specs for Revio and Onso

Near-term 2023 strategy

Drive rapid adoption of Revio by converting existing Sequel II/IIe customers and attracting new PacBio customers

Demonstrate Onso's extraordinary level of accuracy in the field and show how it can transform research in needle-in-haystack applications

Progress development of ultra high-throughput and bench top long-read sequencers and next generation SBB sequencer

Leverage current infrastructure to drive toward positive cash flow

Expand partnerships across ecosystem and workflow to drive customer adoption of SBB and HiFi

How our strategy becomes reality

Scale

2020 | 2021 | 2022

- Create commercial scale
- Demonstrated power of HiFi
- Develop multi product / multiomic portfolio

Accelerate

2023 | 2024 | 2025

- Expand partner ecosystem
- Launch transformative systems
- Drive sample elasticity / consumable growth
- Push deeper into clinical

Durable growth

2026 | 2027

Expect to achieve positive cash flows

Expanded leadership team focused on driving growth

Christian Henry

PRESIDENT
+ CHIEF EXECUTIVE OFFICER

Experience:
11+ years of leadership at Illumina including CCO, CFO and General Manager; VP at Affymetrix

Brett Atkins, JD, PhD

GENERAL COUNSEL

Experience: 18+ years of corporate legal experience with companies in the life sciences industry

Catherience Ball, PhD

SVP, RESEARCH

Experience: 9+ years at AncestryDNA, most recently as Chief Scientific Officer

Jeff Eidel

CHIEF COMMERCIAL OFFICER

Experience: CEO and COO of Cradle Genomics; 13+ years at Illumina including head of corporate and business development

Michele Farmer, CPA

CHIEF ACCOUNTING OFFICER

Experience: 18+ years experience in accounting, finance, and auditing, including over 11 years of accounting experience at Illumina

Mike Goloubef

SVP, MANUFACTURING, QUALITY + SUPPLY CHAIN

Experience: 25+ years at ThermoFisher, Danaher/ABSciex,AppliedBiosystems/MDSSciex in Operations, Quality, Supply Chain

Susan Kim

CHIEF FINANCIAL OFFICER

Experience: 5+ years CFO experience at tech companies; investment banking at Morgan Stanley; semi-conductor process engineering

Jonas Korlach, PhD

COFOUNDER
+ CHIEF SCIENTIFIC OFFICER

Experience: 18+ years at PacBio;
Co-inventor of SMRT technology

David Miller

VP, PRODUCT MARKETING

Experience: 5+ years at Illumina leading marketing teams for high throughput sequencing;

Genomics Facility Project Leader at Garvan Institute of Medical Research

Chris Seipert

VP, CUSTOMER EXPERIENCE

Experience: 12+ years at PacBio across various functions ranging from instrument engineering and manufacturing, to field service, and most recently as head of sales for Americas and EMEA regions

Jennifer Stone, PhD

VP, SEGMENT MARKETING

Experience: 12+ years at Illumina leading oncology marketing & population health teams; research fellow at Mass Gen hospital & Post-Doc at the Broad institute

Stephen Turner, PhD

COFOUNDER +CHIEF TECHNICAL OFFICER

Experience: Cofounder of PacBio and key inventor behind PacBio's sequencing technology

Mark Van Oene

CHIEF OPERATING OFFICER

Experience: 15+ years of sales and leadership at Illumina including CCO, GM Americas at Illumina

Natalie Welch

CHIEF PEOPLE OFFICER

Experience: 14+ years in human resources and development at PacBio

Denis Zaccarin, PhD

SVP, DEVELOPMENT

Experience: 18+ years at PacBio managing development of long-read sequencers

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CHAIRMAN of the BOARD

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PacBio

Unleashing HiFi, long-read sequencing at scale

David Miller | Vice President, Product Marketing

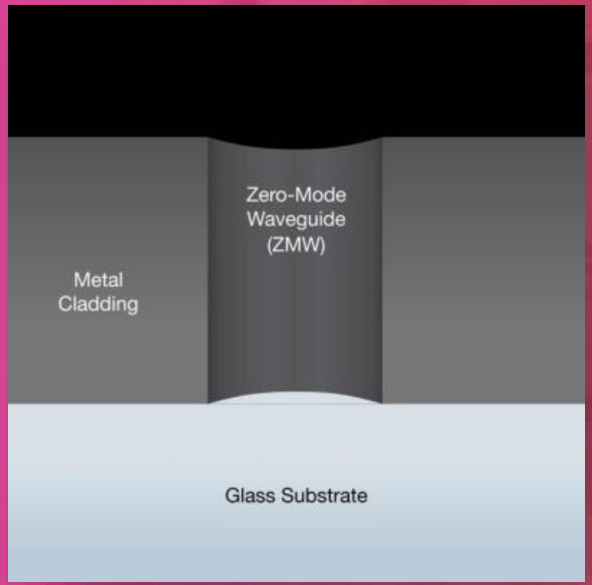
November 15, 2022

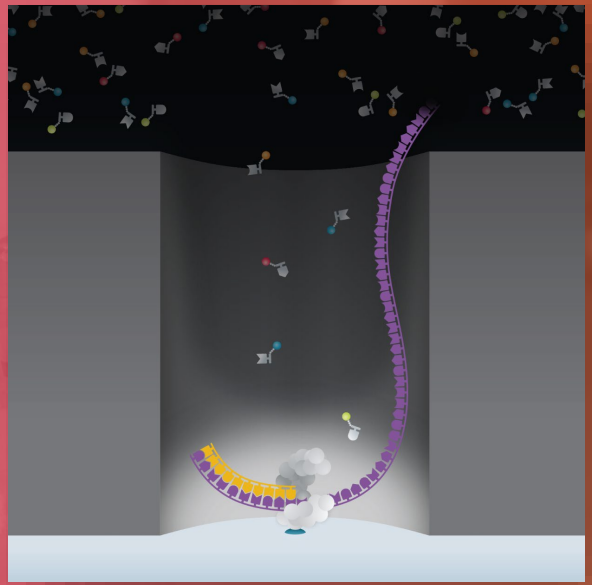
Goals of session

1. Introduce the Revio system which leverages industry-leading SMRT and HiFi technology
2. Show how we're creating an ecosystem around Revio and HiFi that will catalyze further adoption
3. Explain how Revio offers differentiated customer experience vs other long read solutions

SMRT (single molecule, real time) sequencing to read long DNA fragments

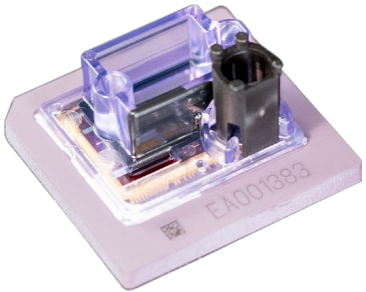
Zero-mode waveguide (ZMW) metallic, semi-conductor-based nanostructures are used for highly sensitive detection



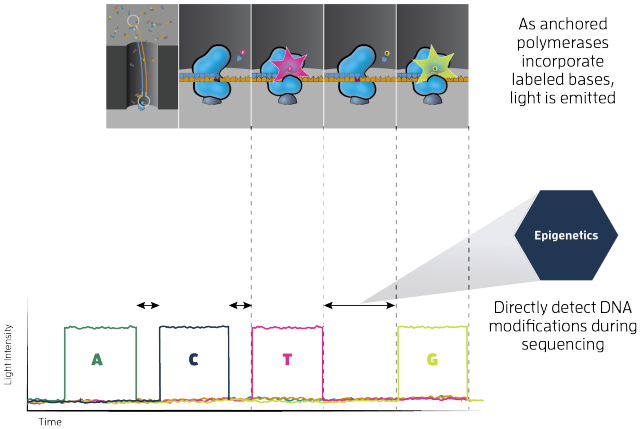


HiFi sequencing continues to transform genomics

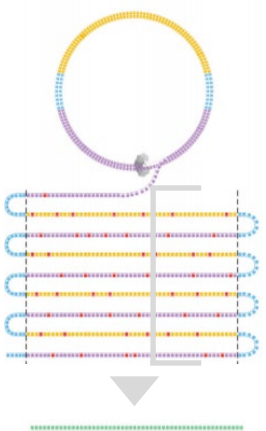
SMRT Cell



What is HiFi sequencing?



>100 kb reads



HiFi read
99.9% accuracy

HiFi provides an optimal combination of read length and accuracy

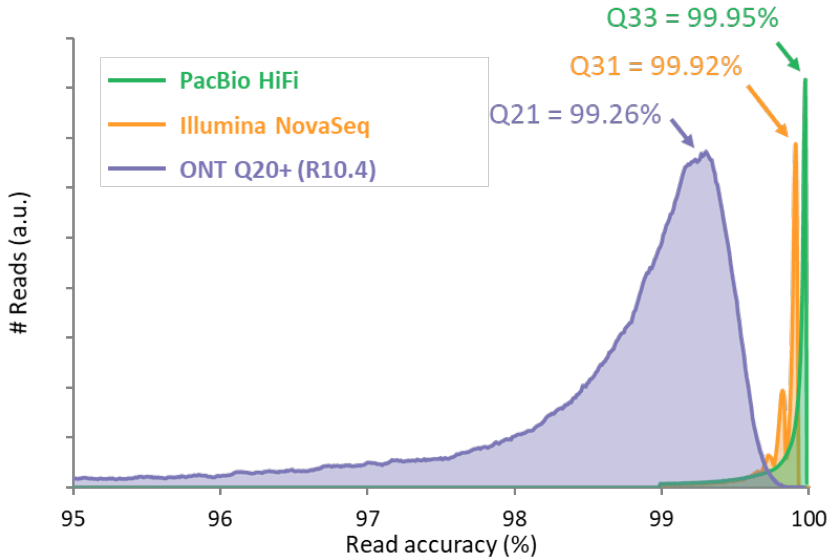
100× longer than short reads

Short-read NGS:
150–200 bp

PacBio HiFi:
15,000–20,000 bp

Drawn to scale

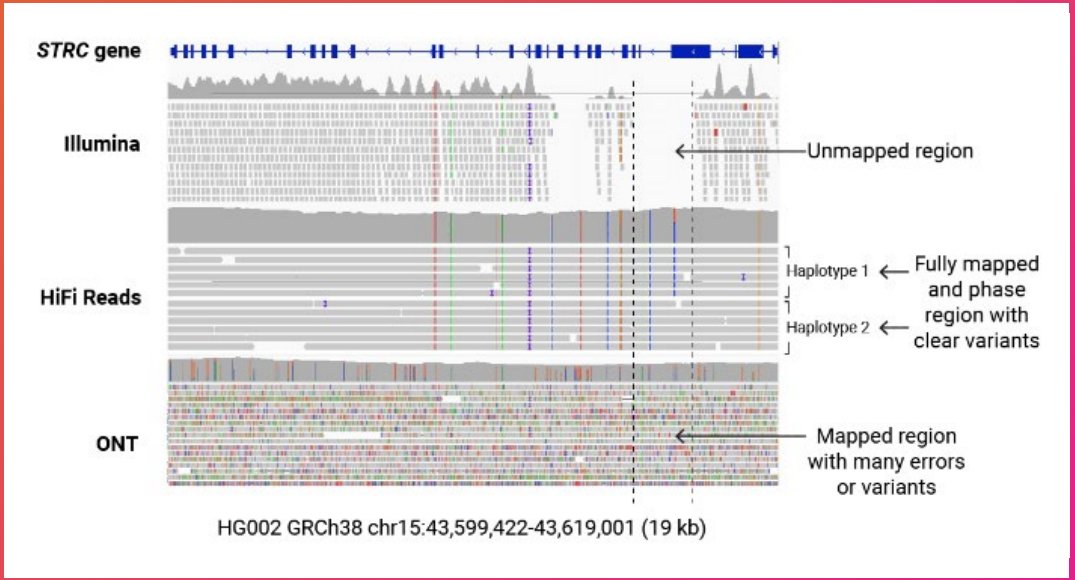
10× more accurate than other long-read approaches



PacBio HiFi: HG003 18 kb library, Sequel II system chemistry 2.0, precisionFDA *Truth Challenge* V2
Illumina: HG002 2×150 bp NovaSeq library, precisionFDA *Truth Challenge* V2
ONT: Q20+ chemistry (R10.4, Kit 12), Oct 2021 GM24385 dataset release

PacBio

HiFi reads provide a clear and complete view of the genome



- Even coverage; no GC bias
- Genome completeness, including methylation
- Extraordinary accuracy
- Allele resolution, long-range phasing
- Extraordinary performance for all variant classes

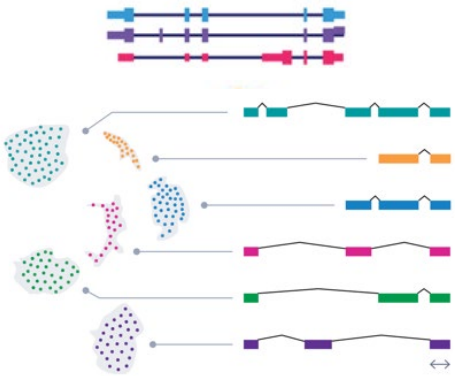
HiFi sequencing continues to transform genomics

Genomes

First telomere-to-telomere assemblies

Nurk et al. (2022) *Science*. **376**(6588):44-53.

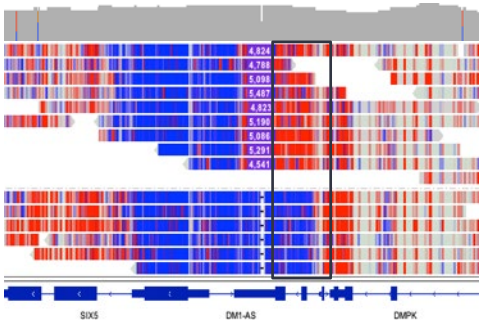
Transcriptomes



First single-cell isoform catalogs

Al'Khafaji et al. (2021). *bioRxiv*. doi:10.1101/2021.10.01.462818.

Epigenomes



First directly phased methylomes

Cheung et al. (2022). *medRxiv*. doi.org:10.110/2022.09.12.22279739.

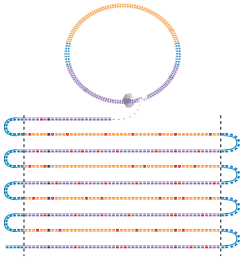
Over a decade of on market technological innovation

RS I /RS II
75k/150k ZMW

2011-2013: PacBio launches groundbreaking single-molecule sequencing platform; named top innovation by *The Scientist* magazine

Sequel
1M ZMW

2015: PacBio launches the Sequel system



HiFi

2018: HiFi enables ultra-high accuracy at long read lengths and establishes PacBio as leader in sequencing accuracy

Sequel II/IIe
8M ZMW

2019 | 2020: PacBio launches Sequel II and Sequel IIe

Revio
25M x4 ZMW

2023: PacBio expected to launch Revio enabling the sub-$1k long-read genome at scale

Increased throughput **>10,000-fold**

Increased read length **>100-fold**

PacBio

Revio™ system

HiFi sequencing
at scale

100M
ZMW/run

24-hr
sequencing time

360 Gb
HiFi yield per run

Revio system designed from the ground up to deliver HiFi at scale

Scale

25M ZMW SMRT Cell

4 independent stages

24-hour cycle time

Ease of use

50% reduction in consumables

Load-in-advance capability

No N_2 requirement

Compute power

20× the relative compute power

GPU-based architecture

Google DeepConsensus on board

Affordability

$1,000* human HiFi genome

<1 minute to load instrument

>50% decrease in file size

"It'll be a game changer in the medical genomics field." — Seo Jeong-sun, Chairman, Macrogen

*U.S. list price is $995 for sequencing reagents for one Revio SMRT Cell, which has an expected yield of 90 Gb, equivalent to a 30× human genome. Price may vary by region.

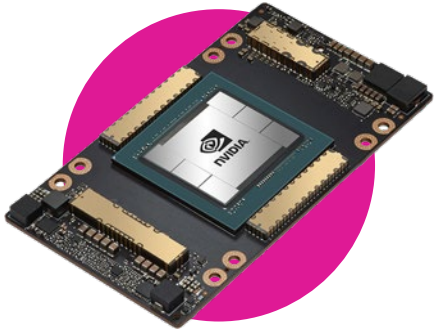
~20× increase in relative compute performance[1]

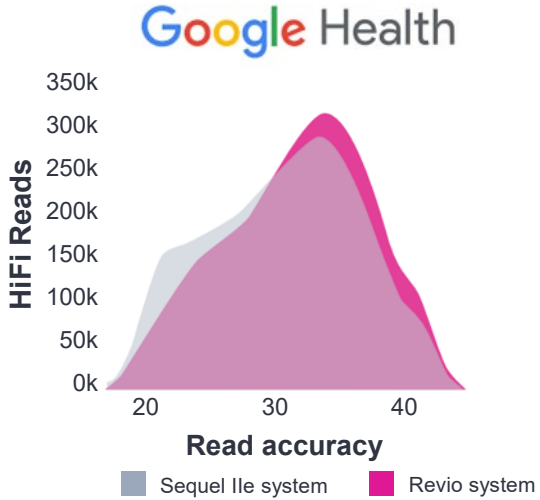
First PacBio system to include GPU on board

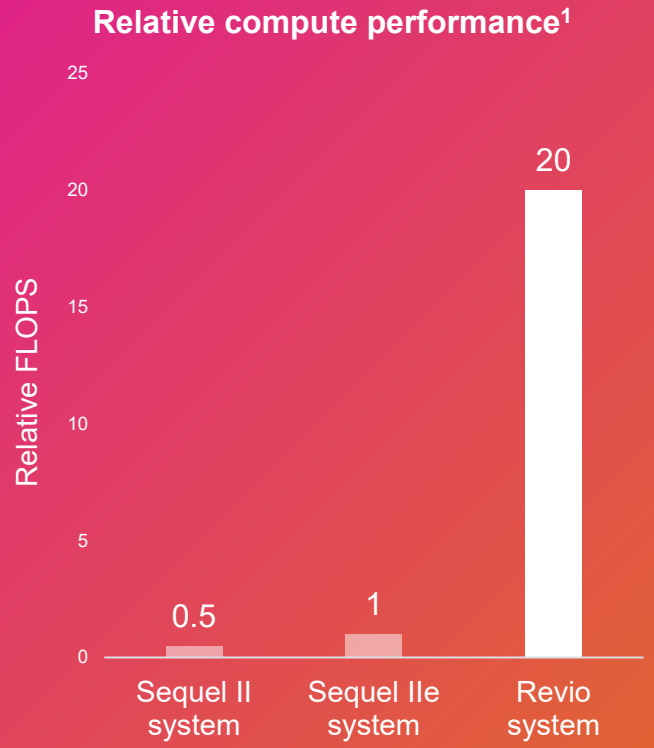
Leverages the latest NVIDIA GPUs

Enables Google Health DeepConsensus on board

Optimized BAM format reduces file size by 50%







1. Floating point operations per second (FLOPS) of all instrument computers, relative to Sequel IIe

Revio system will be transformative for HiFi sequencing

1,300
WGS/year[1]

>3×
Output per SMRT Cell

1-4
SMRT Cells in **parallel**

24-hr
Run time

50%
Fewer **consumables**

"The most important genome sequencer to launch since the Illumina GAIIx"
Brian Krueger, PhD Vice President, Lab R&D, Everly Health

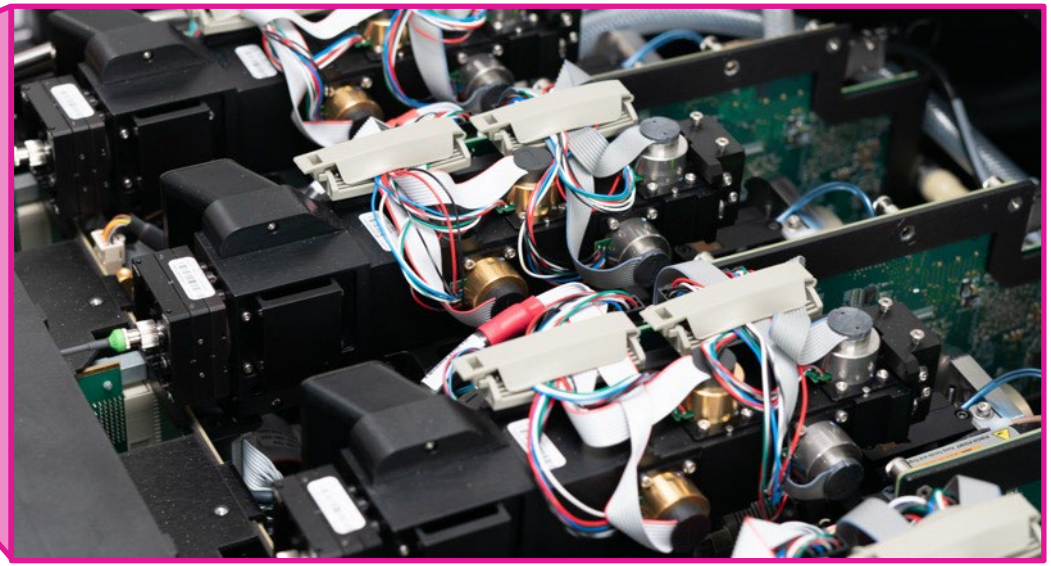
PacBio

[1]Assumes 30x coverage for WHG

Genomes per year at 30×

Four independent stages enable flexible experimental designs

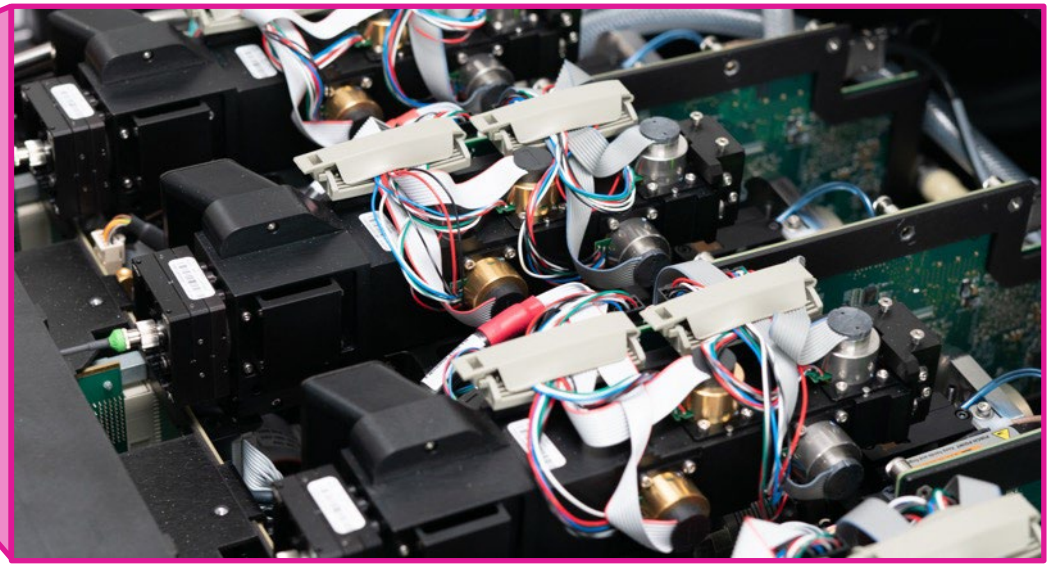
Cell 1	Cell 2	Cell 3	Cell 4
Normal	Tumor	Tumor	MAS-Seq



PacBio

Four independent stages enable flexible experimental designs

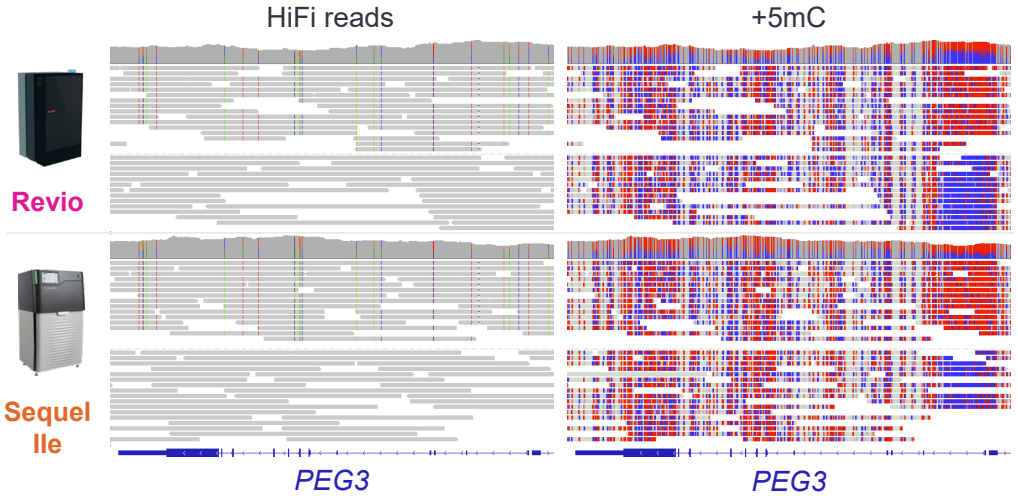
Sample	HiFi yield (Gbp)	Median QV	HiFi reads	HiFi insert length	% Q30 bases
HG003	94.02	Q33	5,401,433	17,406	91.8%
HG004	95.55	Q33	5,853,767	16,323	91.5%
HG002	89.39	Q32	5,104,734	17,510	91.4%
oak+mistletoe	94.51	Q33	5,935,133	15,924	92.0%

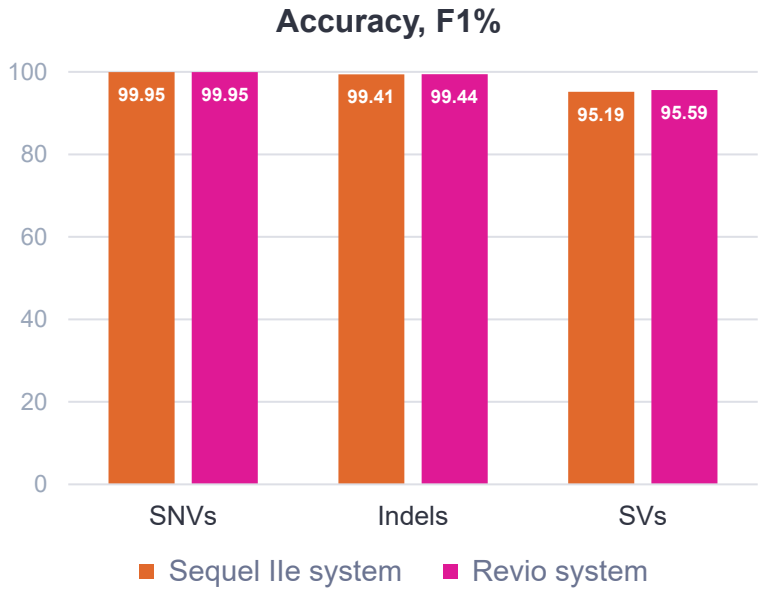


PacBio

Revio system has excellent read and methylation accuracy

Revio **matches the precision FDA-winning variant calling performance** of Sequel IIe

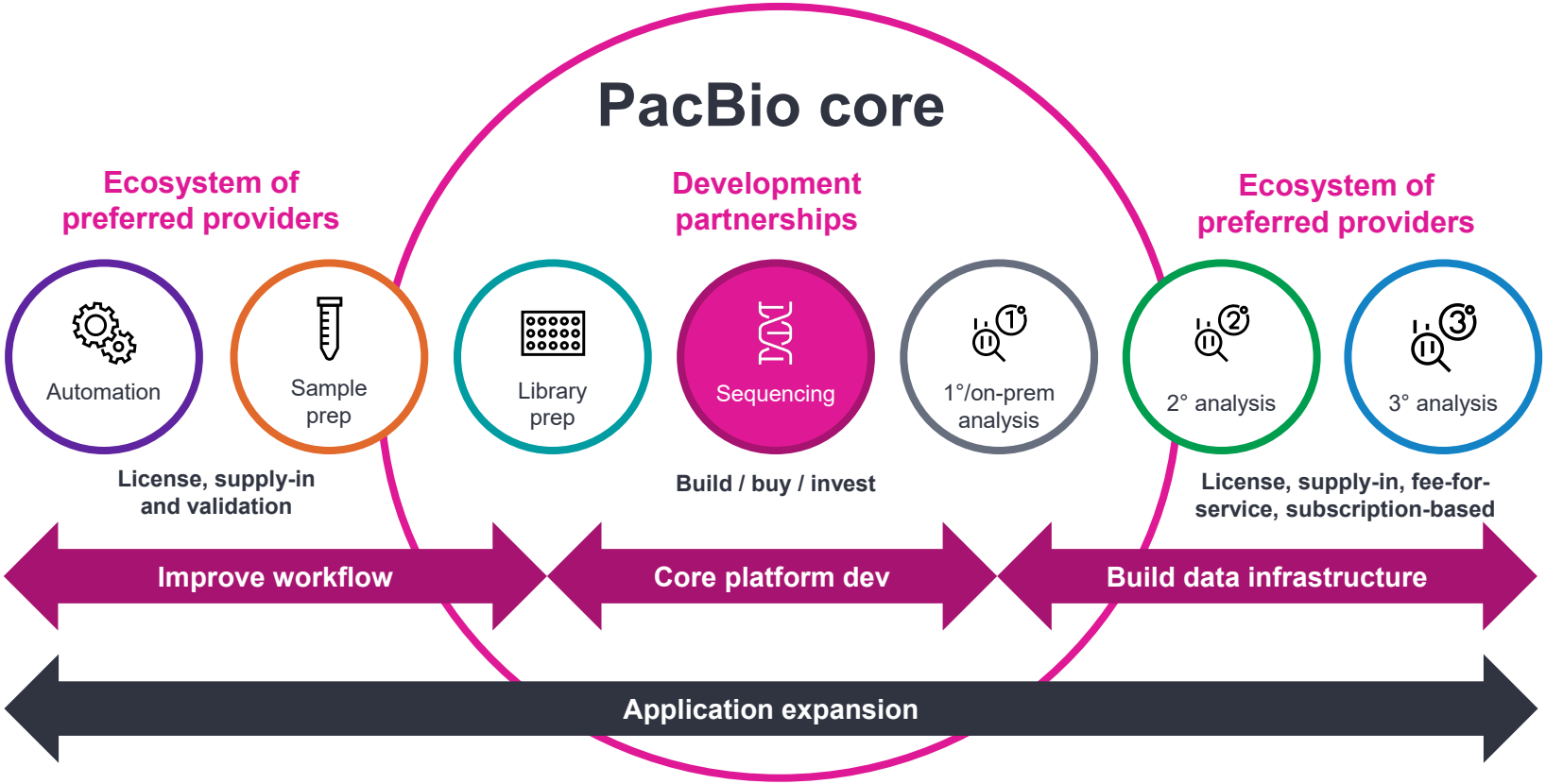




HG002 at maternally imprinted *PEG3* locus
https://downloads.pacbcloud.com/public/revio/2022Q4/HG002-rep3/analysis/HG002.m84005_220827_014912_s1.GRCh38.bam
https://downloads.pacbcloud.com/public/dataset/HG002-CpG-methylation-202202/HG002.GRCh38.haplotagged.bam

PacBio

Ecosystem, partnership + core platform development



Building the ecosystem around the sequencer

HAMILTON

MIROCULUS

diagenode

BROAD INSTITUTE

TWIST BIOSCIENCE

Google Health

DNAnexus

DNASTACK

Automation

Sample prep

Library prep

Sequencing

1°/on-prem analysis

2° analysis

3° analysis

Revio outperforms other long read technology in most categories

	PacBio Revio[1]	High Throughput Nanopore
Price/genome	$995	>$1,200[2]
Read length	15–18 kb	10–100 kb (typical N50 of 20–44 kb[3])
Read quality	Q33	Q21[4]
Variant calling	SNVs, indels, SVs	SNVs, SVs[5]
Run time	24 hrs	72 hrs[6]
Annual throughput	1,300 WGS	2,500 WGS[7]
Ease of use/service/support	+++	

1. Revio specs available at pacb.com/revio/.
2. 60x genome from 2 flowcells. ONT application specification recommends 60x. nanoporetech.com/applications/investigation/snvs-phasing. Least expensive flowcell price is $600 (requires $1.7M purchase). store.nanoporetech.com/us/promethion-flow-cell-packs-r10-4-1-m-version.html
3. doi: 10.1101/2022.07.09.499321; nature.com/articles/s41588-021-00865-4; https://www.nature.com/articles/s42003-022-03953-1
4. labs.epi2me.io/gm24385_q20_2021.10/
5. Poor indel performance for ONT - nature.com/articles/s41592-021-01299-w
6. nanoporetech.com/products/specifications - “72-hour run time”
7. nanoporetech.com/products/specifications - “max 4,992 flowcells / yr” = 2,496 WGS / yr at 2 flowcells each

Native long reads provide significant advantages over synthetic alternatives

Synthetic "CLR"

Need to oversample, potentially up to 7×, costing **$1,400 to $4,200 per genome**[1]

Repeats tend to be one of the *"most challenging"* categories for the technology to tackle *"…not going to get 100 percent."*

Introduces errors to sequencing data – you **get the wrong answer**

Complex library prep and informatics process

Shorter read lengths (6–7 kb)

Limited applications

Peer reviewed publications: 0

"What we are doing is, when we have a long read, we have a number of short reads with marks, and we are merging them together using those marks."

Revio – HiFi

Lower cost: Sub-$1,000 per genome at list price

Native single molecule sequencing

Methylation included with every sequencing run

Industry-leading accuracy

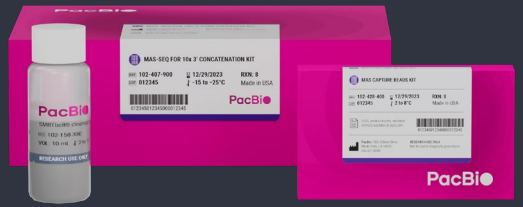
Longer read lengths

Peer reviewed SMRT/HiFi publications: >9,000

Easier sample prep and bioinformatics

1 Based on estimates from Longas
genomeweb.com/sequencing/illumina-shares-data-complete-long-read-tech-stays-mum-technical-details#.Y2ATIHbMKCg
pacb.com/blog/the-hifi-difference-getting-the-right-answer/

MAS-Seq for 10x *Chromium Single Cell* 3’ kit



Application kit containing oligos and reagents for generating MAS-Seq libraries from 10x *Chromium Single Cell* 3’ cDNA (8 reactions)

MAS-Seq + Revio kitted solution gives 40× more throughput vs previous Iso-Seq methods

	MAS-Seq kit (Revio)[1]	MAS-Seq kit (SQ II/IIe)	Homebrew method	Pre-MAS or homebrew
Library preparation	2 days	2 days	3 days	1 day
Sequencing time	24 hours	34 hours	34 hours	24 hours
Read yield (HiFi)	100 million	40 million	20 million	2.5 million
Throughput increase	40×	16×	8×	Baseline
Software	8-hr SMRT Link	8-hr SMRT Link	36-hr community software	24-hr community software

“We were already using MAS-Seq homebrew method for single-cell RNA sequencing. The robust and higher yield on the MAS-Seq kit is a game changer.”
— MAS-Seq early access customer at UK research institution

“Little is known about isoforms in cardiovascular diseases at the single-cell level. MAS-Seq can help uncover that diversity.”
— Cardiovascular researcher at Ivy League institution

“My dream is to do single cell and spatial transcriptomics with long reads – with MAS-Seq, now I can do it and discover how alternative splicing contributes to tumor heterogeneity and therapeutic responses!”
— Researcher studying cancer and aging process at major research institution

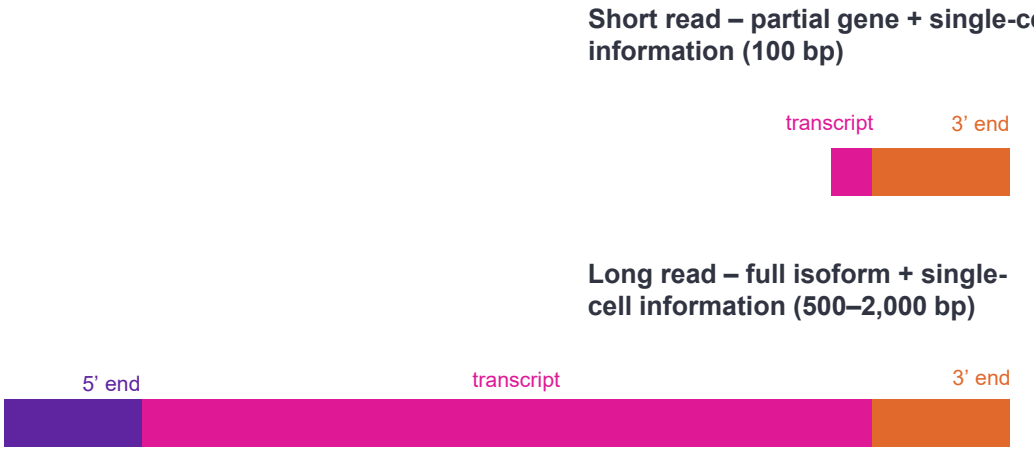
[1]Expected product specs for Mas-Seq kit on Revio

Short reads cannot sequence the whole transcript in single-cell RNA-Seq

Long-read advantage over short reads

Short-read scRNA-Seq can only reveal gene-level information.
But isoforms — not genes — are often the biological drivers of disease.

"It is clear that in the next few years long-read sequencing will become the de facto gold standard in transcriptomics research. Long-reads provide a much more comprehensive view of gene regulation and are already enabling us to uncover novel mechanisms associated with developmental disorders." — Neurology PI at major research institution



A single human gene produces multiple RNA isoforms through alternative splicing

PacBio

Delivering an extraordinary level of short-read accuracy + PacBio's roadmap

Mark Van Oene | Chief Operating Officer

November 15, 2022

Goals of session

1. Introduce Onso — what we believe is the most accurate short-read sequencer
2. Illustrate how accuracy can play an important role in oncology and other applications
3. Share our long-term product roadmap

Accuracy is the hallmark of who we are + matters across many applications

SBB sequencing

Promises significant accuracy improvements over conventional NGS approaches

HiFi sequencing

Delivers long reads with the highest accuracy[1] — even in hard-to-sequence regions

- Complex disease research
- Plant + animal sciences
- Neuroscience
- Immunology
- Rare + inherited disease
- Gene editing confirmation
- Infectious disease/microbiology
- Targeted clinical panels
- Therapy selection
- Noninvasive prenatal screening
- Early-stage cancer screening
- Cancer recurrence monitoring

PacBio

[1]doi: 10.1038/s41587-021-01049-5

SBB enables extraordinary accuracy for short-read sequencing

Onso™

Key platform specifications

- 400–500 M reads
- At launch:
  200 cycle kit – 1×200 and 2×100
  300 cycle kit – 2×150
- ≥90% bases Q40+
- Conversion kits for existing short-read ecosystem

PacBio

Expected specs for Onso

Beta commenced, planned for first half 2023 global ship

Onso™

Broad Institute
Weill Cornell
Corteva Agriscience

2022	2023
Beta testing	Accepting orders and planned shipping
Q4 2022	**1H 2023**
Announced on October 25	Accepting order Q1 2023
Shipped beta units	Planned shipping first half of 2023

How does SBB perform with *needle-in-a-haystack* applications like liquid biopsy and ctDNA?

Sequencing of the same low VAF samples (0.05% to 0.5%) libraries on two platforms, SBB and SBS

DNA/sample	SeraCare ctDNA v3
Sequencing kits	200 cycle – PE 2 x 100
Library prep kits	SureSelect XTHS2 library prep
	Agilent Comprehensive Cancer Panel
Library conversion kit	Onso™ library conversion kit; Converts P5/P7 libraries to PacBio A/P1
QC	Library quant kit
	Spike in sequencing control kit
Instruments	Onso sequencing platform
	Onso cluster generator

PacBio

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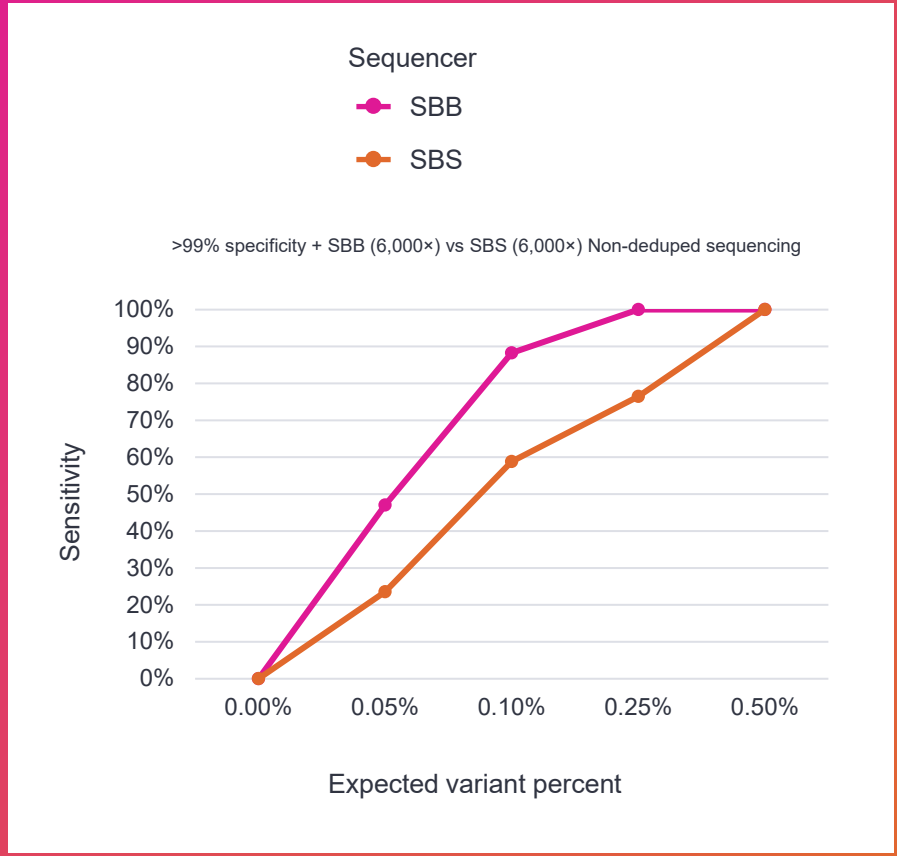
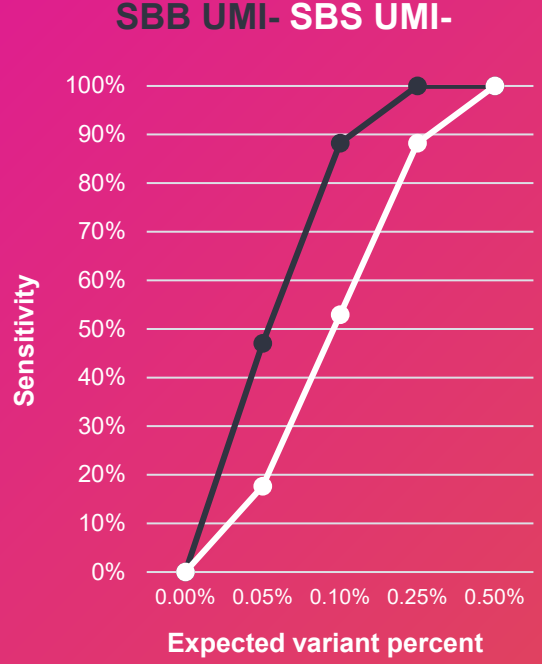
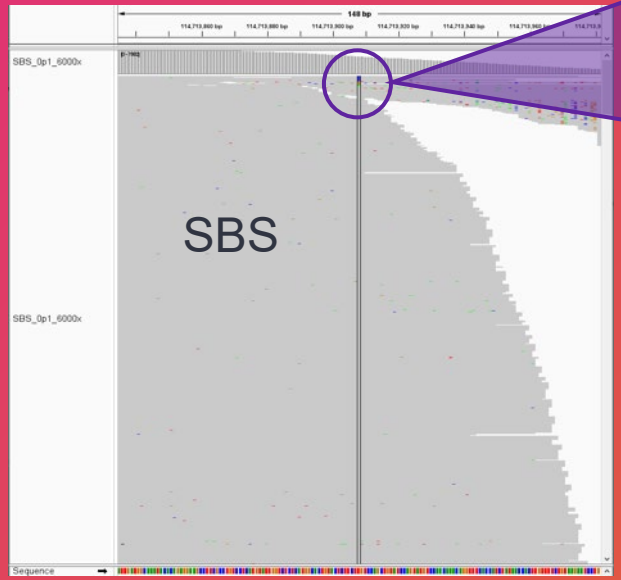


SBB demonstrates improvements in sequencing efficiency

6,000× non-UMI SBB sequencing exceeds 6,000× SBS non-UMI sequencing at 0.05%, 0.1% and 0.25%



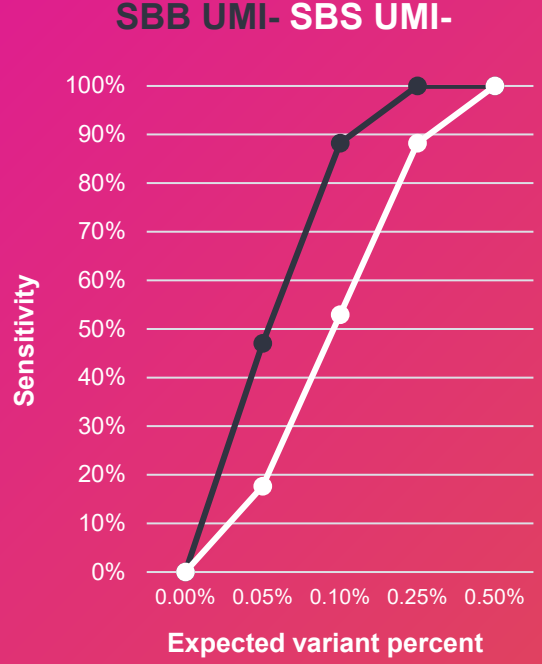
0.1% VAF NRAS Q61R SBS 6,000x



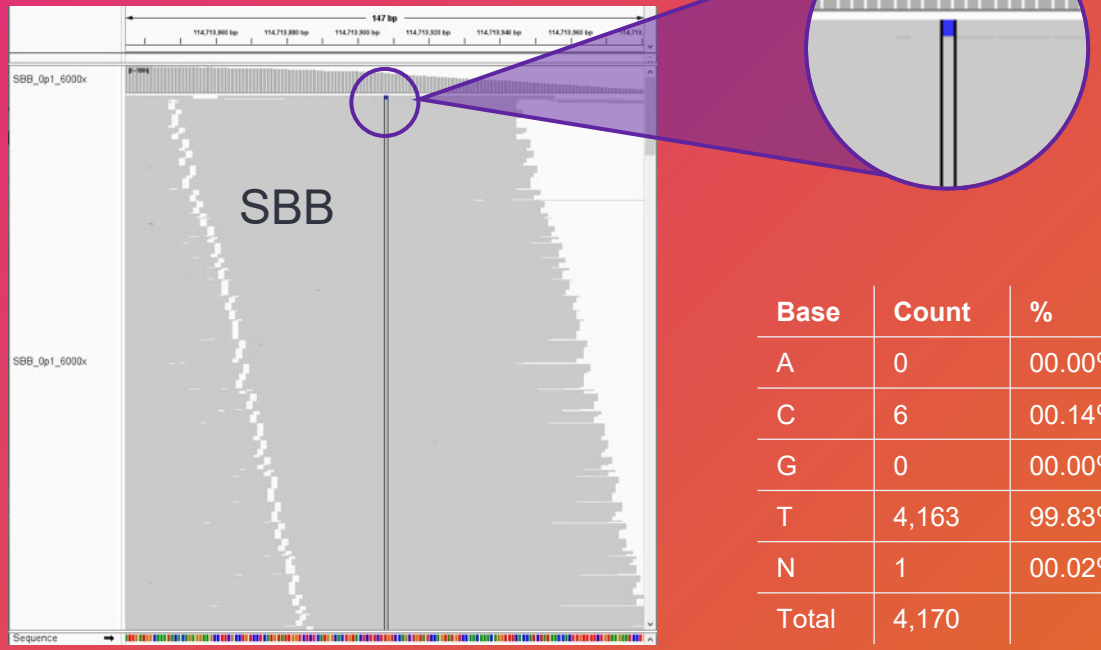
Base	Count	%
A	3	00.05%
C	9	00.15%
G	5	00.09%
T	5,771	99.71%
N	0	00.00%
Total	5,788	

SBB demonstrates improvements in sequencing efficiency

6,000× non-UMI SBB sequencing exceeds 6,000× SBS non-UMI sequencing at 0.05%, 0.1% and 0.25%



0.1% VAF NRAS Q61R SBB 6,000x

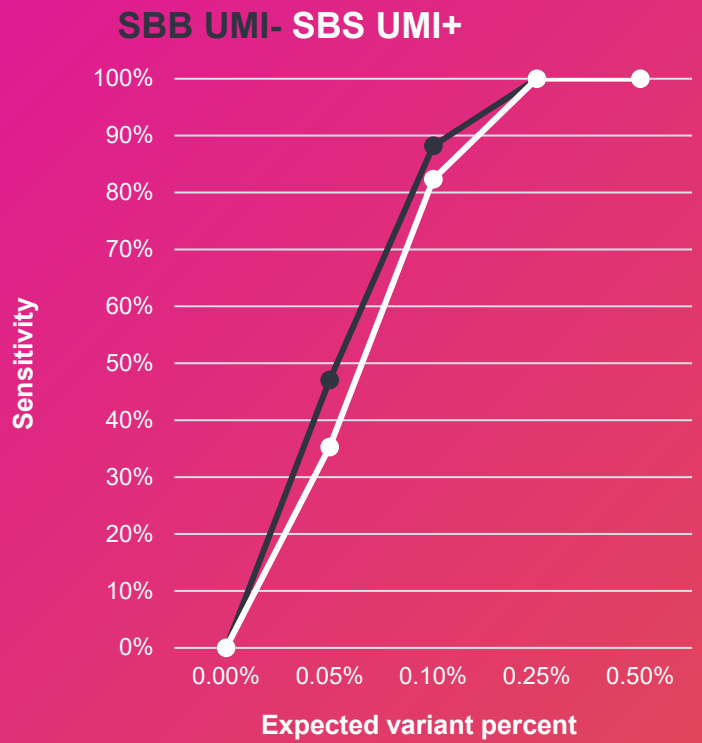


Base	Count	%
A	0	00.00%
C	6	00.14%
G	0	00.00%
T	4,163	99.83%
N	1	00.02%
Total	4,170	

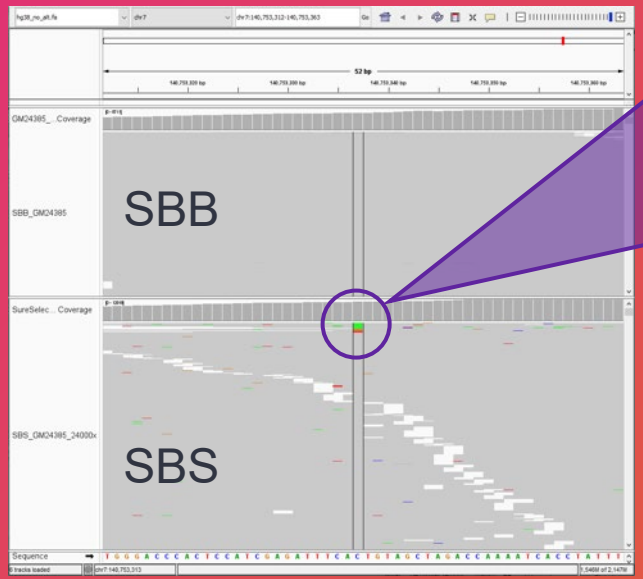
PacBio

SBB demonstrates >4× improvement in sequencing efficiency

6,000× non-UMI SBB sequencing exceeds >24,000× SBS UMI sequencing at 0.05% and 0.1%



Wild type (no mutation)



Base	SBB counts	SBS counts
A	0	11
C	3,272	11,323
G	0	4
T	0	3
N	2	0
Total	3,274	11,341

Revio™

1,300
WGS/year

1–4
SMRT Cells in parallel

24-hr
Run time

50%
Fewer consumables

>3×
Output per SMRT Cell

Onso™

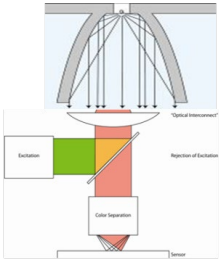
400–500M
Reads

200 + 300
Cycle kits

48-hr
Run time

≥90%
Bases Q40+

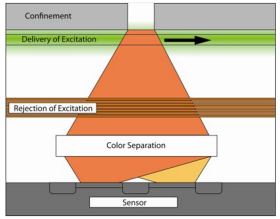
SMRT® Cell product progression



RS II
150k ZMW

On market

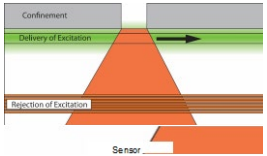
Development of 8” line for fused silica processing with 193 nm lithography



Sequel
1M ZMW

On market

Integrated illumination and collection path on CMOS image sensors (CIS) enables scaling and reduces instrument cost



Sequel II/IIe
8M ZMW

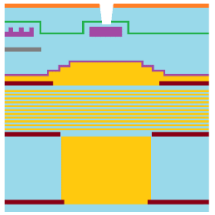
On market

Pitch shrink with new node of CIS and chemistry

Revio
25M x4 ZMW

Planned shipping 1Q23

Pixel shrink with backside illuminated (BSI) CIS flow cell for lower sample amounts



Ultra HT
>2X ZMW / Cell

In development

Shrink with BSI-Stacked 300 mm silicon

Next gen+

Research/ proposals

Smaller pixels (~1 um)

Higher resolution

High speed CIS sensor

On-chip signal processing

Convert legacy 200 mm to 300 mm

Building a multiproduct portfolio

On Market

Sequel IIe
~90 genomes/yr

Addressable applications
Limited # of human genomes
Low-throughput isoforms
Plant + animal genomes

2023

Revio
1,300 long-read genomes

Onso
400–500M Q40 reads

Addressable applications
Larger scale genome projects
High throughput isoforms
Plant + animal genomes
MRD and liquid biopsy research
Metagenomics
Portion of population programs

Future portfolio

Benchtop long-read
1,000s of targeted panels

Revio
1,300 long-read genomes

Onso
400–500M Q40 reads

High-throughput long-read
10s of thousands of genomes

High-throughput short-read
Billions of Q40 reads

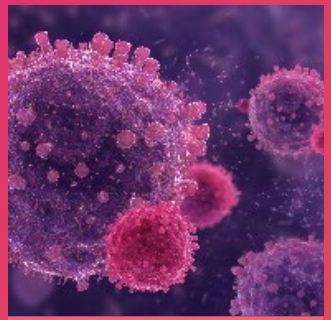
Addressable applications
Largest scale genome projects
High throughput isoforms
Plant + animal genomes
MRD and liquid biopsy research
Metagenomics
Population programs
Liquid biopsy LDT labs
Distributed long-read panels

PacBio

Products to address the entirety of the sequencing landscape

Human Genomics

Oncology



Microbiology / Infectious Disease

Plant and Animal

Emerging

PacBio

Unlocking the multi-billion-dollar revenue opportunity

Dr. Jennifer L. Stone | Vice President, Segment Marketing

November 15, 2022

Goals of session

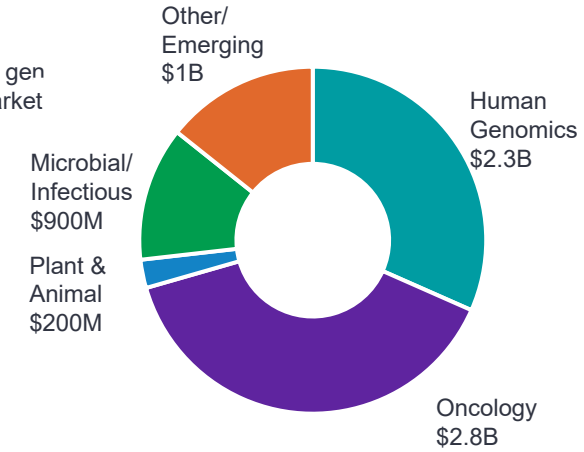
1. Outline market segments, dynamics, and growth assumptions
2. Articulate how PacBio will address these markets and gain share

Sequencing market expected to hit nearly $14B by 2026 with ~18% CAGR[1]

2022

~$7B

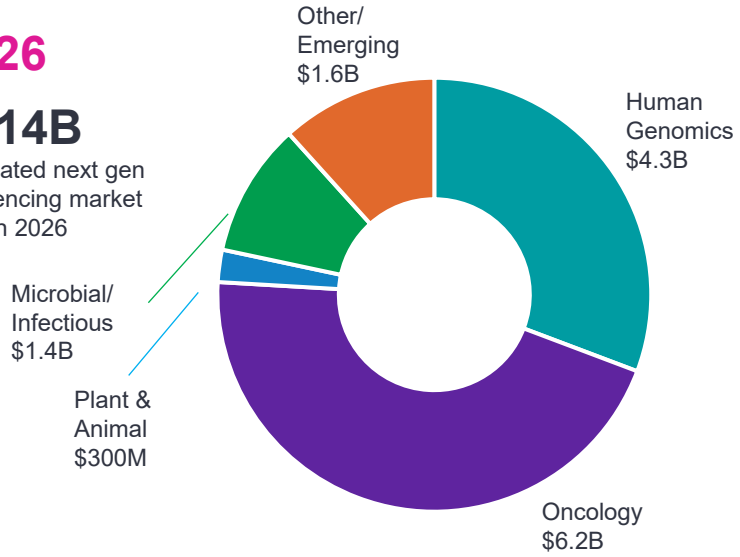
Estimated next gen sequencing market size in 2022



2026

~$14B

Estimated next gen sequencing market size in 2026



Growth predicted across all segments, with highest growth in human germline and oncology

Increased investment in translational studies, including population scale programs and expansion of sequencing into routine clinical testing

[1]Based in Decibio NGS manufacturers report 2021, peer company disclosures, and internal estimates

Human genomics and oncology applications drive revenue growth

	2022 % of PacBio revenue	PacBio estimated CAGR 2022–2026	2022 PacBio market penetration	2026 estimated PacBio market penetration
Human genomics	<40%	~50%	<5%	<10%
Oncology	<10%	~75%	<1%	<5%

PacBio

Market size estimates based on Decibio NGS manufacturers report 2021, peer company disclosures, and internal estimates

PacBio growth is driven by taking market share in WGS, RNA analysis and targeted sequencing in *human genomics* and *oncology* segments

PacBio market share projected to double over 2022–26

		2026 SAM*	Market share 2022	Market share 2026
1	**Whole human genomes** Genetic disease, PopGen or cohorts Research or clinical More value for money; now scalable on Revio	~$2.3B	<5%	~10%
2	**The future of RNA is full-length isoforms** Single cell or bulk Essential for understanding function + associations Increasing utility in rare disease	~$2.7B	<2%	~5%
3	**Targeted applications** SBB opens market for *"needle in a haystack"* applications Challenging genes and dark regions in human genomics	~$5B	<1%	~1%

DeciBio 2021 NGS manufacturers report; internal analysis
*Excludes ~$500M from exome seq in 2026

Whole Human Genomes

Market drivers

Expansion of clinical WGS within routine care for rare disease and other genetic conditions

Consolidation of panels, legacy tech onto WGS backbone

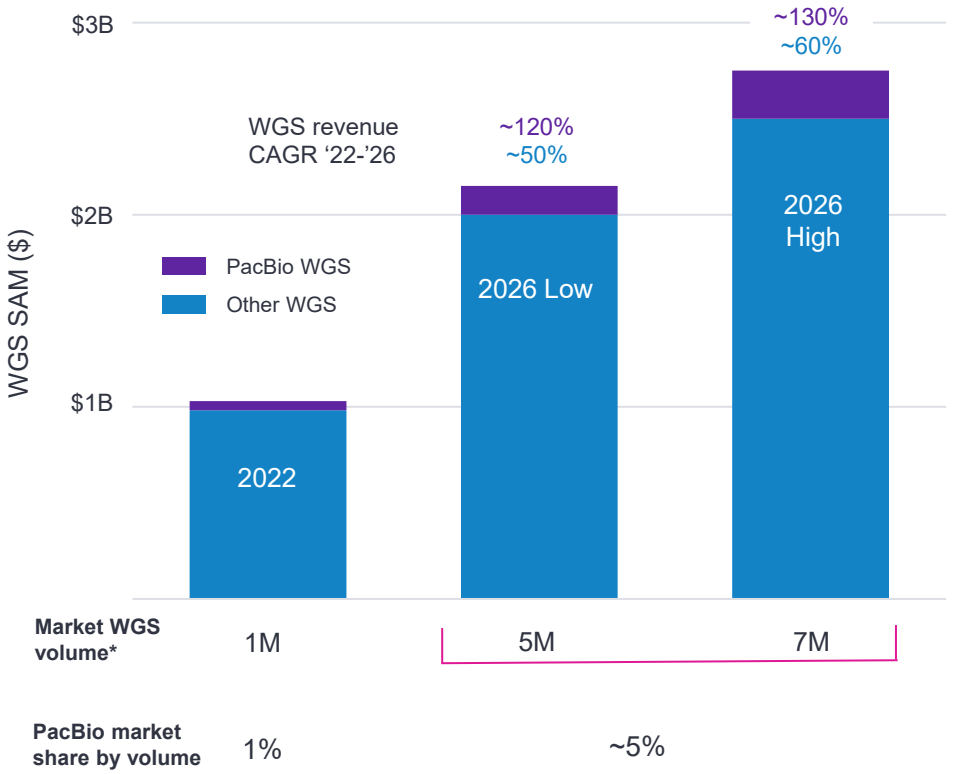
Improved analysis tools and workflows

Conversion of large research cohorts and PopGen projects to WGS (from exomes, arrays, etc.)

PacBio

Continued market growth of WGS

PacBio adoption expected to outpace market growth

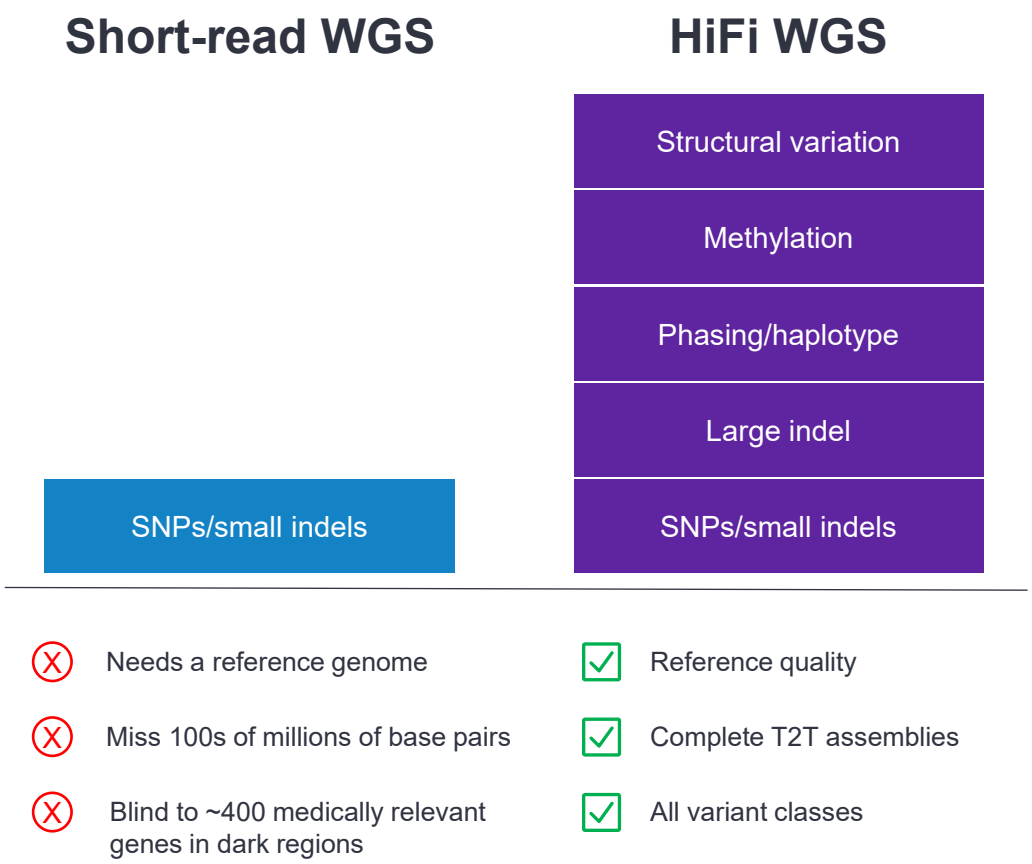


DeciBio 2021 NGS manufacturers report; internal analysis
*Standardized on 1 30x whole-genome equivalent = 1 WGS in this analysis

Whole Human Genomes

Not all genome sequence data is created equally

PacBio HiFi delivers a new class of WGS



PacBio

Rare disease is the tip-of-the-spear use case for clinical WGS

PacBio HiFi WGS already offering insights to improve Dx yield

Whole Human Genomes

Market need in rare disease

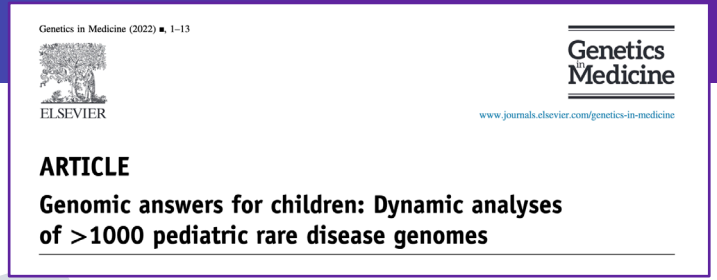
Rare disease affects ~30M Americans + 300–400M people worldwide[1]

Dx yield plateauing at ~50% despite short-read WES + WGS[2]

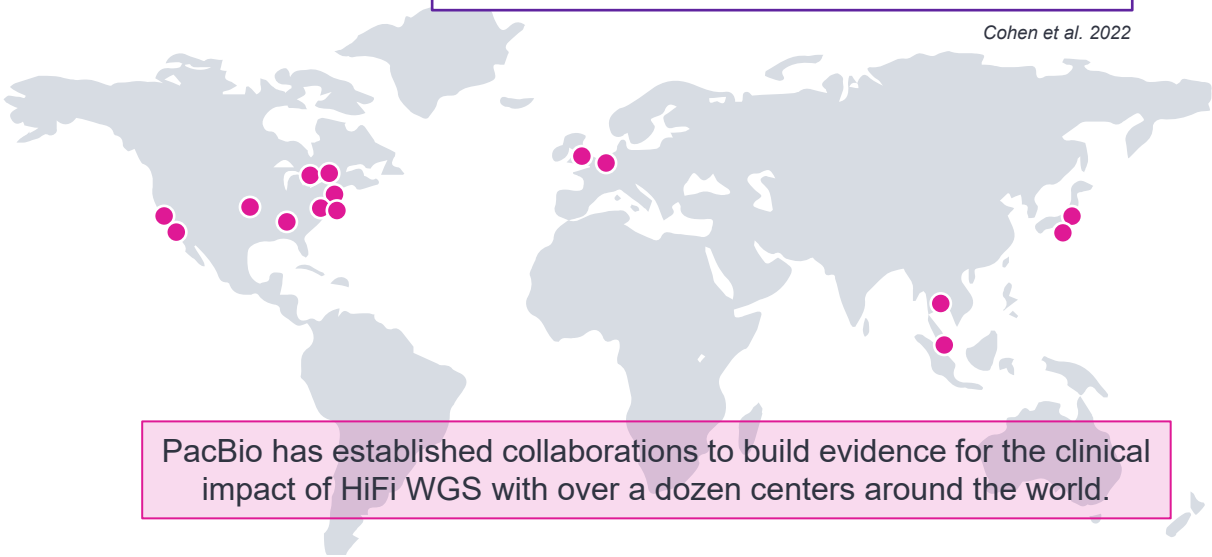
PacBio impact

Cohen et al. (2022) showed HiFi-GS yielded increased discovery rate with >4-fold more rare coding SVs compared with short-read genomes

Incorporating SVs from genome sequencing added up to 13% of new diagnoses in previously unsolved cases



Cohen et al. 2022



PacBio has established collaborations to build evidence for the clinical impact of HiFi WGS with over a dozen centers around the world.

PacBio

1 RARE disease facts [Internet]. Global Genes. 2018 [cited 2021 Dec 20]. Available from: https://globalgenes.org/rare-disease-facts/
2 Fresard et al. 2018

Revio eliminates the need to batch samples in an acute genetic disease setting

Whole Human Genomes

"This is going to change the game... We want to switch entirely to HiFi. I can't wait to get my hands on this instrument!"
— Director of Bioinformatics, clinical lab in a large Children's Hospital

Trio design

1 run	$1k/ WGS*

Would require one NovaSeq SP flow cell at $4,200 – **per-genome price is $1,400**.**

Four probands

1 run	$1k/ WGS*

Would require one NovaSeq S1 flow cell at $5,250 – **per-genome price is $1,300****

One proband

1 run	$1k/ WGS*

Would require one NovaSeq SP flow cell at $4,200 – **per-genome price is $4,200.****

PacBio

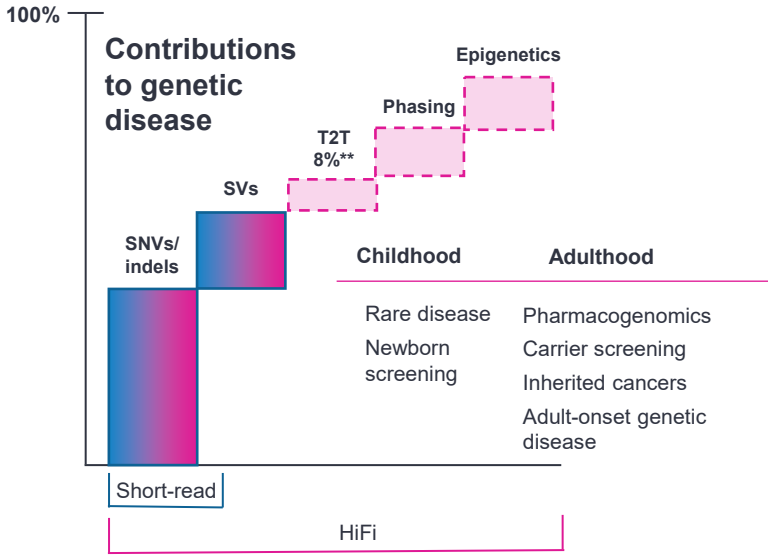
*Assumes 1 SMRT cell per sample on Revio to hit minimum average depth per sample of 30×
**List prices from Illumina open offer letter dated March 29, 2021

Beyond rare disease, HiFi WGS is the backbone to understand the role of genetics across a lifetime

Whole Human Genomes

"I think that with the new competitive pricing of the Revio system we will finally be able apply long read sequencing at-scale for our rare disease cohorts and may eventually be able to replace all of our clinical sequencing efforts with a single long-read sequencing test."

— Professor, European University Medical Center



	SNVs/ indels	SVs	Phasing	Epigenetics	T2T 8%	
PacBio						Cost
30× WGS	☑	☑	☑	☑	☑	**$995^**
Short-read						
30× WGS	☑	☑	☑	⊘	⊘	$200-$5.3k*
Synthetic	?	?	?	⊘	⊘	$1400^^
						$200-$6.7k

^Price includes sequencing and primary analysis
*Pricing range: Low end: NovaSeqX at highest capacity and discounting. Requires running >20K WGS/year to hit highest throughput and lowest pricing. (https://www.genengnews.com/topics/omics/illumina-reveals-new-high-throughput-instrument-novaseq-x/#:~:text=In%20the%20second%20half%20of,comparable%20to%20the%20NovaSeq%206000. https://www.illumina.com/company/news-center/press-releases/press-release-details.html?newsid=8d04df3f-d9c1-4c85-8177-6ea604627ccd); High end: NovaSeq6000 SP flow cell running 1 sample per flow cell (https://s24.q4cdn.com/526396163/files/doc_financials/2022/q2/illumina-source-book-August-2020.pdf); includes only sequencing and primary analysis
**T2T 8%: the additional 8% of the genome that was recently mapped using long read sequencing as part of the T2T consortium (Nurk et al, *Science*, 2022)
^^assumes CLR requires 7x depth compared to standard 30x depth sequencing on ILMN. Assumes standard ILMN 30x @ $200/sample as outlined for NovaSeqX above.

PacBio

Consolidation of panels, legacy tech onto WGS backbone

LinkedIn post, November 1, 2022

“Strictly speaking, the $9 per gigabase price point of the Revio is in the same cost ballpark as the other moderate throughput systems like Illumina’s own NextSeq ($15/gb), the S2 flowcell on the Novaseq ($8/gb) and the new Element Aviti ($5/gb).

Long reads for the same price as short reads? Yes, please.

“But Brian, no one needs long reads.”

Except, they do.

Because in the eternal words of my friend Boromir, “One does not simply sequence a short-read genome.”

One thing you learn pretty quickly when doing clinical diagnostics is that you actually have to cover all the edge cases because missing a diagnosis is a big deal.

And gap filling a short-read genome ($500) gets expensive, fast:

aCGH for structural variants: $400
MLPA for difficult CNVs and Pseudogenes: $50 each (you’ll need a bunch of these)
Genome wide methylation profiling: $300
Total: $1,500+

“At $950, a Revio genome looks downright cheap for diagnostic applications.”

Brian Krueger, PhD

Vice President, Lab Research and Development, Everly Health

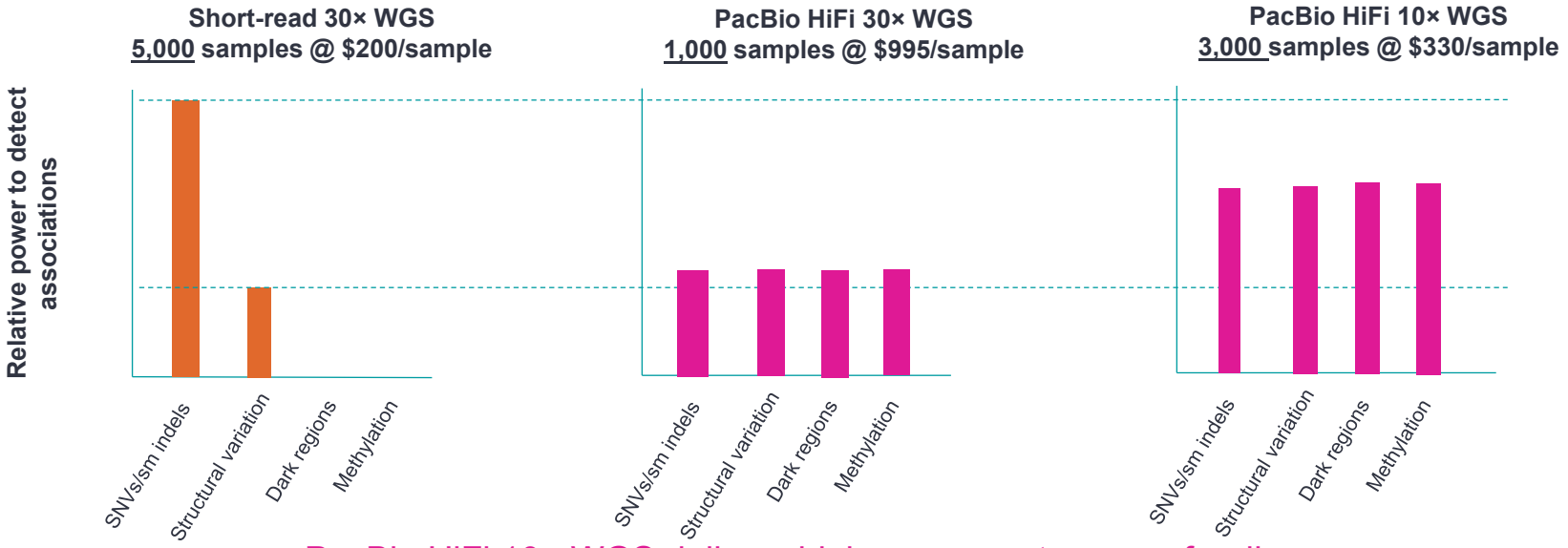
Previously:
Associate Vice President, Technical Director II, R&D, LabCorp

Revio further opens HiFi to large-scale cohort studies and population genomics

Mutations across all variant classes underlie complex phenotypes.

Power to detect associations and identify biomarkers is a function of variant detection and sample size.

For a hypothetical $1,000,000 consumables budget*, a research will seek to choose a technology that will maximize power for discovery.



PacBio HiFi 10× WGS delivers higher aggregate power for discovery.

PacBio

*Sequencing consumables only, $995 & $330 per genome (and for that matter the $200 for short read) is at US list price.

Full-length isoforms

Market drivers

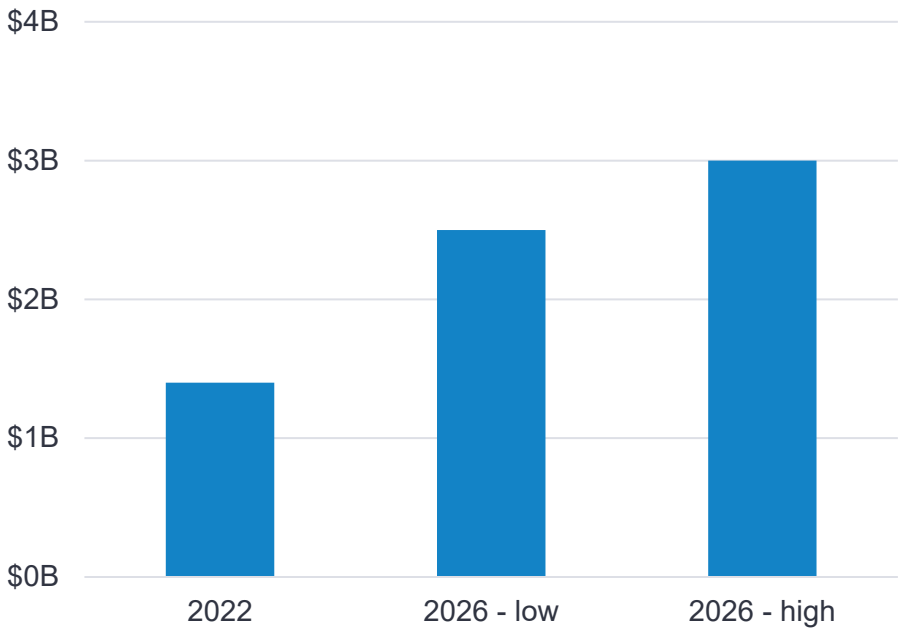
Expansion of single-cell technologies, including spatial

Growth in funding for multiomic studies of disease

Long-read technology offers new, complete view of transcriptome; expanded investment in discovery

Transition of some RNA-based biomarkers/data into routine clinical service

RNA market growing at 15–20% CAGR 2022-26[1]



PacBio market share goal to reach mid-single digits by 2026

[1]Decibio NGS manufacturers report 2021, peer company disclosures, and internal estimates

The future of RNA analysis is full-length isoforms

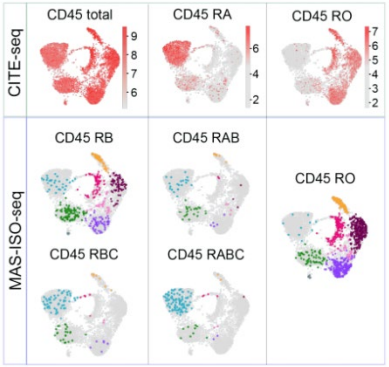
Full-length isoforms

Long-read analysis of RNA delivers >2.5× isoform discovery power compared to short-read[1]

MAS-Seq (concatenation) further increases discovery power >30-fold for single-cell experiments[2]

"…if you can get isoform sequences for about the same price as short reads, why in the world would anyone still use short-reads???"

— Professor and Core Lab Director at a major university in NYC area



Error rate in isoform reconstruction

43% SRS

0.4% HiFi

	SRS	PacBio
10x Prep	$1500	$1500
Library Prep	NA	$475
Sequencing	$800[1]	$995
	$2300	$2970

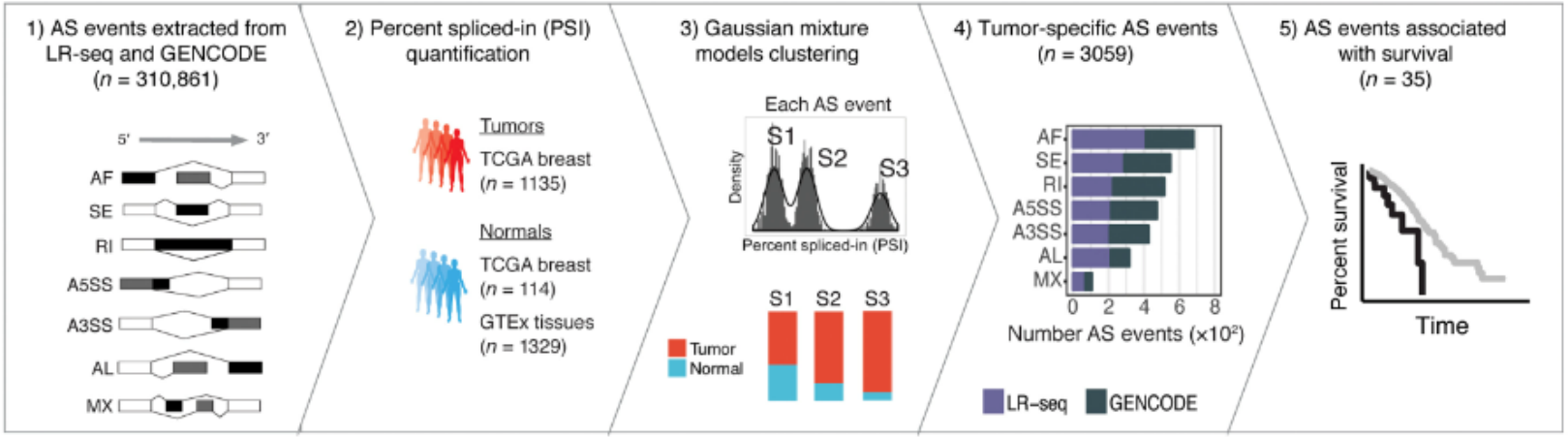
1. Viega et al. 2022
2. Al'Khafaji et al. 2021

Figures from Al'Khafaji, et al., BioRxiv 2021

[1]based on 6000-cell 10x library, with recommended 20,000 reads/cell coverage and pricing from Illumina open offer letter

Early long-read RNA sequencing studies demonstrate potential clinical relevance

Veiga et al. identified thousands of novel isoforms in breast cancer samples; 35 correlated with survival



"In conclusion, **LR-seq is particularly well suited for the discovery of isoforms containing novel targets for immuno-oncology.** These include the identification of **cell surface isoforms against which specific monoclonal antibodies can be generated for use as therapeutics or as backbones for chimeric antigen receptor (CAR) T-cells.** Isoforms also generate peptides that could be used for vaccination protocols, possibly in combination with checkpoint inhibitors."

Veiga, et al. A comprehensive long-read isoform analysis platform and sequencing resource for breast cancer. *Sciences Advances*, 2022.

Market drivers

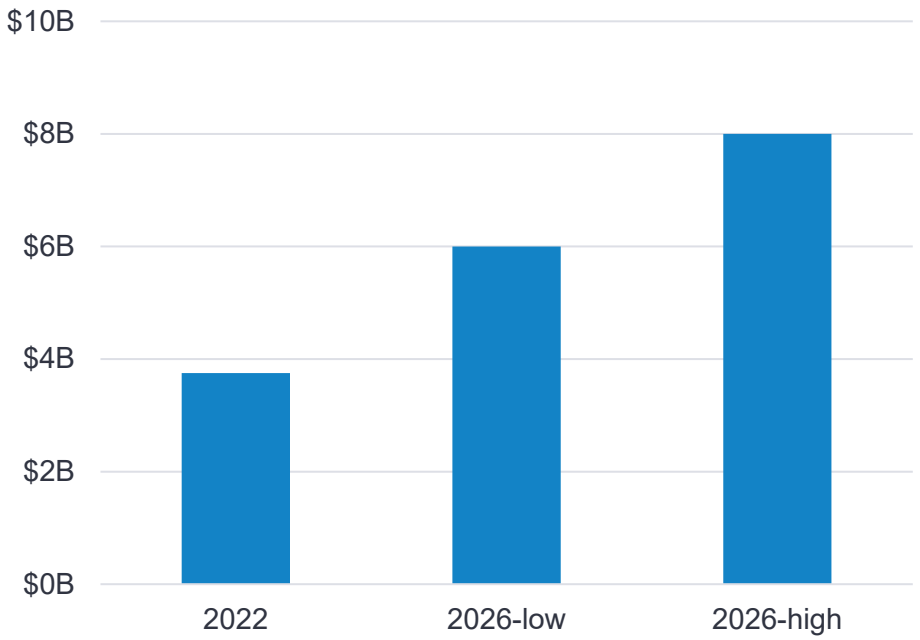
Expansion of sequencing panels for therapy selection in cancer indications

Increased investment by pharma to find biomarkers and use to support drug go to market

Widespread adoption of cell-free and *needle-in-a-haystack* applications, primarily for cancer monitoring indications

Increased access to single gene or small panel assays for genetic disease

Targeted sequencing market growing at 10–20% CAGR 2022–26[1]



PacBio market share expected to reach low-single digits by 2026

[1]Decibio NGS manufacturers report 2021, peer company disclosures, and internal estimates

Targeted sequencing as a stepping stone to WGS in genetic disease

PacBio enters this $4B market in 2022 with a portfolio of solutions

Medically relevant but challenging genes

Opening doors to lower-cost, higher-throughput market segments to build value for PacBio WGS

Complex disease research + PopGen

Add dark regions to existing WES/WGS/microarray cohorts

Estimate 5M eligible samples globally[3]

Single gene disorders

e.g. Thalassemia

~5% of world population has a thalassemia trait, with 12%-60% of people potentially being genetic carriers depending on ancestry.[4]

BerryGenomics 贝瑞和康

Carrier screening

SMA1/2 → spino muscular atrophy → ACOG recommends screening for all women considering pregnancy[1]

>4M pregnancies per year in the US alone[2]

Pharmacogenomics

99% of adults have an actionable PGx variant[2]

Broad US CMS reimbursement decisions implemented in mid-2020

Tracking >10 programs for population-scale PGx testing in health systems worldwide

1 https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-for-genetic-conditions
2 (US, UK Biobank Studies)
3 Internal analysis
4 https://www.news-medical.net/health/Thalassemia-Prevalence.aspx

PacBio

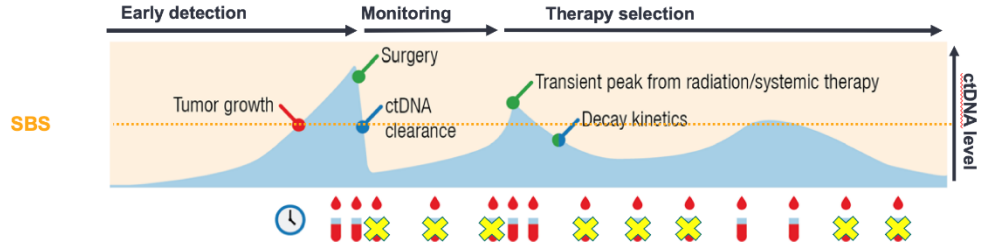
Targeted assays on Onso open noninvasive biomarker market for PacBio

MRD/monitoring TAM >3× larger than comprehensive genomic profiling to guide therapy selection in advanced cancer patients**

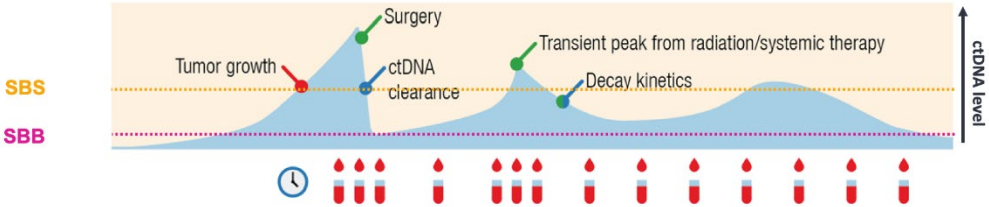
2022 Volume TAM ~2M**
– Growing @ 32% CAGR

70% of precision oncology companies are developing tests for monitoring and residual disease*

Current sequencing-based liquid biopsy approaches have limited sensitivity



15× increase in accuracy of Onso can mean earlier detection and improved monitoring of cancer



*Decibio: https://www.decibio.com/insights/the-precision-oncology-landscape-infographic
**Cowen Liquid Biopsy Deep Dive 2022

PacBio

Beyond human genomics and oncology, applied and emerging markets contribute to PacBio's growth

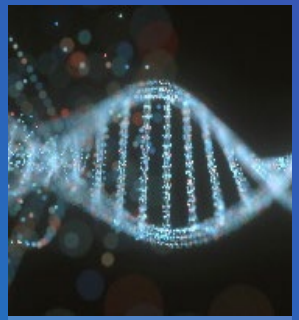
PacBio in early stages of penetrating applied markets

	Market size 2022 (CAGR '22–'26)	PacBio market share '22	PacBio expected market share '26
Microbial + infectious disease	~$900M (11%)	<3%	~4%
Plant + animal	~$200M (15%)	~15%	~20%
Other/ Emerging	~$1B (12%)	<1%	~2%

Decibio NGS manufacturers report 2021, peer company disclosures, and internal estimates

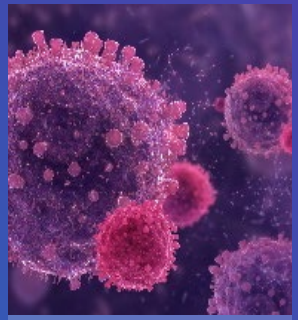
PacBio

Products to address the entirety of the sequencing landscape



Human Genomics

Oncology



Microbiology / Infectious Disease

Plant and Animal

Emerging

?

PacBio

Q&A

David Miller
Mark Van Oene
Christian Henry
Dr. Jennifer Stone

November 15, 2022

Fueling the commercial engine

Jeff Eidel | Chief Commercial Officer

November 15, 2022

Goals of session

1. Showcase the Commercial team we have in place now to capitalize on large market opportunities
2. Illustrate system robustness and global support capabilities that enable customer success
3. Demonstrate how PacBio's scaled Commercial team enabled our recent launches and a robust funnel for Revio & Onso

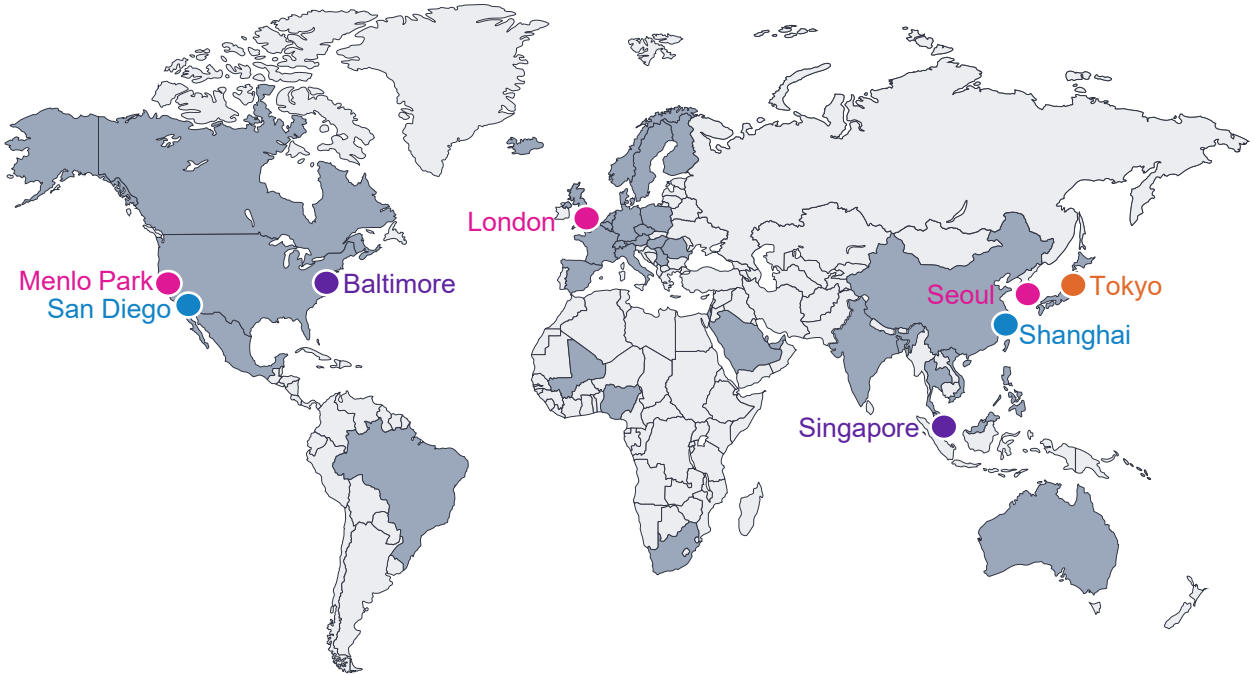
Global commercial team

225 Commercial Employees

8 Global Locations

67 Commissioned Sales Reps

25 Distributors



As of 10/31/22

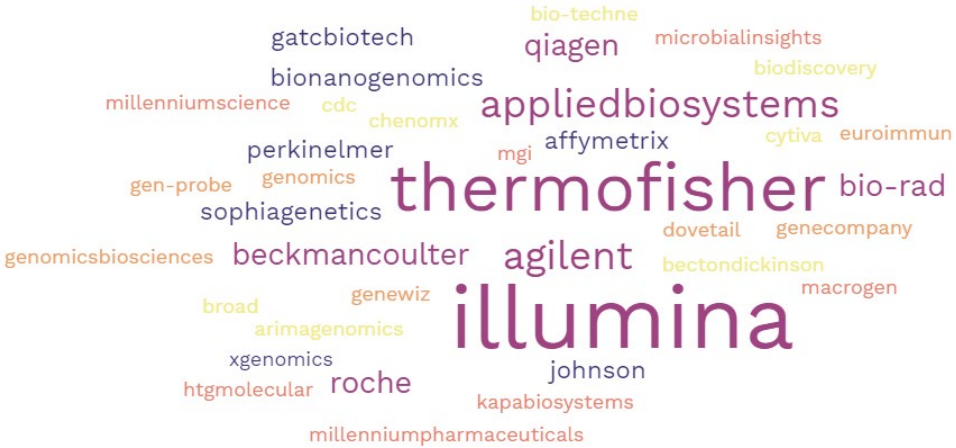
Experienced sales & marketing team driving growth across regions

133 sales & marketing FTEs
4x growth since start of 2021

67 commissioned reps
3× growth since start of 2021

Rapid new customer growth
91 new customers purchased systems since start of 2021

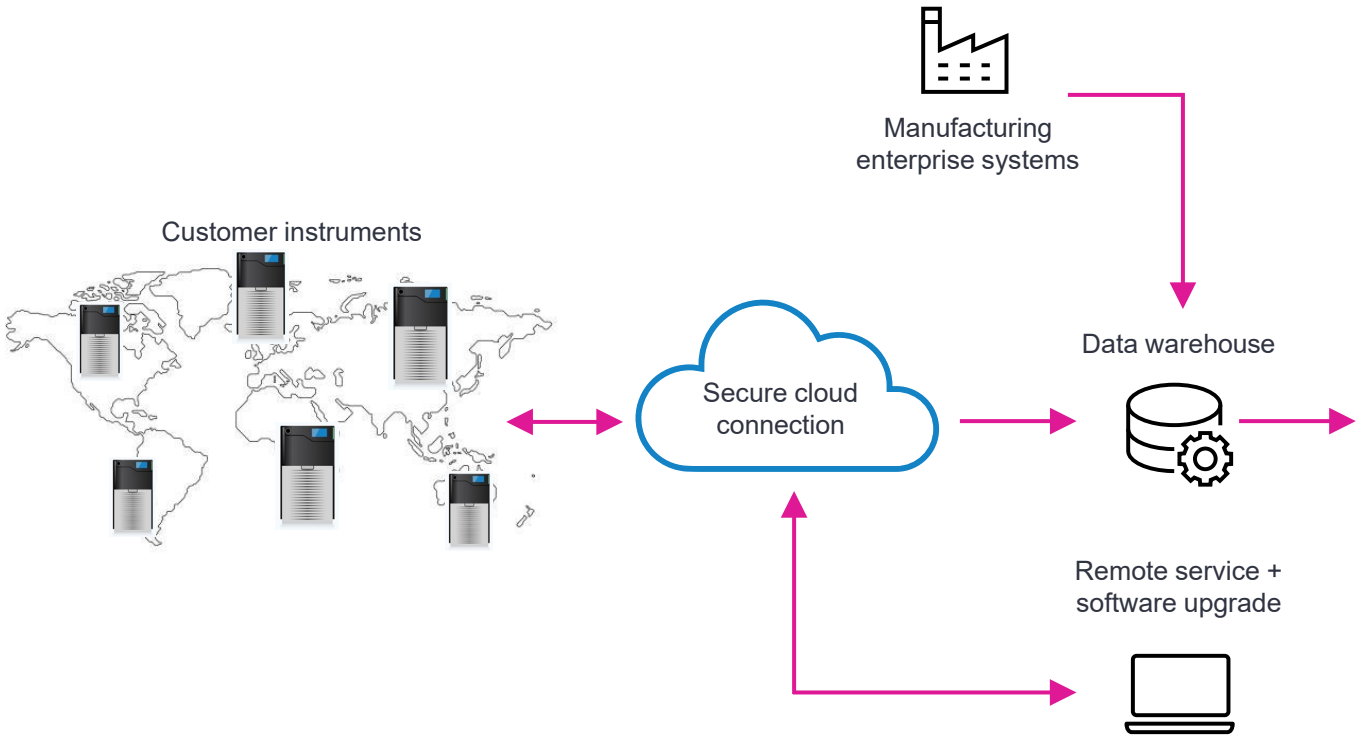
11 years
Average genomics/sequencing sales experience per sales rep



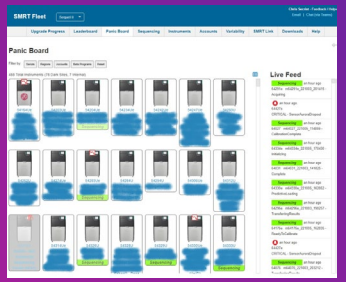
As of 10/31/22

PacBio

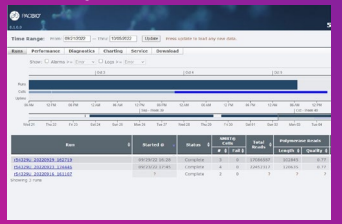
Proven secure remote service + global reach through Sequel Insights



SMRT fleet user interface



System details



Global analytics

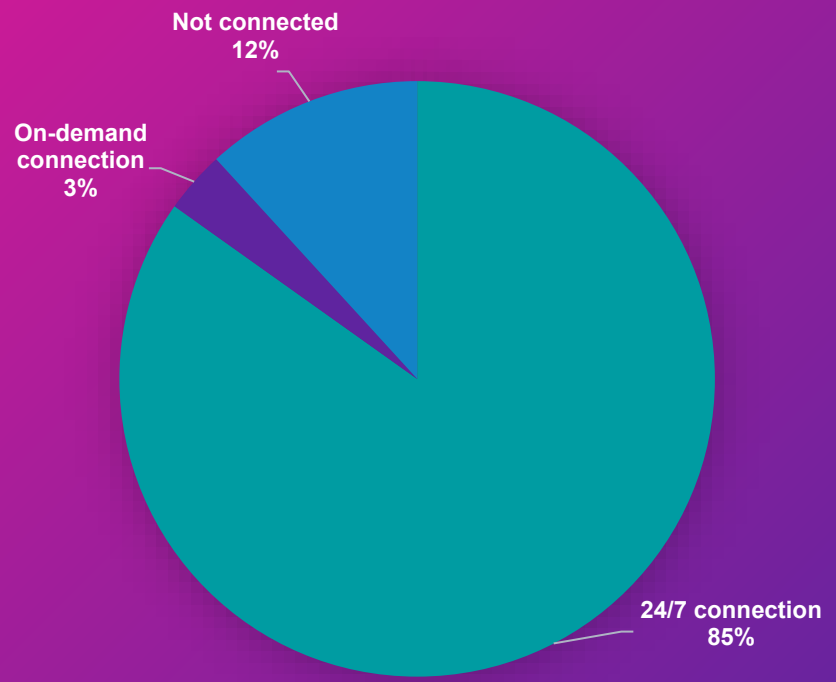
High Sequel Insight adoption rates + system robustness + large, experienced service team = great customer experience

MTBF >300 Days since 2019
"MTBF" = Mean Time Between Failure

4 years
Average tenure of service org

70 service & support reps
17% growth since start of 2021

Sequel Insight customer adoption



Commercial excellence + scale in action

Cross-functional scale

ASHG

Game, changed.

RESULTS

ASHG event attended by **1,200 people**

1,000 new customer leads

13M social media impressions (4 days)

30+ TV/press/media articles

6 press releases

Multi-unit pre-orders

Robust post-ASHG funnel

Game changed. Revio orders off to a great start

Several multi unit orders received from global launch partners, with more on the way

BROAD INSTITUTE

解码DNA® JMDNA.COM 让医疗更精准

Humanizing Genomics macrogen

HUDSONALPHA INSTITUTE FOR BIOTECHNOLOGY

Berry Genomics 贝瑞基因

HAORUI GENOMICS 浩瑞基因

组 GrandOmics 希望组

"Precision Genomics" DNA LINK

ANORAD 安诺优达

PacBio

Building exceptional quality at scale

Mike Goloubef | Senior Vice President, Manufacturing, Quality + Supply Chain

November 15, 2022

Goals of session

1. Our mission
2. Current state capabilities
3. Areas of focus & investment
4. Future state

OUR MISSION

Deliver an exceptional customer experience through superior product quality, at a cost and scale that maximizes profitability

PacBio manufacturing – current state

Our current infrastructure & supplier network supports our growth through 2026

Menlo Park, CA

R&D, Manufacturing, SG&A
Mfg sq ft ~ 75k

Revio, Onso, SQIIe

- Instrument, SMRTCell & Reagent manufacturing
- Manufacturing, Quality, Sourcing/Supply Chain & Sustaining Engineering
- ISO9001, 13485 certified, ROHS3, WEEE, REACH & Conflict Mineral compliant
- ISO7 cleanroom

San Diego, CA

R&D, Manufacturing, SG&A
Mfg sq ft ~ 20k

Onso

- Flow Cell & Reagent manufacturing
- Manufacturing, Quality, Sourcing & Sustaining Engineering
- ISO8 cleanroom

Baltimore, MD

R&D, Manufacturing
Mfg sq ft ~ 5k

Sample Prep

- Nanobind disc manufacturing
- Manufacturing, Quality
- Transitioning to fully outsourced model

Contract Manufacturers

USA, Mexico, APAC
~50% of COGS spend

Revio, Onso, SQIIe, Reagents

- Manufacturing, Quality & Sourcing
- Outsourced content
  - Instruments ~ 70%
  - SMRTCells ~ 50%
  - Flow Cells ~ 60%
  - Reagents ~ 10%

Areas of focus & investment

Key supplier partners & contract manufacturers

Technology centers of excellence

IVD/Clinical market & product readiness

Business continuity planning

Improved gross margin

PacBio

PacBio manufacturing – future state

Building capacity & capability for 2026 onward

- PacBio factory network will be technology focused, lower cost and closer to customer
- Our contract manufacturers will provide cost & volume advantage
- We will be ready to supply and support IVD/clinical market products and services
- Cost, efficiency & yield will be key drivers for continuous margin improvement
- Business continuity planning & supplier risk management will ensure redundancy & uninterrupted supply of materials

PacBio

Building a sustainable P&L

Susan Kim | Chief Financial Officer

November 15, 2022

Financial snapshot

% new customer shipments (LTM)

Sequencers installed to-date[1]

Consumable growth (LTM)

Instrument customers[1]

Installed base Sequel II/IIe

Cash, cash equivalents and investments

As of Sept 30, 2022; LTM = Last twelve months; [1]Since 2011

Our financial targets

Grow revenues 40-50% CAGR through 2026, or >$500M

Improve gross margins[1] to 55-60%+ by 2026

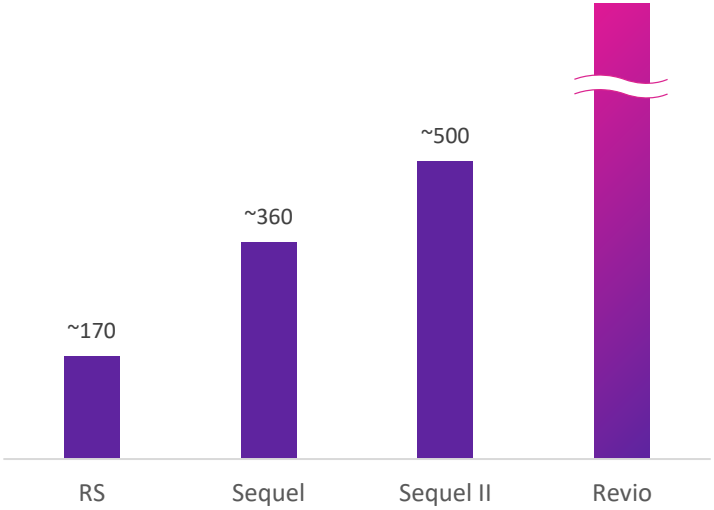
Deliver sustained operating leverage through disciplined capital allocation

Achieve positive cash flow in 2026

PacBio

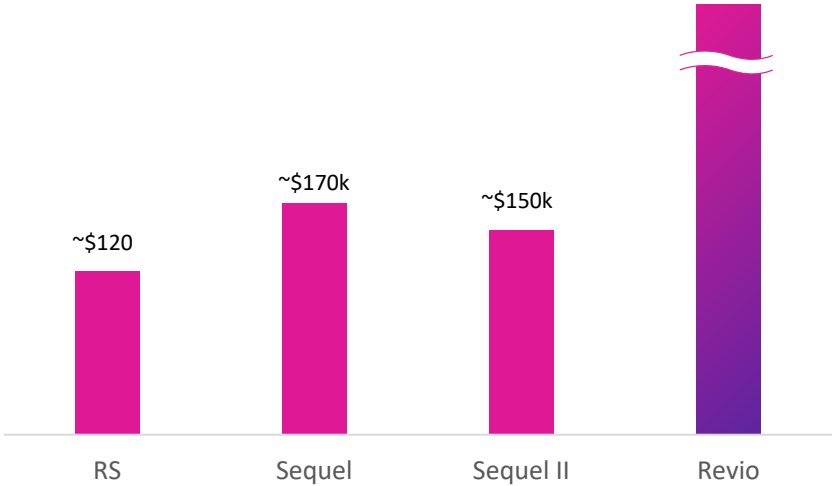
[1]Non-GAAP

Revio revenue contribution higher than previous platforms



Installed base

Higher throughput and lower cost expands addressable customers and installed base



Average pull through

Revio's throughput capacity enables higher average consumable pull through

Average pull through and installed base for RS, Sequel, Sequel II based on disclosed figures and internal data; Revio is internal estimate as of 11/15/2022

Path to >$500M revenues by 2026

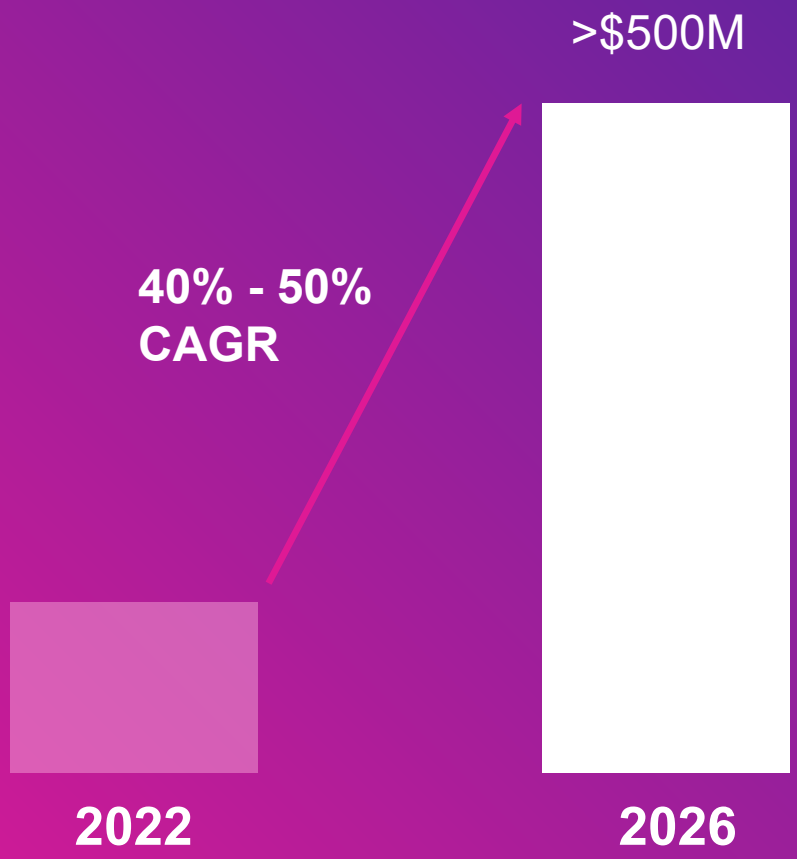
From one platform to **multiple platforms** across long-and-short reads

More frequent platform launches to expand product portfolio and build momentum

Expanding pull-through with faster run-time, multiple chips and denser flow cell

End-to-end workflows and kitted solutions targeting applications

Expanding market opportunity and increased market share underpinning growth



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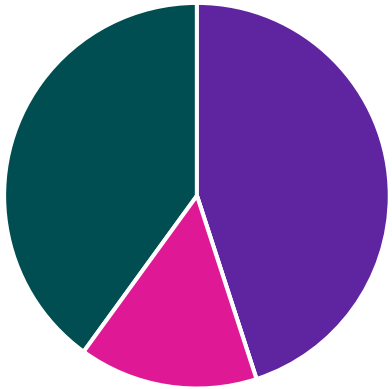
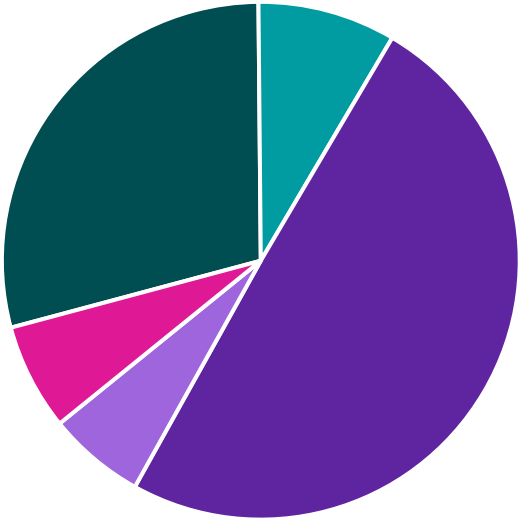
Diverse multi-product portfolio expands revenue growth drivers

Long-read instruments
Long-read consumables
Short-read instruments
Short-read consumables
Other



2022[1]



2026

>$500M

PacBio

[1]YTD as of 9/30/2022

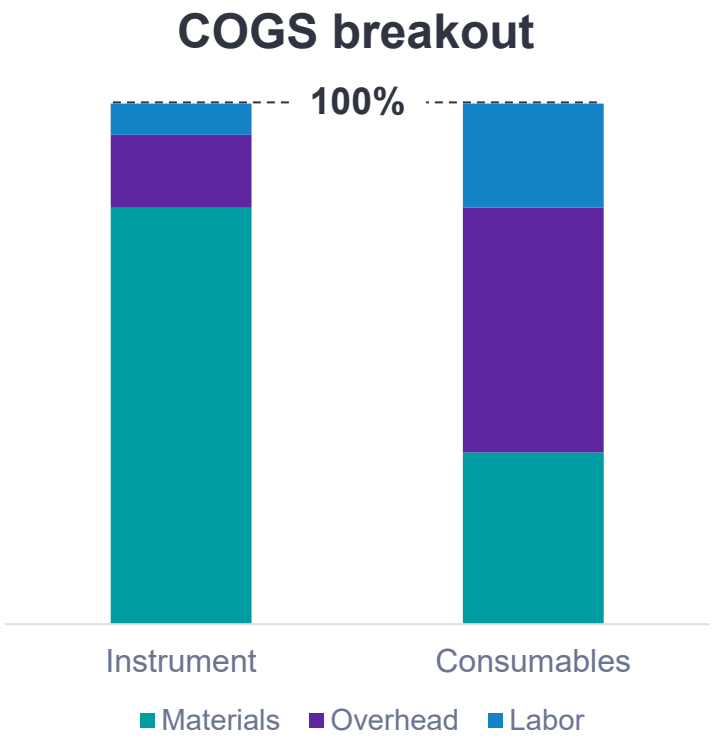
Product mix largest contribution to higher gross margins in 2026

Non-GAAP Gross Margins. For illustrative directional purposes only; boxes not to scale.

Volume enables improved instrument and consumable margins

Instruments

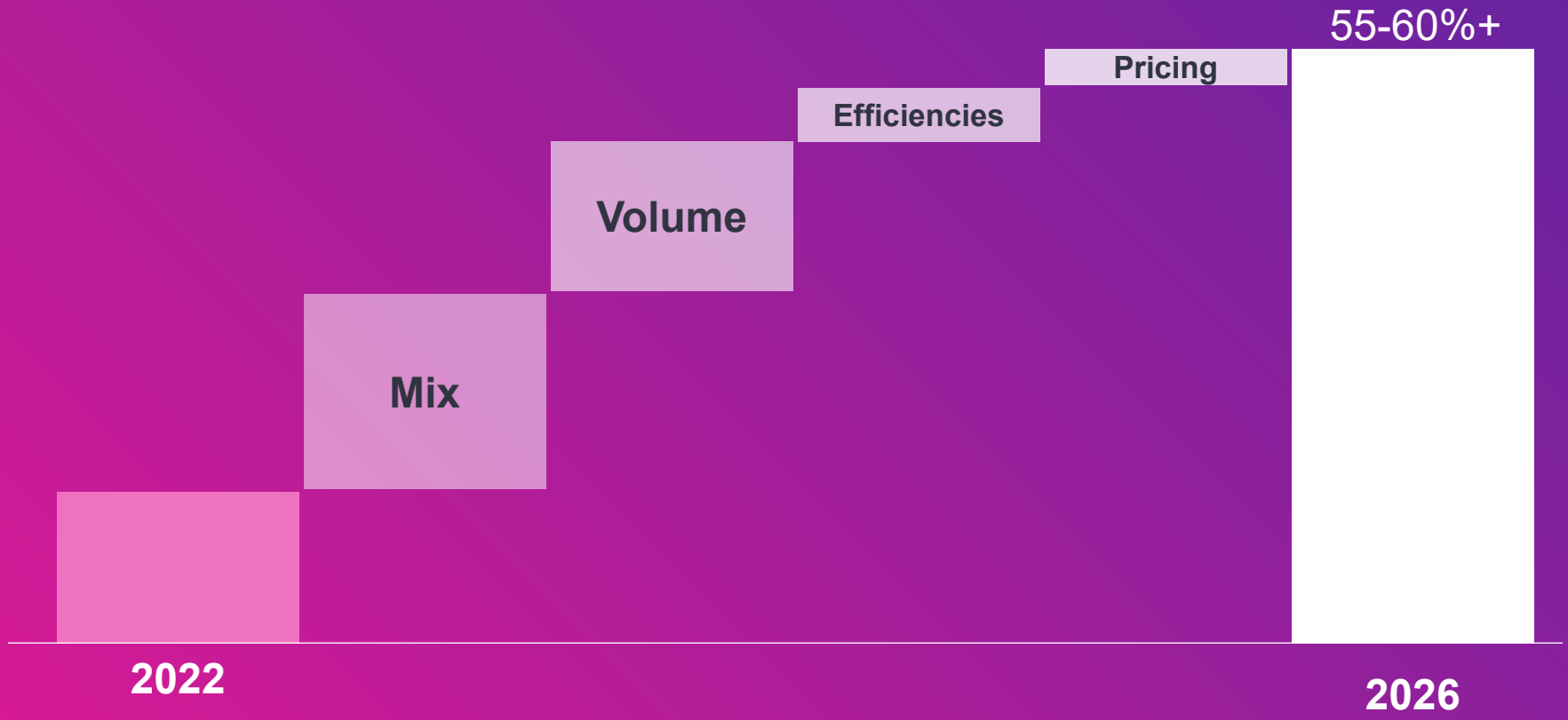
- Spread fixed costs
- Volume pricing
- Common components across platforms
- Leverage contract manufacturers



Consumables

- Spread fixed costs
- Volume pricing
- Long-term supply agreements
- Common consumables across platforms
- Reagent formulation, fill & packaging automation
- Larger batch reagent manufacturing
- Transition from 8inch to 12inch chip manufacturing
- Leverage contract manufacturers

Product mix largest contribution to higher gross margins in 2026



Non-GAAP Gross Margins. For illustrative directional purposes only; boxes not to scale.

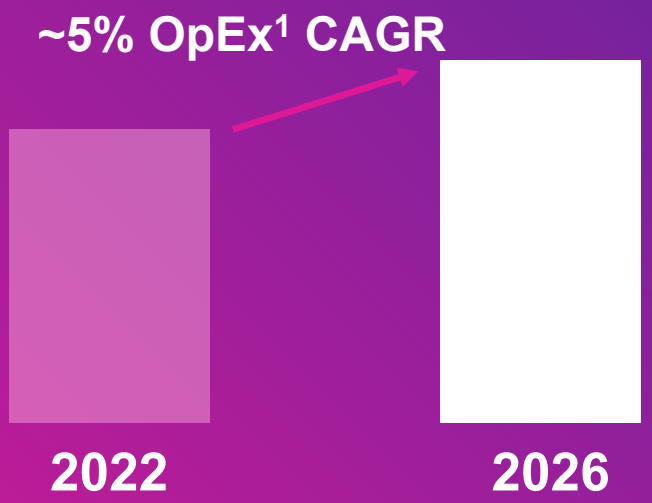
Disciplined expense management

Disciplined growth on labor force through enhanced FTE productivity

Centers of excellence organizational structure enable R&D program efficiencies

Commercial synergies across multiproduct platforms

Non-headcount related expenses moderate with staggered product launches



[1]Non-GAAP

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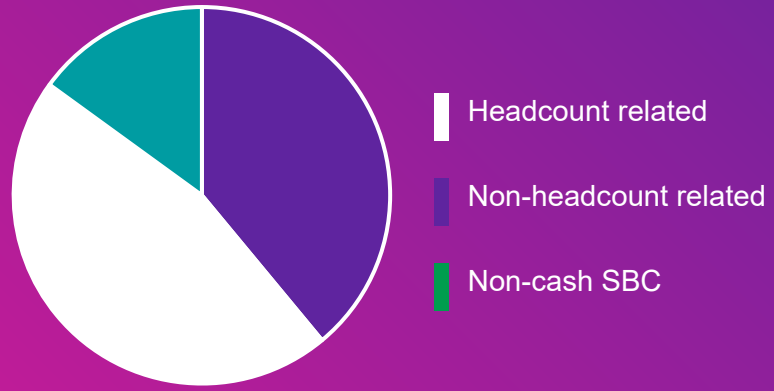
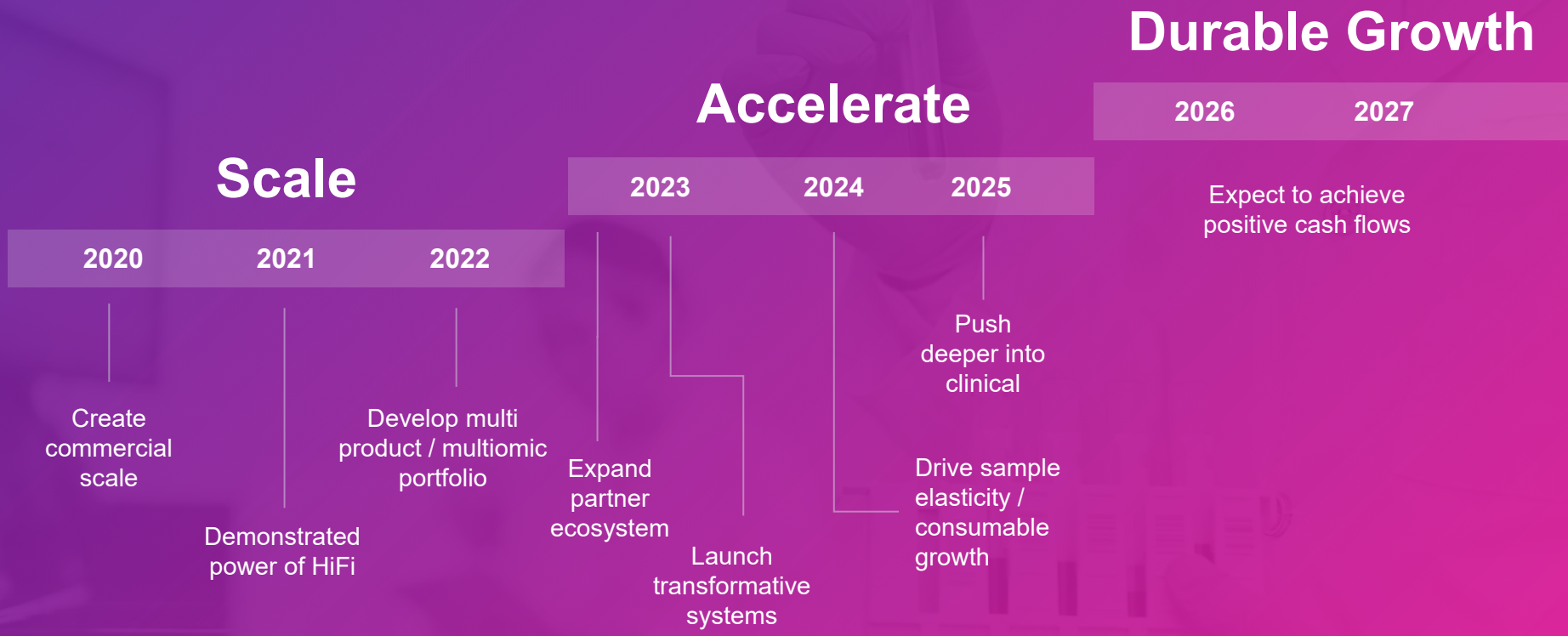


2022 OpEx[1] breakdown

[1]Non-GAAP, estimated as of 11/15/2022

How our strategy becomes reality



PacBio

Q&A

Susan Kim
Christian Henry
Jeff Eidel
Mike Goloubef

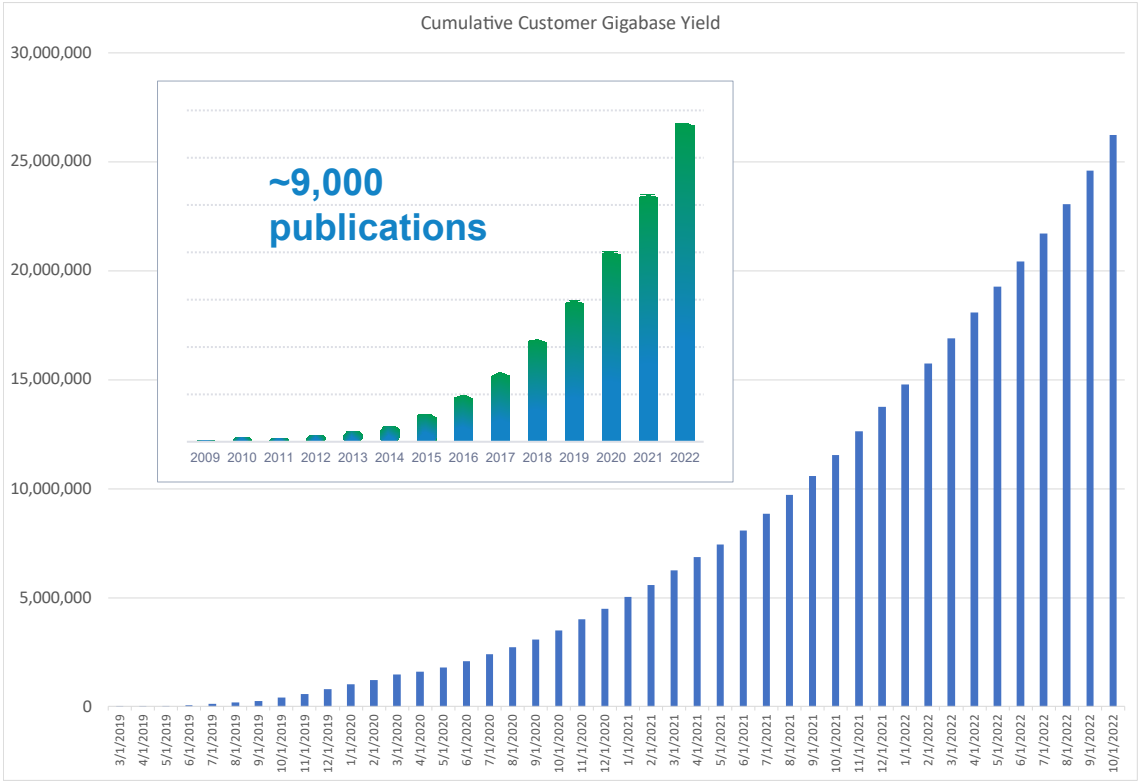
November 15, 2022

Shifting paradigms

Jonas Korlach | Chief Scientific Officer & Co-founder

November 15, 2022

What are our customers doing with their PacBio data?



Last month, our customers surpassed 25 Pb (that's 25 million billion bases)!

Recent customer statements

We find that trio-based approaches using HiFi are the **current gold standard**

*HiFi long-read sequencing is **helpful for understanding genes with long, repetitive regions***

Long-read sequencing has proven **invaluable** for resolving complex genomic regions, resulting in **drastic improvements** in variant detection

the resources presented here **herald a new era**

*To **overcome these limitations**, we employed PacBio long-read sequencing*

full length reads with **>99.997% accuracy and high reproducibility**

***a powerful method** to detect undesired genome modifications*

discovering the relevant variant in this family with autism that **had remained a mystery for several years** and will **potentially have great benefits in the clinic** once it is widely available

long reads allowed for the comprehensive characterization of genetic diversity in these regions **effectively and accurately**

*Obtaining such a high degree of base accuracy (QV of 50 or higher) with long reads has only been a **recent advance**, due to the **higher accuracy of HiFi reads***

100% diagnostic yield for our cohort

*assembles **more** … **from one** … **sample** … **than all … published previously**. Such high-quality metagenome assemblies may **fundamentally change the practice** in metagenome analysis*

Fiber-seq could **uniquely enable** the interrogation of the genetic and chromatin architectures

*Using high-quality CCS reads, QuasiSeq can produce quasispecies sequences with **100% accuracy***

improved sequencing technologies is **critical to properly analyze** complex genomic regions

*we identify over 1.99 million nonredundant SNVs in a gene-rich portion of the genome **previously considered largely inaccessible***

References available upon request

Recent customer statements

hindering accurate mapping of shorter sequencing reads, and therefore likely causes **artifactual** LD **in [the short-read data]** but not the [PacBio] Pangenome

*Using PacBio sequencing we can detect mutations that **otherwise would be missed in Illumina sequencing***

orders of magnitude **smaller set of high-quality long-read** sequencing data has the potential to **more effectively characterizing genetic variation** than larger sets of sequencing data from other platforms

*Approaches that used **highly accurate long reads … outperformed those that did not***

To realize the promise of biodiversity genomics, we **call for greater uptake of highly accurate long-reads** in future studies

*HiFi reads **consistently outperform all other data types** for both plants and animals*

*the complexity of the IG loci **severely limits the effective use of short read sequencing, limiting our knowledge***

An additional 16 mutations were found only by long-read sequencing, all of them with frequencies **below the limit of detection for Sanger** sequencing

*We **no longer** consider collapsed 3 Gbp genome assemblies as **state-of-the-art***

scRNA-seq … fails to capture the diversity in transcript isoforms

*All **HiFi-based diploid assemblies outperformed … the ONT diploid assemblies**, the latter was due to the **high indel error rate in ONT reads***

likely **artifacts of inaccurate [short-read] sequence mapping**

*microarray and **short-read sequencing are not able to fully and accurately resolve***

we show a **high propensity for false-positives in the short read datasets**

*Despite shorter reads and less coverage, **HiFi reads outperformed ONT reads** in all assembly metrics tested*

rare thalassemia variants are not rare but have been **misdiagnosed by conventional methods**

PacBio

References available upon request

- A human genome was completed for the first time
- The human genome is now 6 Gb in size, no longer 3 Gb
- A human *pangenome* reference
- Whole genome sequencing, with the “W”
- Out-of-the-box 5-base sequencing
- Not “gene expression analysis,” but “isoform expression analysis”
- No plant + animal genome is too big or complex to get a high-quality reference genome
- Extraordinary resolution of microbiomes
- Gene therapy vector QC is now possible
- Extraordinary accuracy + sensitivity for short-read applications

…

Fundamental paradigm shifts, powered by PacBio sequencing

A human genome was completed for the first time

Telomere-to-telomere consortium

"The basis of the T2T-CHM13 assembly is a high-resolution **assembly** string graph **built directly from HiFi reads**."

RESEARCH ARTICLE

T2T

The complete sequence of a human genome

Sergey Nurk[1]†, Sergey Koren[1]†, Arang Rhie[1]†, Mikko Rautiainen[1]†, Andrey V. Bzikadze[2], Alla Mikheenko[3], Mitchell R. Vollger[4], Nicolas Altemose[5], Lev Uralsky[6,7], Ariel Gershman[8], Sergey Aganezov[9]†, Savannah J. Hoyt[10], Ma… Matthew Borchers[13], G… Haoyu Cheng[16,17], Cher… Richard Durbin[19,20], Ta… Arkarachai Fungtamma… Ira M. Hall[27], Nancy F. … Michael W. Hunkapiller… Melanie Kirsche[9], Mikh… Valerie V. Maduro[33], To… James C. Mullikin[14,28], … Pavel A. Pevzner[32], David Porubsky[4], Tamara Potapova[13], Evgeny I. Rogaev[6,7,38,39], Jeffrey A. Rosenfeld[40], Steven L. Salzberg[9,41], Valerie A. Schneider[42], Frit… Alaina Shumate[41], Ying Sims[19], Arian F. A. Smit[45], Aaron Streets[5,47], Beth A. Sullivan[48], Françoise Th… Brian P. Walenz[1], Aaron Wenger[29], Jonathan M. D… Alice C. Young[14], Samantha Zarate[9], Urvashi Surti… Ivan A. Alexandrov[3,7,51], Jennifer L. Gerton[13,52], Ra… Michael C. Schatz[9,49], Evan E. Eichler[4,53]*, Karen …

A complete reference genome improves analysis of human genetic variation

Sergey Aganezov†, Stephanie M. Yan†, Daniela C. Soto†, Melanie Kirsche†, Samantha Zarate†, Pavel Avdeyev, Dylan J. Taylor, Kishwar Shafin, Alaina Shumate, Chunlin Xiao, Justin Wagner, Jennifer McDaniel, Nathan D. Olson, Michael E. G. Sauria, Mitchell R. Vollger, Arang Rhie, Melissa Meredith, Skylar Martin, Joyce Lee, Sergey Koren, Jeffrey A. Rosenfeld, Benedict Paten, Ryan Layer, Chen-Shan Chin, Fritz J. Sedlazeck, Nancy F. Hansen, Danny E. Miller, Adam M. Phillippy, Karen H. Miga, Rajiv C. McCoy*, Megan Y. Dennis*, Justin M. Zook*, Michael C. Schatz*

Segmental duplications and their variation in a complete human genome

Mitchell R. Vollger, Xavi Guitart, Philip C. Dishuck, Ludovica Mercuri, William T. Harvey, Ariel Gershman, Mark Diekhans, Arvis Sulovari, Katherine M. Munson, Alexandra P. Lewis, Kendra Hoekzema, David Porubsky, Ruiyang Li, Sergey Nurk, Sergey Koren, Karen H. Miga, Adam M. Phillippy, Winston Timp, Mario Ventura, Evan E. Eichler*

https://www.science.org/doi/10.1126/science.abj6987; https://www.science.org/doi/10.1126/science.abj6965; https://www.science.org/doi/10.1126/science.abl3533

The human genome is now 6 Gb in size, no longer 3 Gb

Human pangenome reference consortium (>50 global institutions)

"We no longer consider collapsed 3 Gbp genome assemblies as state-of-the-art but instead consider **two genomes for every diploid genome assembled (i.e., 6 Gbp vs. 3 Gbp) where parental haplotypes are phased and fully resolved**."

Automated assembly of high-quality diploid human reference genomes

Erich D. Jarvis, Giulio Formenti, Arang Rhie, Andrea Guarracino, Chentao Yang, Jonathan Wood, Alan Tracey, Francoise Thibaud-Nissen, Mitchell R Vollger, David Porubsky, Haoyu Cheng, Mobin Asri, Glennis A Logsdon, Paolo Carnevali, Mark Chaisson, Chen-Shan Chin, Sarah Cody, Joanna Collins, Peter Ebert, Merly Escalona, Olivier Fedrigo, Robert S Fulton, Lucinda L Fulton, Shilpa Garg, Jay Ghurye, Edward Green, Ira M Hall, William H Harvey, Patrick Hasenfeld, Alex Hastie, Marina Haukness, Miten Jain, Melanie Kirsche, Mikhail Kolmogorov, Jan O Korbel, Sergey Koren, Jonas Korlach, Joyce Lee, Daofeng Li, Tina Lindsay, Julian Lucas, Feng Luo, Tobias Marschall, Jennifer McDaniel, Fan Nie, Hugh E Olsen, Nathan Olson, Trevor Pesout, Daniela Puiu, Allison Regier, Jue Ruan, Steven L Salzberg, Ashley D Sanders, Michael C Schatz, Anthony Schmitt, Valerie A Schneider, Siddarth Selvaraj, Kishwar Shafin, Alaina Shumate, Catherine Stober, James Torrance, Justin Wagner, Jianxin Wang, Aaron Wenger, Chuanle Xiao, Aleksey V Zimin, Guojie Zhang, Ting Wang, Heng Li, Erik Garrison, David Haussler, Justin M Zook, Evan E Eichler, Adam M Phillippy, Benedict Paten, Kerstin Howe, Karen H Miga, Human Pangenome Reference Consortium

A Draft Human Pangenome Reference

Wen-Wei Liao, Mobin Asri, Jana Ebler, Daniel Doerr, Marina Haukness, Glenn Hickey, Shuangjia Lu, Julian K. Lucas, Jean Monlong, Haley J. Abel, Silvia Buonaiuto, Xian H. Chang, Haoyu Cheng, Justin Chu, Vincenza Colonna, Jordan M. Eizenga, Xiaowen Feng, Christian Fischer, Robert S. Fulton, Shilpa Garg, Cristian Groza, Andrea Guarracino, William T Harvey, Simon Heumos, Kerstin Howe, Miten Jain, Tsung-Yu Lu, Charles Markello, Fergal J. Martin, Matthew W. Mitchell, Katherine M. Munson, Moses Njagi Mwaniki, Adam M. Novak, Hugh E. Olsen, Trevor Pesout, David Porubsky, Pjotr Prins, Jonas A. Sibbesen, Chad Tomlinson, Flavia Villani, Mitchell R. Vollger, Human Pangenome Reference Consortium, Guillaume Bourque, Mark JP Chaisson, Paul Flicek, Adam M. Phillippy, Justin M. Zook, Evan E. Eichler, David Haussler, Erich D. Jarvis, Karen H. Miga, Ting Wang, Erik Garrison, Tobias Marschall, Ira Hall, Heng Li, Benedict Paten

Increased mutation rate and interlocus gene conversion within human segmental duplications

Mitchell R. Vollger, William S. DeWitt, Philip C. Dishuck, William T. Harvey, Xavi Guitart, Michael E. Goldberg, Allison N. Rozanski, Julian Lucas, Mobin Asri, The Human Pangenome Reference Consortium, Katherine M. Munson, Alexandra P. Lewis, Kendra Hoekzema, Glennis A. Logsdon, David Porubsky, Benedict Paten, Kelley Harris, PingHsun Hsieh, Evan E. Eichler

Gaps and complex structurally variant loci in phased genome assemblies

David Porubsky, Mitchell R. Vollger, William T. Harvey, Allison N. Rozanski, Peter Ebert, Glenn Hickey, Patrick Hasenfeld, Ashley D. Sanders, Catherine Stober, The Human Pangenome Reference Consortium, Jan O. Korbel, Benedict Paten, Tobias Marschall, Evan E. Eichler

https://doi.org/10.1101/2022.07.06.498021; https://doi.org/10.1101/2022.07.09.499321;
https://doi.org/10.1101/2022.07.06.498874; https://doi.org/10.1101/2022.03.06.483034

A human *pangenome* reference

A Draft Human Pangenome Reference

Wen-Wei Liao, Mobin Asri, Jana Ebler, Daniel Doerr, Marina Haukness, Glenn Hickey, Shuangjia Lu, Julian K. Lucas, Jean Monlong, Haley J. Abel, Silvia Buonaiuto, Xian H. Chang, Haoyu Cheng, Justin Chu, Vincenza Colonna, Jordan M. Eizenga, Xiaowen Feng, Christian Fischer, Robert S. Fulton, Shilpa Garg, Cristian Groza, Andrea Guarracino, William T Harvey, Simon Heumos, Kerstin Howe, Miten Jain, Tsung-Yu Lu, Charles Markello, Fergal J. Martin, Matthew W. Mitchell, Katherine M. Munson, Moses Njagi Mwaniki, Adam M. Novak, Hugh E. Olsen, Trevor Pesout, David Porubsky, Pjotr Prins, Jonas A. Sibbesen, Chad Tomlinson, Flavia Villani, Mitchell R. Vollger, Human Pangenome Reference Consortium, Guillaume Bourque, Mark JP Chaisson, Paul Flicek, Adam M. Phillippy, Justin M. Zook, Evan E. Eichler, David Haussler, Erich D. Jarvis, Karen H. Miga, Ting Wang, Erik Garrison, Tobias Marschall, Ira Hall, Heng Li, Benedict Paten

Built from diploid, phased, *de novo* PacBio HiFi assemblies of 47 genetically diverse individuals (94 haplotypes):

- >99% sequence completeness
- >99% gene completeness
- >99% structural accuracy
- >99.999% base pair accuracy

Added 120 Mb of sequence

Added >1,500 gene duplications

Improved variant calling:

- 34% fewer errors in small variant discovery
- 104% more detected SVs per haplotype

Improved resolution of complex regions

Improved representation of tandem repeats

Improved RNA-seq mapping

Improved ChIP-seq analysis

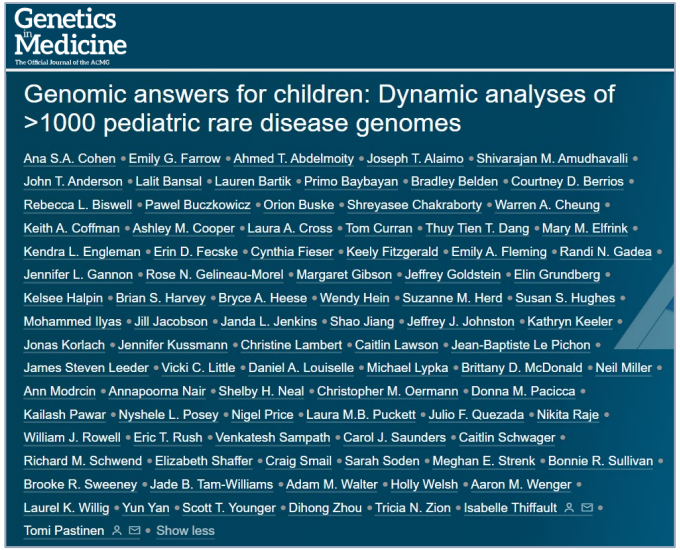
https://doi.org/10.1101/2022.07.06.498021; https://doi.org/10.1101/2022.07.09.499321;
https://doi.org/10.1101/2022.07.06.498874; https://doi.org/10.1101/2022.03.06.483034

Whole genome sequencing, with the “W”

Voice of Debbie Nickerson (UW), 2014 NHGRI Workshop - Future Opportunities for Genome Sequencing and Beyond

https://www.genome.gov/27558042/future-opportunities-for-genome-sequencing-and-beyond-a-planning-workshop-for-the-national-human-genome-research-institute

Now being realized:



Genetics in Medicine
The Official Journal of the ACMG

Genomic answers for children: Dynamic analyses of >1000 pediatric rare disease genomes

Ana S.A. Cohen • Emily G. Farrow • Ahmed T. Abdelmoity • Joseph T. Alaimo • Shivarajan M. Amudhavalli • John T. Anderson • Lalit Bansal • Lauren Bartik • Primo Baybayan • Bradley Belden • Courtney D. Berrios • Rebecca L. Biswell • Pawel Buczkowicz • Orion Buske • Shreyasee Chakraborty • Warren A. Cheung • Keith A. Coffman • Ashley M. Cooper • Laura A. Cross • Tom Curran • Thuy Tien T. Dang • Mary M. Elfrink • Kendra L. Engleman • Erin D. Fecske • Cynthia Fieser • Keely Fitzgerald • Emily A. Fleming • Randi N. Gadea • Jennifer L. Gannon • Rose N. Gelineau-Morel • Margaret Gibson • Jeffrey Goldstein • Elin Grundberg • Kelsee Halpin • Brian S. Harvey • Bryce A. Heese • Wendy Hein • Suzanne M. Herd • Susan S. Hughes • Mohammed Ilyas • Jill Jacobson • Janda L. Jenkins • Shao Jiang • Jeffrey J. Johnston • Kathryn Keeler • Jonas Korlach • Jennifer Kussmann • Christine Lambert • Caitlin Lawson • Jean-Baptiste Le Pichon • James Steven Leeder • Vicki C. Little • Daniel A. Louiselle • Michael Lypka • Brittany D. McDonald • Neil Miller • Ann Modrcin • Annapoorna Nair • Shelby H. Neal • Christopher M. Oermann • Donna M. Pacicca • Kailash Pawar • Nyshele L. Posey • Nigel Price • Laura M.B. Puckett • Julio F. Quezada • Nikita Raje • William J. Rowell • Eric T. Rush • Venkatesh Sampath • Carol J. Saunders • Caitlin Schwager • Richard M. Schwend • Elizabeth Shaffer • Craig Smail • Sarah Soden • Meghan E. Strenk • Bonnie R. Sullivan • Brooke R. Sweeney • Jade B. Tam-Williams • Adam M. Walter • Holly Welsh • Aaron M. Wenger • Laurel K. Willig • Yun Yan • Scott T. Younger • Dihong Zhou • Tricia N. Zion • Isabelle Thiffault • Tomi Pastinen • Show less

13% of new explanations in previously unsolved cases by incorporating SVs (and many more with candidate variants)

https://www.gimjournal.org/article/S1098-3600(22)00653-0/fulltext

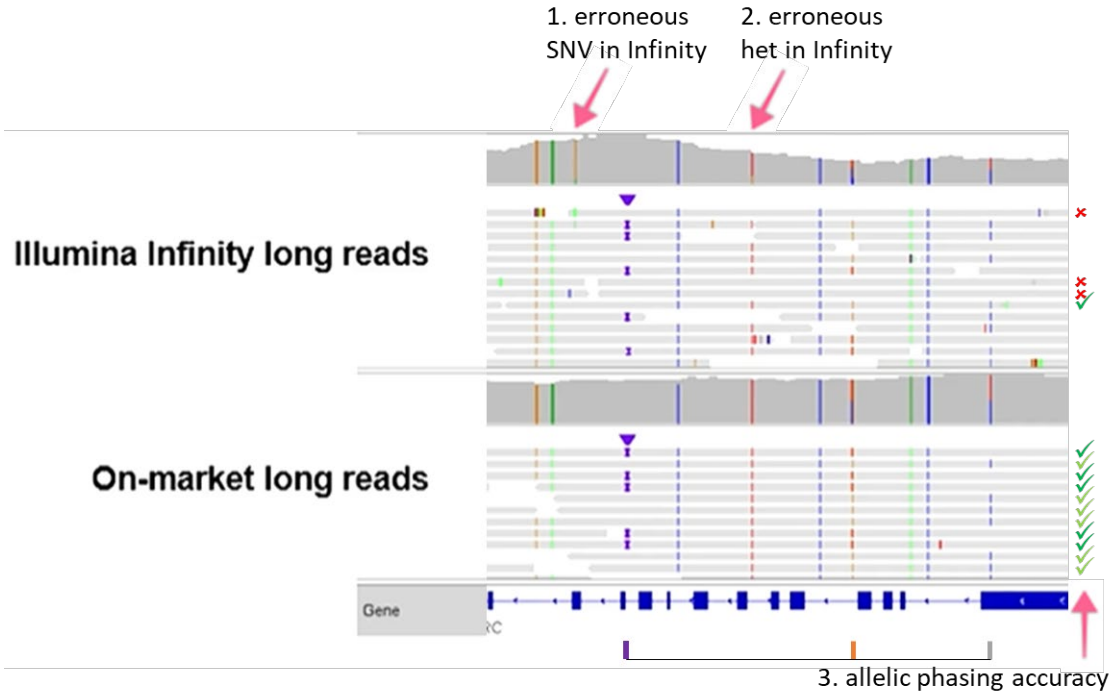
Whole genome sequencing, with the “W”

Genome	HiFi [1,2]	Short-read [3]
Small variants (SNVs + indels)	✓	✓
Structural variants (SVs)	✓	✗
Tandem repeats (TRs)	✓	✗
Dark regions	✓	✗
Phasing	✓	✗
Methylation	✓	✗

[1]Ebert et al. (2021) *Science* 372(6537):eabf7117
[2]Cohen et al. (2022) *Genetic Med*. doi:10.1016/j.gim.2022.02.007
[3]Byrska-Bishop et al. (2021) *bioRxiv* doi:10.1101/2021.02.06.430068

PacBio HiFi *vs* Illumina Infinity/CLR

From Illumina presentations[1]:



wrong answer:
Illumina Infinity/CLR

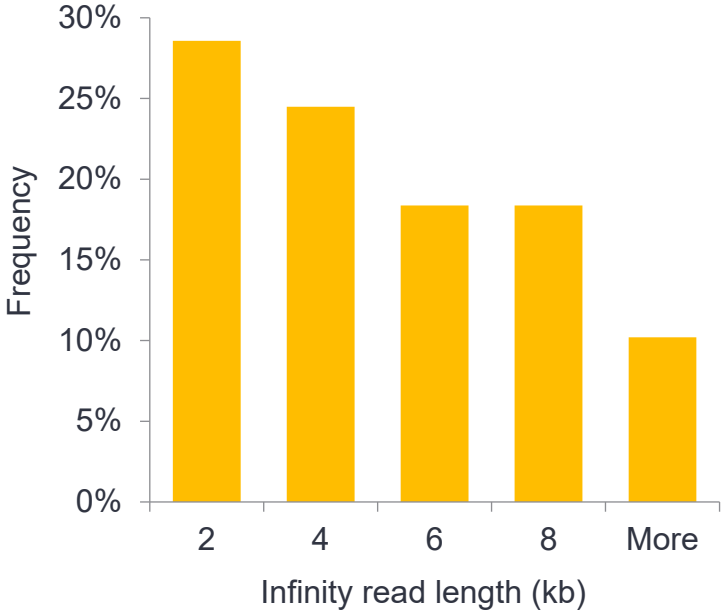
right answer:
PacBio HiFi

[1]https://www.illumina.com/events/webinar/2022/illumina-infinity-long-read-technology.html; https://www.pacb.com/blog/the-hifi-difference-getting-the-right-answer/;

PacBio HiFi *vs* Illumina Infinity/CLR

From Illumina presentations[1]:

Infinity/CLR read lengths *(STRC)[1]:*



MARCH 17, 2022

The HiFi difference – true long reads *vs.* synthetic long reads

MAY 12, 2022

The HiFi difference – Getting the right answer

SEPTEMBER 30, 2022

The HiFi difference – not being CLR

[1]https://www.illumina.com/events/webinar/2022/illumina-infinity-long-read-technology.html; https://www.pacb.com/blog/the-hifi-difference-getting-the-right-answer/; https://www.pacb.com/blog/hifi-difference-not-being-clr/; https://www.pacb.com/blog/the-hifi-difference-true-long-reads-vs-synthetic-long-reads/

Out-of-the-box 5-base sequencing

"this is the **first step for linking epigenetic sequencing and DNA sequencing in a high-resolution view of function and genetic variation**. This has potential in rare and complex diseases … because we know that 90% of susceptibility to common disease is encoded in the regulatory DNA rather than the coding DNA."

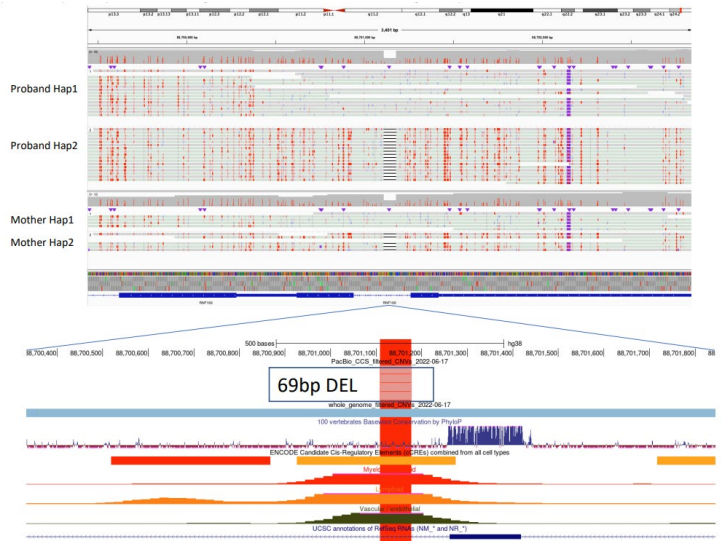
- Tomi Pastinen, CMKC

Direct haplotype-resolved 5-base HiFi genome sequencing reveals non-coding function of rare disease variants

Warren A Cheung, William J Rowell, Emily G Farrow, Adam F Johnson, Richard Hall, Ana SA Cohen, John Means, Tricia N Zion, Daniel M Portik, Christopher T Saunders, Boryana Koseva, Chengpeng Bi, Carl Schwendinger-Schreck, Byunggil Yoo, Jeffrey J Johnston, Margaret Gibson, Isabelle Thiffault, Scott T Younger, Thomas Curran, Aaron M Wenger, Elin Grundberg, Tomi Pastinen

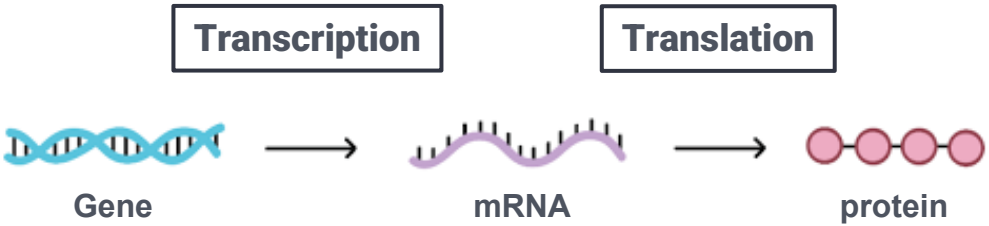
- Average hypermethylation events per sample:

- Long-range phasing allows linking hypermethylation events with rare SNVs or SVs

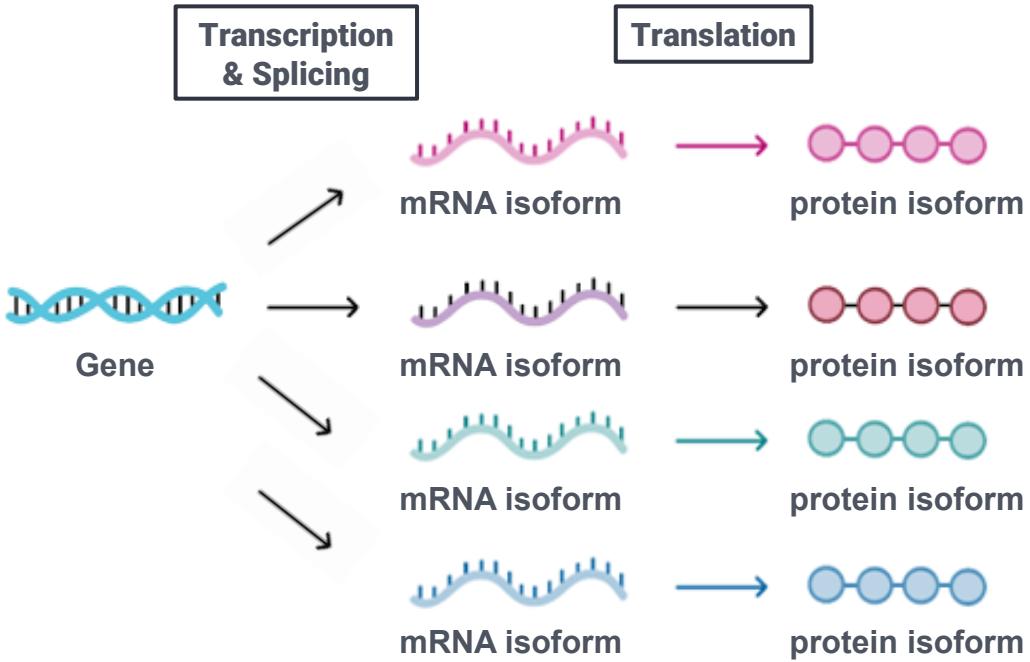


https://www.medrxiv.org/content/10.1101/2022.09.12.22279739v3; https://mendelspod.com/podcasts/5-base-sequencing-jonas-korlach-and-tomi-pastinen/

The (incomplete) central dogma of molecular biology



The actual central dogma of molecular biology



95% of human multi-exon genes have more than one isoform[1]

>7 isoforms per gene on average[2]

15% of inherited diseases & cancers associated with alternative splicing[1]

[1]https://www.sciencedirect.com/science/article/pii/S2001037020305341; [2]https://www.biorxiv.org/content/10.1101/2022.06.08.495354v1.full

Not “gene expression analysis,” but “isoform expression analysis”

SCIENCE ADVANCES | RESEARCH ARTICLE

CANCER

A comprehensive long-read isoform analysis platform and sequencing resource for breast cancer

Diogo F. T. Veiga[1]†, Alex Nesta[1,2]†, Yuqi Zhao[1], Anne Deslattes Mays[1], Richie Huynh[1], Robert Rossi[1], Te-Chia Wu[1], Karolina Palucka[1], Olga Anczukow[1,2,3]*, Christine R. Beck[1,2,3]*, Jacques Banchereau[1]*

Identification of a novel fusion transcript between human relaxin-1 (*RLN1*) and human relaxin-2 (*RLN2*) in prostate cancer

Gregor Tevz[a, 1], Sean McGrath[b], Ryan Demeter[b], Vincent Magrini[b], Varinder Jeet[a], Anja Rockstroh[a], Stephen McPherson[a], John Lai[a], Nenad Bartonicek[d], Jiyuan An[a], Jyotsna Batra[a], Marcel E. Dinger[d, e], Melanie L. Lehman[a, c], Elizabeth D. Williams[a], Colleen C. Nelson[a, c]

Huang et al. Genome Biology (2021) 22:44
https://doi.org/10.1186/s13059-021-02261-x

Genome Biology

RESEARCH Open Access

Long-read transcriptome sequencing reveals abundant promoter diversity in distinct molecular subtypes of gastric cancer

Kie Kyon Huang[1], Jiawen Huang[1], Jeanie Kar Leng Wu[1], Minghui Lee[1], Su Ting Tay[1], Vikrant Kumar[1], Kalpana Ramnarayanan[1], Nisha Padmanabhan[1], Chang Xu[1], Angie Lay Keng Tan[1], Charlene Chan[2], Dennis Kappei[2,3], Jonathan Göke[4] and Patrick Tan[1,2,4,5]*

PacBio Fusion and Long Isoform Pipeline (PB_FLIP) for Cancer Transcriptome-based Resolution of Isoform Complexity

Anthony R Miller [1], Saranga Wijeratne [1], Sean D McGrath [1], Kathleen M Schieffer [1], Katherine E Miller [2], Kristy Lee [3], Mariam Mathew [1], Stephanie LaHaye [1], James R Fitch [1], Benjamin J Kelly [1], Peter White [2], Elaine R Mardis [4], Richard K Wilson [2], Catherine E Cottrell [5], Vincent Magrini [2]

Discovery of Novel *IL3RA* (CD123) Isoforms By Long Read Transcriptomics, Heterogeneous Expression Among AML Patient Cohorts and the Implications for Anti-CD123 Therapeutics

Jason G Underwood, PhD[1*], Jenny L. Smith, MSc, MEd[2*], Lindsey F. Call, B.A.[3*], Elizabeth Tseng, Ph.D[4*], Tiffany A. Hylkema, BS[2*], Rhonda E. Ries, MA[2*], Amanda R. Leonti, MS[2*], Jason E. Farrar, MD[5], Timothy Junius Triche Jr., PhD[6] and Soheil Meshinchi, MD, PhD[2]

Detecting intragenic *trans*-splicing events with hybrid transcriptome sequencing in cancer cells

Yu-Chen Chen, Chia-Ying Chen, Tai-Wei Chiang, Ming-Hsien Chan, Michael Hsiao, Huei-Mien Ke, Isheng Jason Tsai, Trees-Juen Chuang

High-throughput RNA isoform sequencing using programmable cDNA concatenation

Aziz M Al'Khafaji PhD, Jonathan T Smith, Kiran V Garimella PhD, Mehrtash Babadi PhD, Moshe Sade-Feldman PhD, Michael Gatzen, Siranush Sarkizova PhD, Marc A Schwartz MD, PhD, Victoria Popic PhD, Emily M Blaum, Allyson Day, Maura Costello, Tera Bowers, Stacey Gabriel PhD, Eric Banks PhD, Anthony A Philippakis MD, PhD, Genevieve M Boland MD, PhD, Paul C Blainey PhD, Nir Hacohen PhD

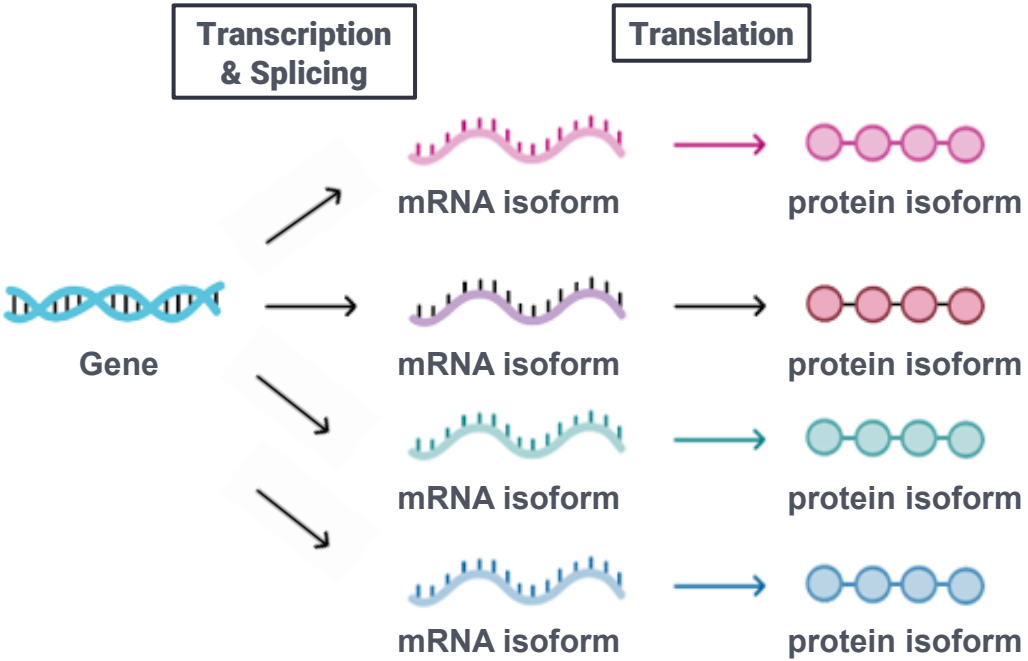
PB1511 - Isoform usage differences in schizophrenia.

Author Block: **P. Giusti-Rodriguez**[1], A. Abrantes[2], N. Ancalade[2], S. Sekle[2], F. Memic[3], A. Dijkstra[4], E. Tseng[5], G. Sheynkman[6], J. Hjerling-Leffler[3], A. B. Smit[4], P. Sullivan[7,3]; [1]Univ. of Florida Coll. of Med., Gainesville, FL, [2]Univ. of North Carolina,

PB3063 - Long-read isoform sequencing reveals aberrant splicing of *PSEN2*, but not *PSEN1*, in individuals with sporadic Alzheimer's disease.

Author Block: **P. Valdmanis**[1], K. Gudsnuk[1], C. D. Keene[1], T. D. Bird[1], S. Jayadev[1], M. M. Course[1,2]; [1]Univ of Washington, Seattle, WA, [2]Colorado Coll., Colorado Springs, CO

Example learnings from Iso-Seq analysis



2,900 of brain expressed genes are heritable at isoform level[1]

20-40% resolved by short-read sequencing[2,3]

[1]https://www.medrxiv.org/content/10.1101/2022.10.18.22281204v1; 2https://doi.org/10.1073/pnas.1400447111; [3]https://www.nature.com/articles/nbt.2705;

No plant + animal genome is too big or complex to get a high-quality reference genome

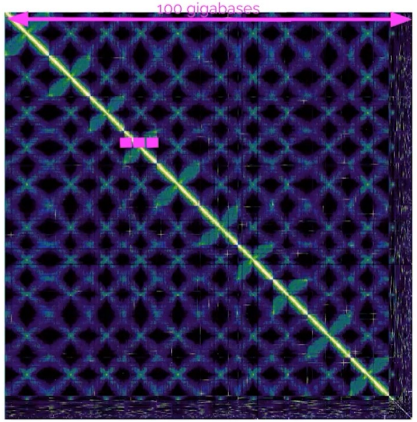
"With the desert locust, we were dealing with a much larger genome in many fewer pieces – about **8.8 Gb in just 12 chromosomes**. Next to the fruit fly, it's like an 18-wheeler next to a compact car."

- Scott Geib

Photo by B. Woo

USDA-ARS Releases Genome of the Voracious Desert Locust

Locusts: Jekyll & Hyde or the Incredible Hulk of the insect world



https://www.ars.usda.gov/news-events/news/research-news/2022/usda-ars-releases-genome-of-the-voracious-desert-locust/
https://www.dnazoo.org/post/locusts-jekyll-hyde-or-the-incredible-hulk-of-the-insect-world; https://virtual.venue-av.co.uk/e/Biodiversity_2022/WAS-Science-Keynote-Speakers

PacBio technology is the core technology of biodiversity genomics initiatives

Darwin TREE of LIFE

EARTH BIOGENOME PROJECT
sequencing life for the future of life

VGP

international BARCODE OF LIFE

i5k

ERGA
EUROPEAN REFERENCE GENOME ATLAS

African BioGenome Project
Genomics for the future of biological diversity across Africa

CALIFORNIA CONSERVATION GENOMICS PROJECT
CCGP

GAGA
The Global Ant Genomics Alliance

FISH10K
The 10,000 Fish Genomes Project

جامعة الملك عبدالله للعلوم والتقنية
King Abdullah University of Science and Technology

Desert Agriculture Initiative

CanSeq150

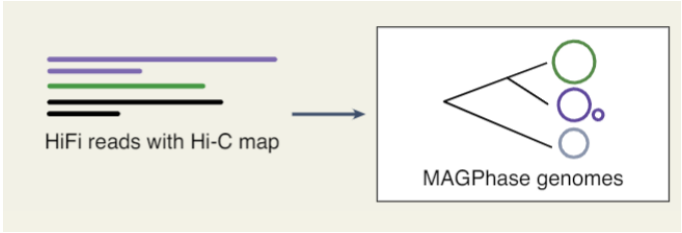
Extraordinary resolution of microbiomes

"No previous study has reported lineage-resolved high-quality MAGs at the strain level in a complex metagenome." [1]

nature biotechnology
ARTICLES
https://doi.org/10.1038/s41587-021-01130-z
Check for updates

Generating lineage-resolved, complete metagenome-assembled genomes from complex microbial communities

Derek M. Bickhart[1,10], Mikhail Kolmogorov[2,10], Elizabeth Tseng[3], Daniel M. Portik[3], Anton Korobeynikov[4], Ivan Tolstoganov[4], Gherman Uritskiy[5], Ivan Liachko[6], Shawn T. Sullivan[6], Sung Bong Shin[7], Alvah Zorea[8], Victòria Pascal Andreu[9], Kevin Panke-Buisse[1], Marnix H. Medema[9], Itzhak Mizrahi[8], Pavel A. Pevzner[2] ✉ and Timothy P. L. Smith[7] ✉



genomeweb

Tech-Boosted Genome Assembly Helps Resolve Closely Related Microbes in Metagenomic Sample

Jan 03, 2022 | Andrew P. Han

MICROBIAL GENOMICS

MAGs achieve lineage resolution

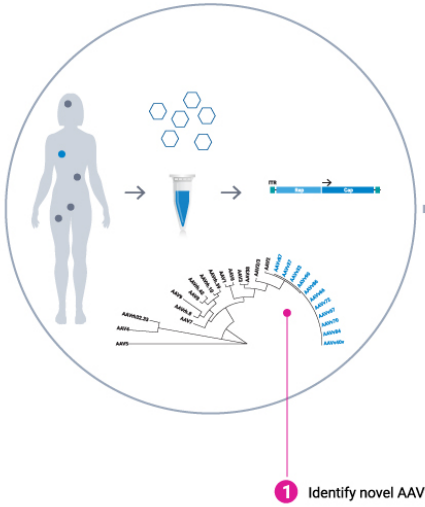
Taylor E. Reiter & C. Titus Brown ✉

[1]https://www.nature.com/articles/s41587-021-01130-z; https://www.genomeweb.com/sequencing/tech-boosted-genome-assembly-helps-resolve-closely-related-microbes-metagenomic-sample; https://www.nature.com/articles/s41564-021-01027-2

Gene therapy vector QC is now possible

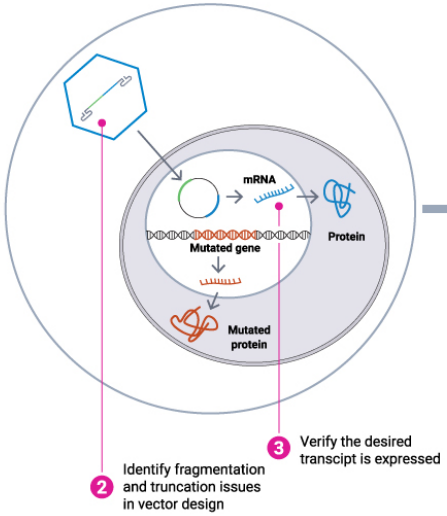
Phase 1: Discovery

Use HiFi reads to sequence tissues for **novel AAV vector discovery**



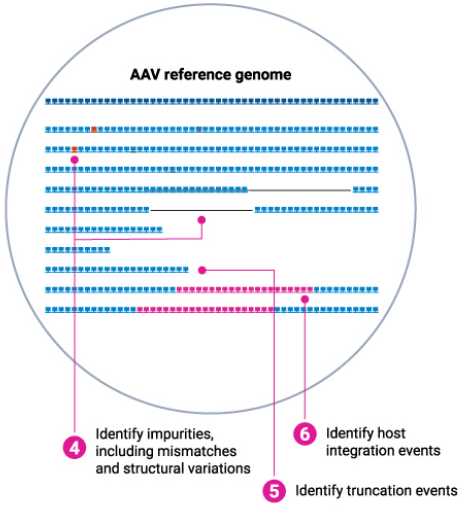
Phase 2: Design

Use HiFi reads to **improve vector design**



Phase 3: Validate

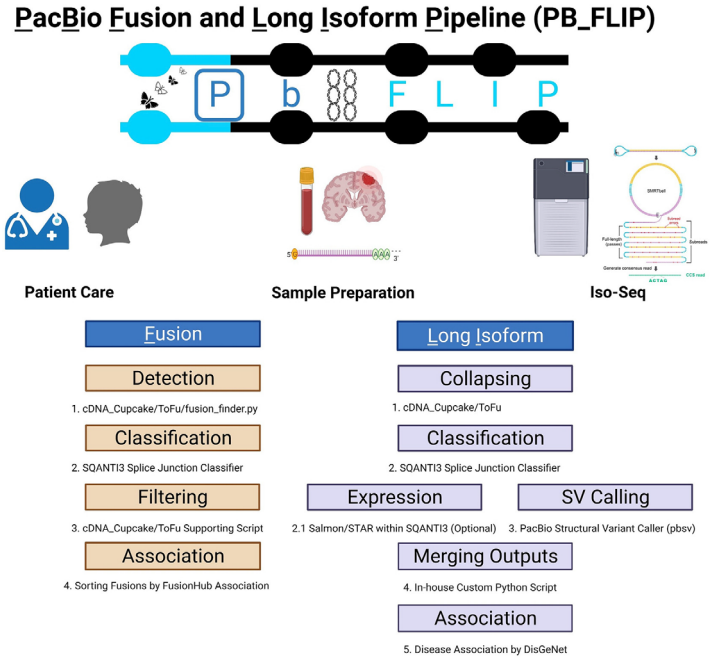
Use HiFi reads to **identify truncation, impurity, and host integration events**



Increased adoption by clinical labs

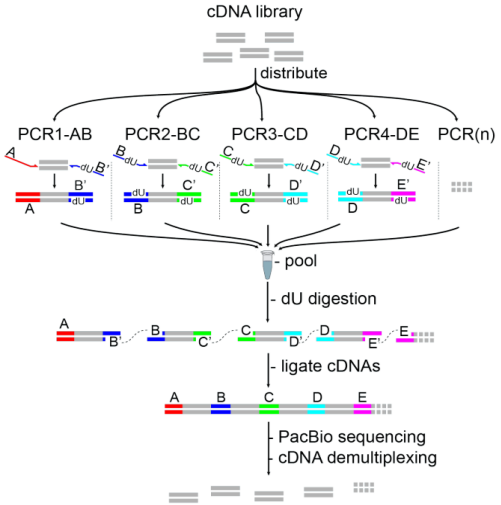
- Cancer fusion genes & somatic SVs[1]
- Thalassemia carrier screening[2-7]
- Rare disease causes[8-10]
- *BCR-ABL*, TKI resistance[11]
- Comprehensive Gaucher disease (*GBA*)[12]
- Congenital adrenal hyperplasia (*CYP21A2*)[13]

[1]PacBio Fusion and Long Isoform Pipeline (PB_FLIP) for Cancer Transcriptome-based Resolution of Isoform Complexity
[2]The value of single-molecule real-time technology in the diagnosis of rare thalassemia variants and analysis of phenotype–genotype correlation
[3]A More Universal Approach to Comprehensive Analysis of Thalassemia Alleles (CATSA)
[4]Long-Molecule Sequencing: A New Approach for Identification of Clinically Significant DNA Variants in α-Thalassemia and β-Thalassemia Carriers
[5]Detection of rare thalassemia mutations using long-read single-molecule real-time sequencing
[6]A novel 15.8 kb deletion α-thalassemia confirmed by long-read single-molecule real-time sequencing: Hematological phenotypes and molecular characterization
[7]Analysis of rare thalassemia genetic variants based on third-generation sequencing
[8]Direct haplotype-resolved 5-base HiFi sequencing for genome-wide profiling of hypermethylation outliers in a rare disease cohort
[9]Genomic answers for children: Dynamic analyses of >1000 pediatric rare disease genomes
[10]Approaches to long-read sequencing in a clinical setting to improve diagnostic rate
[11]Migrating to Long-Read Sequencing for Clinical Routine BCR-ABL1 TKI Resistance Mutation Screening
[12]https://www.wadsworth.org/sema4-opco-inc-95
[13]Long-read Amplicon Sequencing of the CYP21A2 in 48 Thai Patients With Steroid 21-Hydroxylase Deficiency

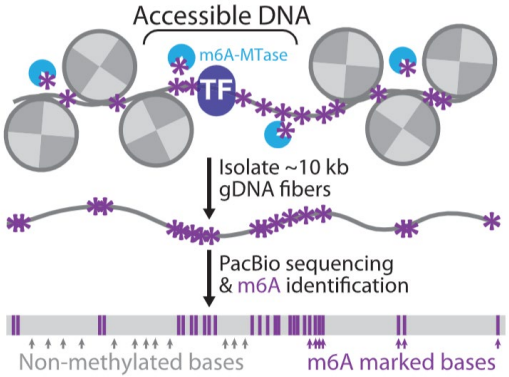


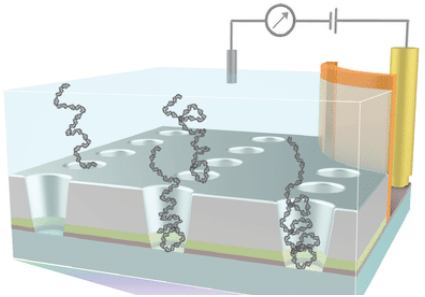
"The ability to generate long (5,000 – 15,000 bp range) **accurate reads uniquely poises long-read sequencing to revolutionize clinical NGS applications."**[1]

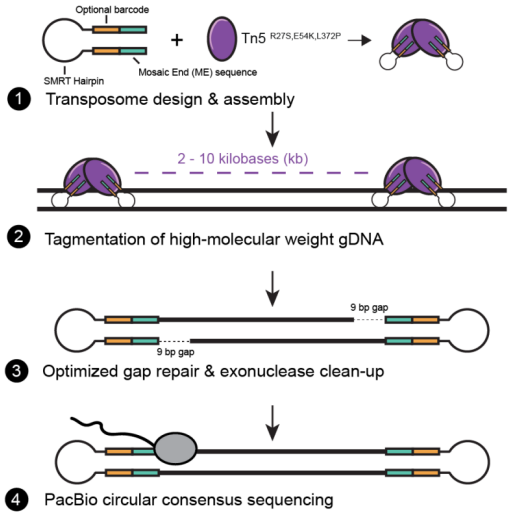
Growing innovation by the scientific community



DeepConsensus 1.0.0



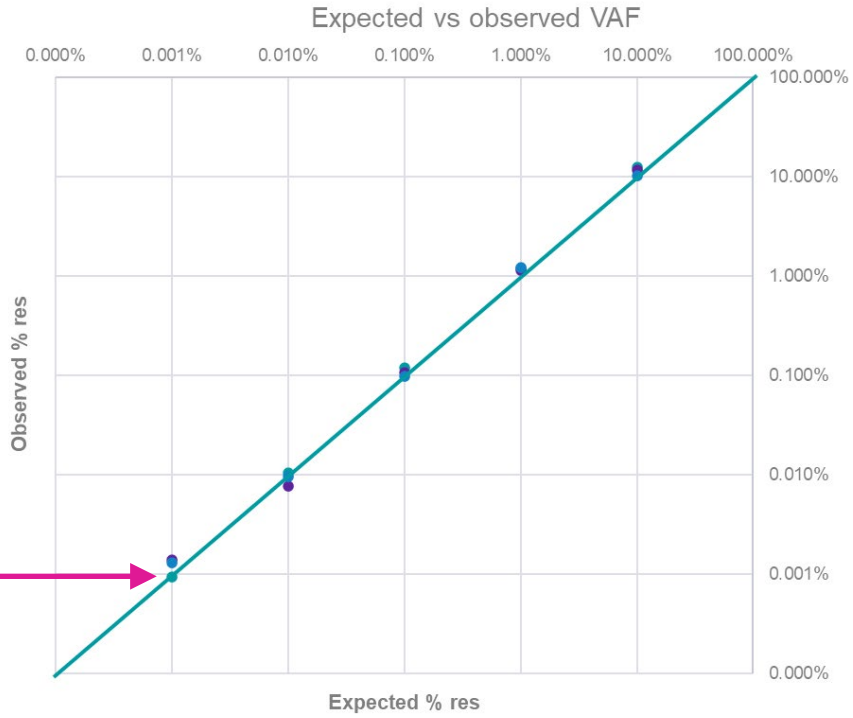




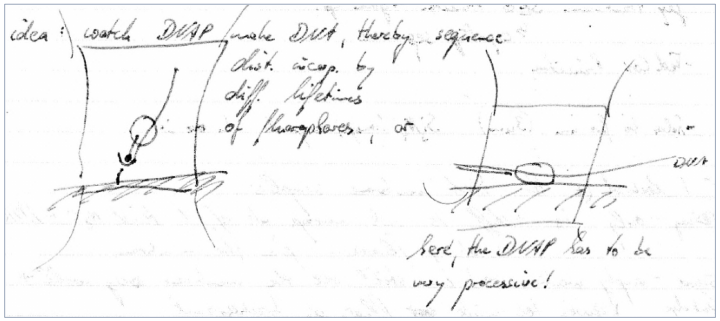
https://www.science.org/doi/10.1126/science.aaz1646; https://www.biorxiv.org/content/10.1101/2022.08.07.502893v2;
https://www.biorxiv.org/content/10.1101/2021.10.01.462818v1; https://github.com/google/deepconsensus/releases/tag/v1.0.0;
https://onlinelibrary.wiley.com/doi/10.1002/adma.202108479

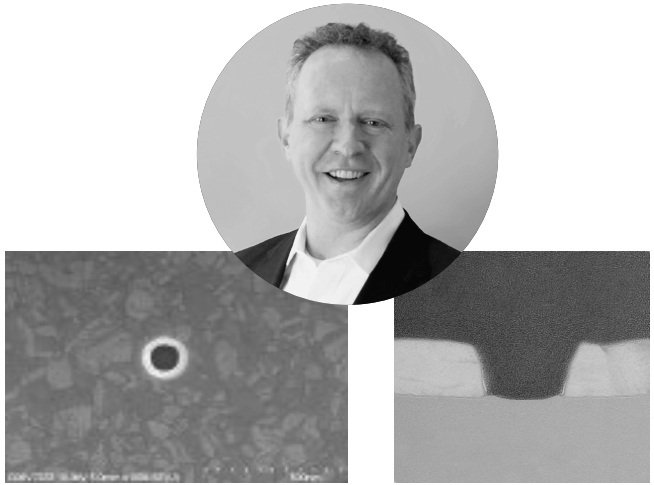
Extraordinary accuracy + sensitivity for short reads

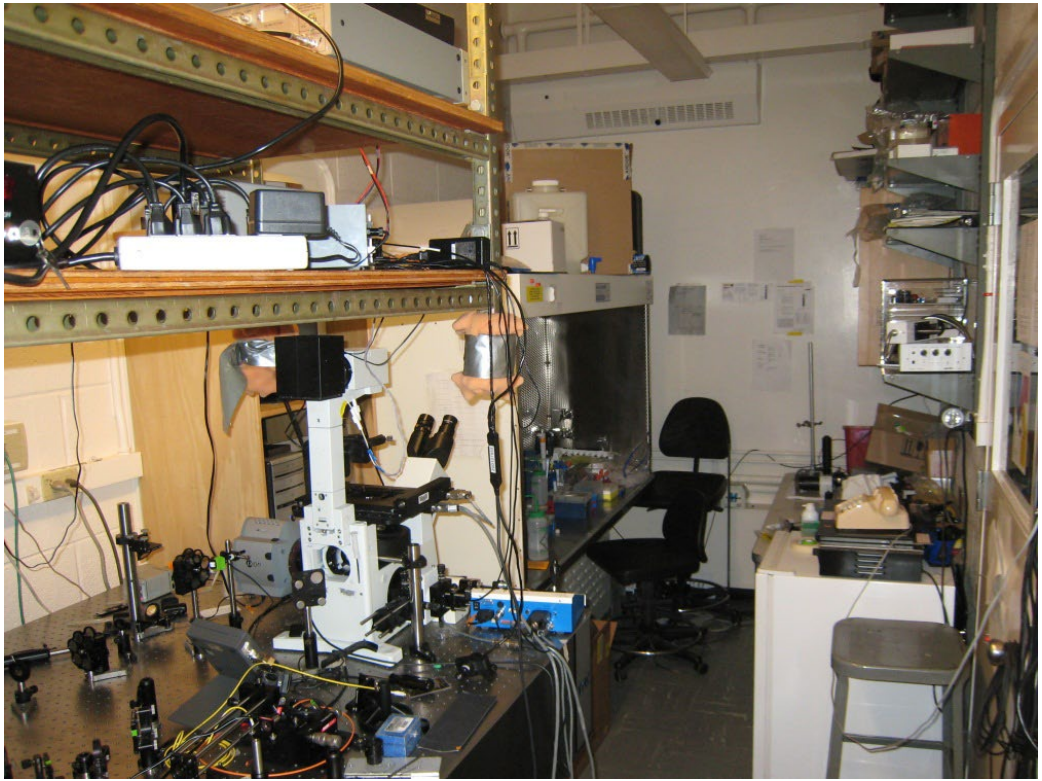
Detecting **100 molecules with** the resistance mutation, in the presence of **10 million molecules without it**



25 years ago


idea: watch DNAP make DNA, thereby sequence
distinguish by
diff. lifetimes
of fluorophores, at
DNA
Hard, the DNAP has to be
very processive!





Enabling the promise of genomics to better human health…

…by scaling paradigm changing sequencing and providing extraordinary accuracy

Revio™

Onso™

PacBio

Closing remarks

Christian Henry | President & Chief Executive Officer

November 15, 2022

Takeaways from today

1. Outlined our strategy for addressing the multi-billion-dollar revenue opportunity
2. Introduced latest sequencing technology that is poised to disrupt the market
3. Showed that we have the right team and scale to deliver
4. Demonstrated our ability to create a long-term sustainable and profitable business

Statement regarding use of non-GAAP financial measures

The Company reports non-GAAP results for net (loss) income, net (loss) income per share, gross profit, gross margins, and operating expenses in addition to, and not as a substitute for, or because it believes that such information is superior to, financial measures calculated in accordance with GAAP. The Company believes that non-GAAP financial information, when taken collectively, may be helpful to investors because it provides consistency and comparability with past financial performance. However, non-GAAP financial information is presented for supplemental informational purposes only, has limitations as an analytical tool and should not be considered in isolation or as a substitute for financial information presented in accordance with GAAP. In addition, other companies may calculate similarly titled non-GAAP measures differently or may use other measures to evaluate their performance, all of which could reduce the usefulness of the Company's non-GAAP financial measures as tools for comparison.

The Company's financial measures under GAAP include substantial charges such as merger-related expenses, change in fair value of contingent consideration and others that are listed in the itemized reconciliations between GAAP and non-GAAP financial measures included in this 2022 Investor Day Presentation. The amortization of intangible assets excluded from GAAP financial measures relates to acquired intangible assets that were recorded as part of purchase accounting last year. Such intangible assets contribute to revenue generation and its amortization will recur in future periods until they are fully amortized. Management has excluded the effects of these items in non-GAAP measures to assist investors in analyzing and assessing past and future operating performance. In addition, management uses non-GAAP measures to compare the Company's performance relative to forecasts and strategic plans and to benchmark its performance externally against competitors.

The Company has not reconciled the forward-looking non-GAAP gross margin and non-GAAP operating expenses included in this 2022 Investor Day Presentation to the most directly comparable GAAP measures because this cannot be done without unreasonable effort due to the variability and low visibility with respect to certain costs, the most significant of which are certain fair value measurements, acquisition-related items, including future amortization of developed technology, and others that may arise during the years, each of which are potential adjustments to future earnings. The Company expects the variability of these items to have a potentially unpredictable, and a potentially significant, impact on our future GAAP financial results.

The Company encourages investors to carefully consider its results under GAAP, as well as its supplemental non-GAAP information and the reconciliation between these presentations, to understand its business more fully. For historical periods, a reconciliation of the Company's non-GAAP financial measures to the most directly comparable financial measure stated in accordance with GAAP has been provided in the financial statement tables included in this 2022 Investor Day Presentation.

Pacific Biosciences of California, Inc.
Reconciliation of Non-GAAP Financial Measures
(in thousands, except per share amounts)
(unaudited)

	Nine Months Ended	Twelve Months Ended	
	September 30, 2022	December 31, 2021	December 31, 2020
GAAP net (loss) income	$ (229,864)	$ (181,223)	$ 29,403
Merger-related expenses [1]	—	31,129	—
Income tax expense (benefit) resulting from acquisitions [2]	—	(93,649)	—
Fair value adjustment to Circulomics inventory at acquisition date	—	183	—
Change in fair value of contingent consideration [3]	(2,221)	1,143	—
Amortization of intangible assets	685	380	—
Gain from Reverse Termination Fee from Illumina	—	—	(98,000)
Loss (gain) from Continuation Advances from Illumina	—	52,000	(34,000)
Non-GAAP net loss	$ (231,400)	$ (190,037)	$ (102,597)
GAAP net (loss) income per share - diluted	$ (1.03)	$ (0.89)	$ 0.17
Merger-related expenses [1]	—	0.15	—
Income tax benefit resulting from acquisitions [2]	—	(0.46)	—
Fair value adjustment to Circulomics inventory at acquisition date	—	—	—
Change in fair value of contingent consideration [3]	(0.01)	0.01	—
Amortization of intangible assets	—	—	—
Gain from Reverse Termination Fee from Illumina	—	—	(0.59)
Loss (gain) from Continuation Advances from Illumina	—	0.25	(0.21)
Other adjustments and rounding differences	0.01	0.01	0.01
Non-GAAP net loss per share - diluted	$ (1.03)	$ (0.93)	$ (0.62)
GAAP gross profit	$ 43,895	$ 58,860	$ 32,566
Fair value adjustment to Circulomics inventory at acquisition date	—	183	—
Amortization of intangible assets	550	306	—
Non-GAAP gross profit	$ 44,445	$ 59,349	$ 32,566
GAAP gross profit %	43%	45%	41%
Non-GAAP gross profit %	44%	45%	41%
GAAP total operating expense	$ 264,007	$ 269,295	$ 136,951
Merger-related expenses [1]	—	(31,129)	—
Change in fair value of contingent consideration [3]	2,221	(1,143)	—
Amortization of intangible assets	(135)	(74)	—
Non-GAAP total operating expense	$ 266,093	$ 236,949	$ 136,951

(1) Merger-related expenses consisted of transaction costs arising from the acquisitions of Omniome and Circulomics and stock-based compensation expense resulting from the acceleration of certain equity awards in connection with the Omniome merger.

(2) A deferred income tax expense (benefit) was related to the release of the valuation allowance for deferred tax assets due to the recognition of deferred tax liabilities in connection with the Omniome and Circulomics acquisitions.

(3) Change in fair value of contingent consideration was related to fair value adjustments of milestone payments payable upon the commercialization of acquired IPR&D.

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