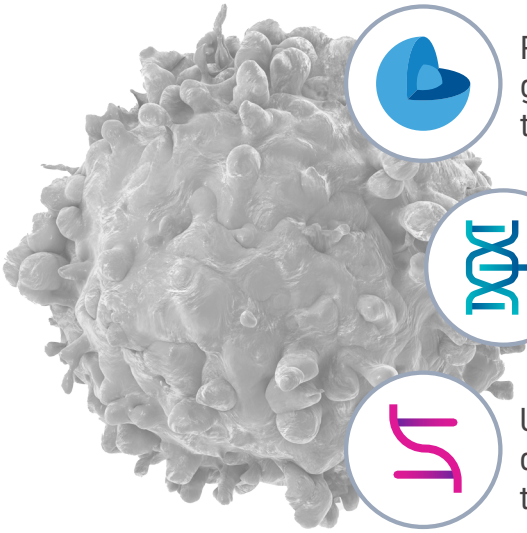
HIFI SOLUTIONS FOR CANCER GENOMICS

A more complete understanding of cancer biology and potential clinical outcomes

In order to fulfill the promise of cancer precision medicine, a more complete understanding of the complexity of cancer biology is critical. Crucial to this knowledge are multiomic tools that can accurately and comprehensively profile all types of somatic and germline variation, including rare somatic variants at low frequency that can indicate emerging recurrence or subclonal drug resistance. Existing methods can typically only capture only a fraction of this variation, requiring multiple assays and technologies to gain the whole picture. Highly accurate long-read sequencing from PacBio® allows cancer researchers to characterize the complete spectrum of cancer variation in a single assay, yielding a clearer view of its biology, helping to identify new therapeutic targets and inform clinical decision making.



Reveal hidden variation in fully phased genomes from structural variation to repetitive regions.

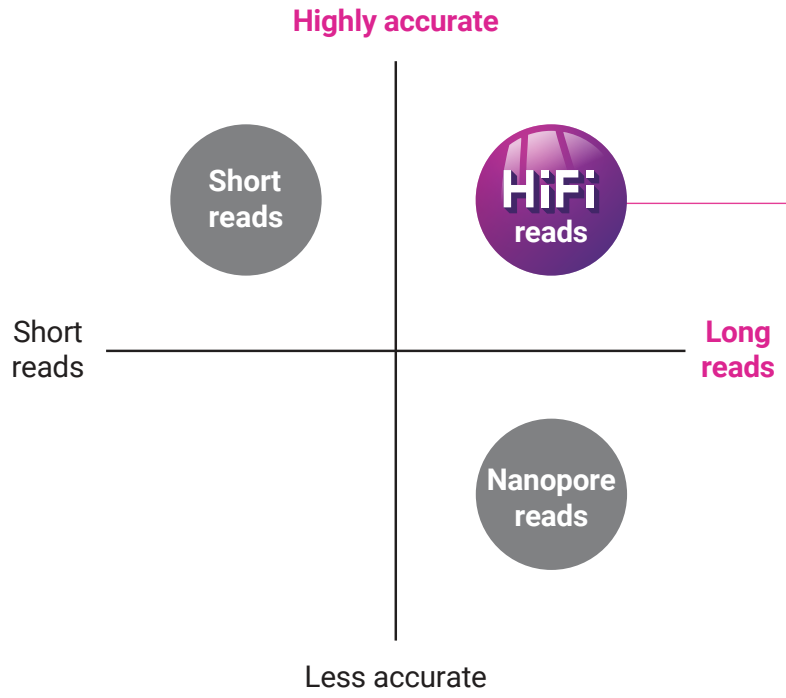
Explore the full epigenome through 5mC and 5hmC methylation detection and chromatin accessibility

Understand mechanisms of RNA dysregulation with bulk + single-cell transcriptomes

PacBio

What is HiFi sequencing?

PacBio HiFi sequencing unites long reads and accuracy, giving you the highest quality genomic data. When it comes to your cancer research, why compromise with technologies that provide limited information?



HiFi sequencing offers the best of long-read technology at 99.9% accuracy while overcoming the limitations of short-read sequencing

The benefits of HiFi reads

- Long read lengths
- Low DNA input requirements and easy library prep
- Low coverage requirements
- Small file sizes to minimize compute time
- Supported analysis tools consolidated into a single pipeline
- High read accuracy
- Fully automated sequencing and no manual washing steps
- A single technology solution

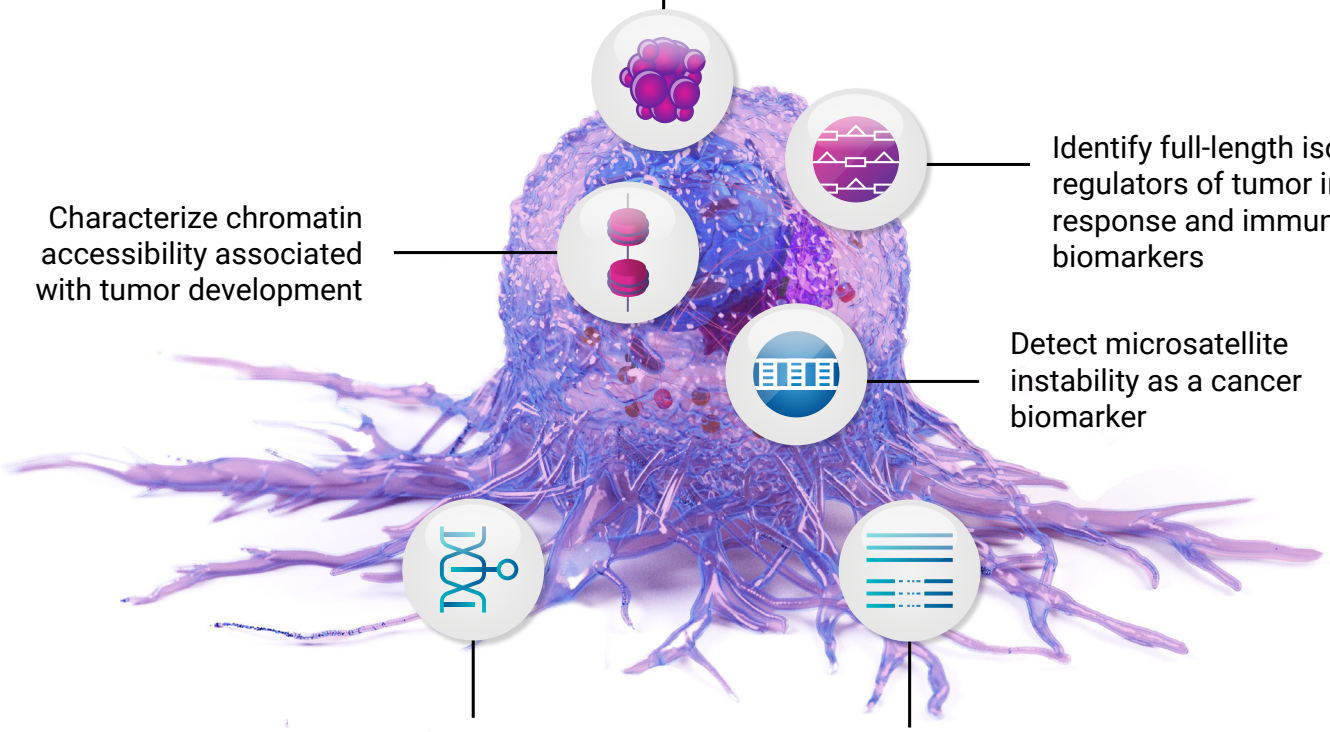
Explore the full range of cancer variants for biomarker detection and therapeutic development

Discover tumor-specific isoforms that can serve as neoantigens for cancer vaccine development

Identify full-length isoforms as regulators of tumor immune response and immunotherapy biomarkers

Characterize chromatin accessibility associated with tumor development

Detect microsatellite instability as a cancer biomarker



Identify methylation, structural variants and RNA fusions in tumors that are missed by short reads

Fully phase mutations associated with increased oncogenicity and treatment response to determine whether mutations are in *cis* or in *trans*

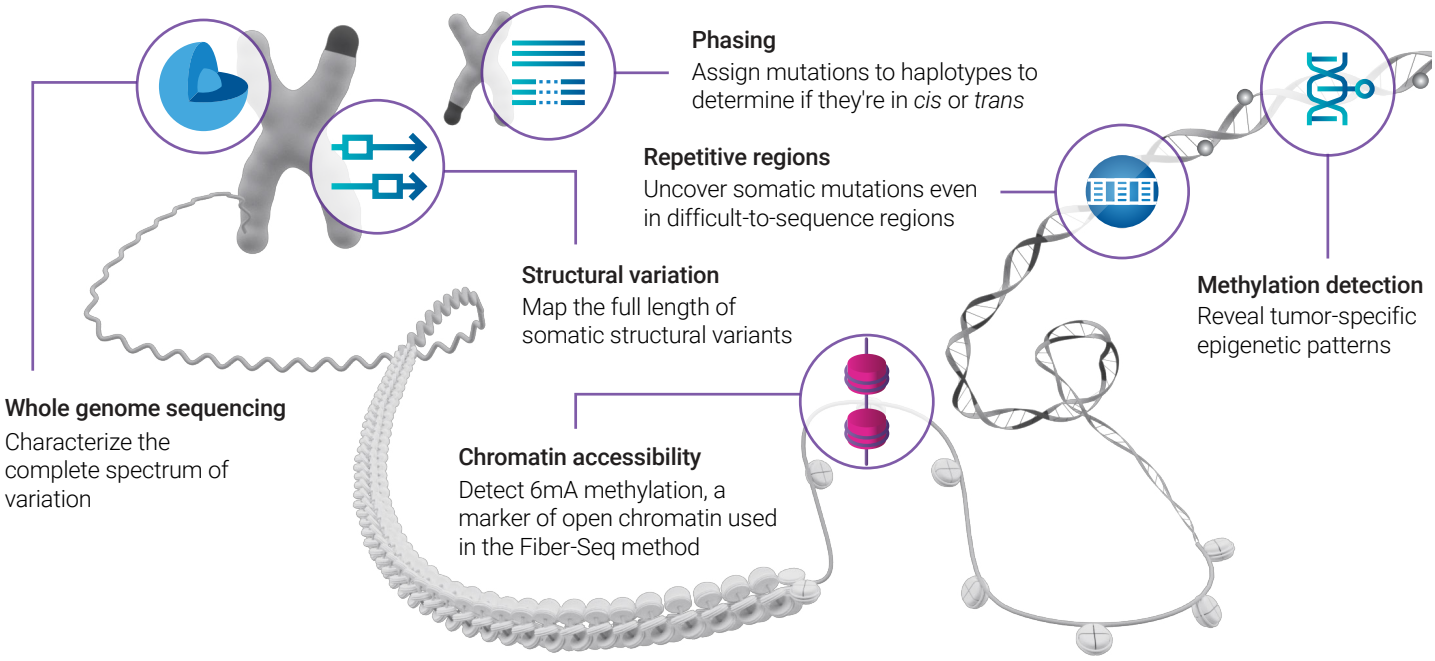
Reveal hidden variation with more complete cancer genomes and epigenomes

Characterize the full spectrum of variants and biomarkers with a single assay

- **Discover** more structural variants with long reads while maintaining the accuracy needed for small variant detection.
- **Resolve and assign** variants to haplotypes, meaning you can differentiate between *cis* and *trans* mutations to identify compound heterozygosity.
- **Detect 5mC, 5hmC, and 6mA methylation** in a single assay to reveal epigenetic silencing and changes in chromatin accessibility linked to tumor growth or treatment resistance.
- **Optimize** somatic variant detection with a complete bioinformatics workflow[4] for long-read tumor/normal whole genome sequencing.

Understanding the complexity of cancer genomes requires methods that can reveal the full breadth of cancer genomic variation, from SNVs and indels to structural variants (SVs), copy number variants (CNVs), and differential methylation. HiFi long-read sequencing allows cancer researchers to characterize the complete spectrum of somatic and germline variation, including SVs and methylation, yielding a clearer view of cancer biology and helping to identify new therapeutic targets and inform clinical decision making.

For example, researchers at Children's Mercy Kansas City identified clinically relevant SVs in pediatric leukemia samples using HiFi sequencing that were missed by routine clinical approaches[1], providing insight that impacted treatment decisions. Researchers at University of Melbourne discovered tumor-specific *BRCA2* promoter hypermethylation as a second hit leading to loss of function of the tumor suppressor in sarcoma[2]. Finally, Fiber-seq pioneers at University of Washington revealed changes in chromatin accessibility, including enhancer hijacking and biased X-chromosome inactivation, in a Mendelian condition involving bilateral retinoblastomas[3].



Understand mechanisms of RNA dysregulation with bulk + single-cell transcriptomes

Reveal more of the tumor transcriptome through comprehensive detection of isoforms, fusions, and expressed mutations

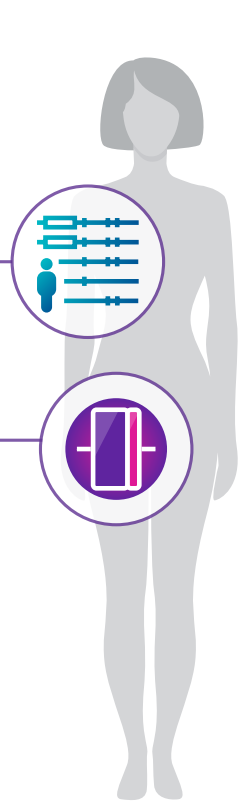
- **Discover** RNA isoforms as a source of cancer biomarkers and drug targets
- **Identify** known, novel, and complex RNA fusions with more accurate breakpoints and a complete sequence readout of associated fusion transcripts.
- **Detect** expressed mutations in RNA for genotyping and neoantigen discovery

While cancer is often considered a disease of the genome, much of the effects of cancer-causing mutations are expressed at the level of RNA. Current short-read methods rely on transcript assembly to identify isoforms and fusions, but fail to uncover much of the variation present in the tumor transcriptome. Long-read RNA sequencing with the Iso-Seq® method powered by Kinnex™ kits offers an exceptional look at alternative splicing, fusion events, and expressed somatic mutations, elevating our understanding of RNA dysregulation in cancer.

For example, a study published in *Science Advances*[5] showed that bulk long-read RNA sequencing with Iso-Seq in HER2+ breast cancer discovered 2.5× the number of novel isoforms. These isoforms were enriched in oncogenes and led to altered protein domains and localization. Another *Nature Communications* study[6] used PacBio single-cell RNA sequencing in ovarian cancer to discover a novel fusion that was previously miscategorized as an overexpression of the 3' fusion partner in short-read data. Finally, single-cell RNA sequencing with Iso-Seq in colorectal cancer discovered many tumor-specific isoforms[7], which when combined with mass spectrometry and HLA binding affinity could be used as neoantigens to develop cancer vaccines.

Bulk RNA sequencing
Characterize the complete transcriptome with full-length transcript sequencing

RNA fusions
Discover novel fusions driving tumor development

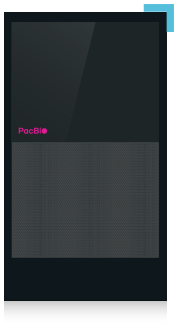


RNA isoforms
Uncover the complete repertoire of alternatively spliced transcripts

Single-cell RNA sequencing
Characterize clonality and isoform usage at the single cell level

Sequence on your terms

Whether you need the scalability of the Revio® system or the flexibility of the Vega™ system, power your research with PacBio HiFi-long read sequencing



Revio long-read system

- The Revio system with SPRQ™-Nx chemistry delivers an impressive 120 Gb per SMRT® Cell, making it the clear choice for broad-scale population genomics or precision health programs.
- With independent sequencing stages, you can run up to 4 SMRT Cells simultaneously, enabling multiomic assays on a single platform.
- Only 500 ng of sample input allows access to samples and applications previously not possible.
- The Revio system is ideal for human genomes, single cell sequencing, full-length isoform sequencing, and human methylation profiles.

Vega long-read benchtop system

- The Vega system delivers 60 Gb of premium HiFi data per SMRT Cell — accessibly priced to enable your application of choice.
- A single SMRT Cell configuration puts you in full control for streamlined, immediate sequencing.
- Innovative Revio technology packed to fit on a benchtop — equivalent HiFi data in a reduced instrument footprint.
- The Vega system is ideal for full-length isoform sequencing and targeted panels like the PureTarget™ repeat expansion kit.

Multiomic tumor profiling in a single run

SMRT Cell 1

Tumor WGS (40×)
+ native 5mC and 6mA

SMRT Cell 2

Tumor WGS (40×)
+ native 5mC and 6mA

SMRT Cell 3

Normal WGS (40×)
+ native 5mC and 6mA

SMRT Cell 4

Kinnex scRNA-seq
(100-120M reads)

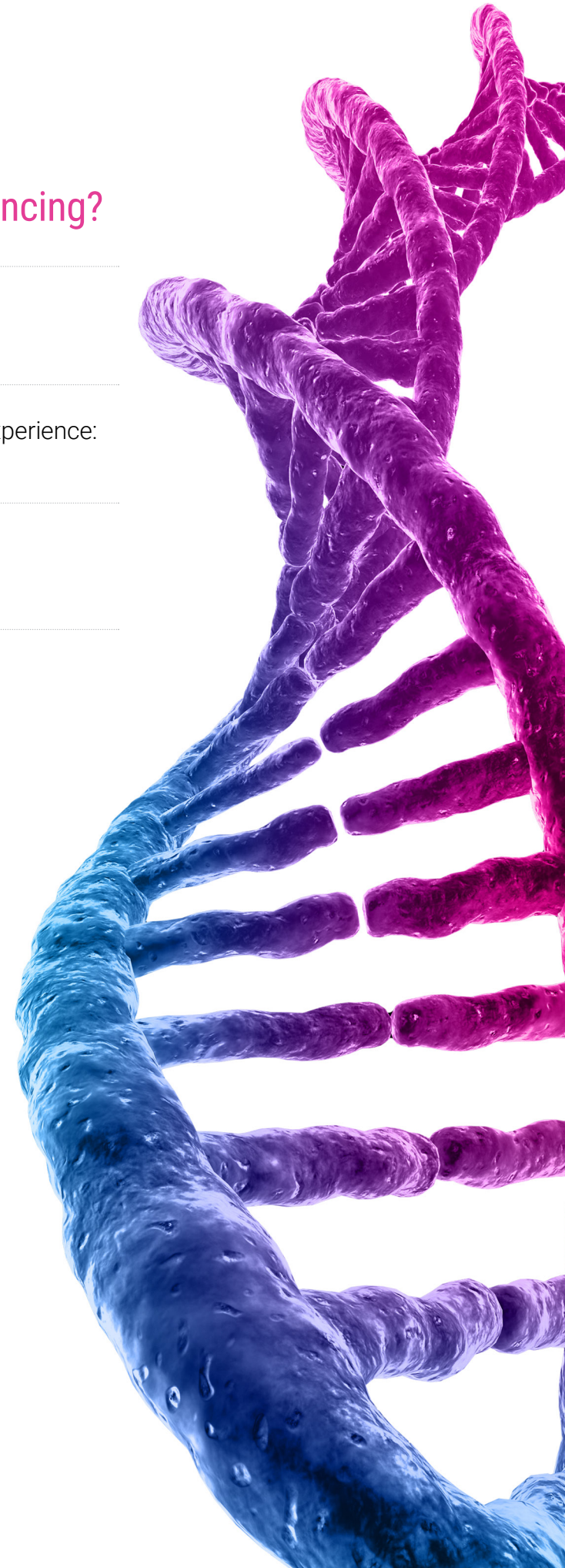
PacBio

Ready to get started with PacBio sequencing?

Learn more about cancer genomics:
pacb.com/cancer-genomics

Explore the cancer breakthrough interactive experience:
pacb.com/cancer-interactive

Connect with a PacBio scientist to get started:
pacb.com/scientist



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