Pharma Research Solutions

Comprehensive genomics for drug discovery and preclinical development

Personalis®

Genomic Insights for Optimizing Drug Development

With our Pharma Research Services portfolio of broad-content next-generation sequencing (NGS) assays and analytics, we can comprehensively address the needs of biopharmaceutical companies who wish to integrate high-quality and high-accuracy genomic and/or transcriptomic analyses to drive drug development at the discovery and preclinical research stages across a range of therapeutic programs and disease areas.

Our research assays and bioinformatics capabilities can be utilized for numerous applications that are critical in the early drug discovery and development process such as the identification of novel drug targets and the generation of deeper insights into drug candidates' mechanism of action and associated resistance mechanisms. These solutions are not only cost-effective, but can also facilitate the processing of large-scale projects in a high-throughput and reliable manner and can be used for the profiling of both human and animal models.

A select number of our Pharma Research Solutions leverage our proprietary Accuracy and Content Enhanced (ACE) Technology to provide augmented coverage of difficult-to-sequence regions of the genome and are thus optimized for exceptional sequencing performance on even the most difficult sample types.

ACE Assays	Standard Assays
• ACE Research Exome • ACE Research Transcriptome • ACE Extended Cancer Panel for DNA • ACE Extended Cancer Panel for RNA	• Whole Genome • Whole Transcriptome • miRNA-Seq

Personalis, Inc.

Powered by ACE Technology

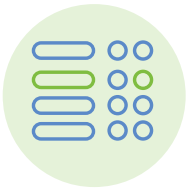
We help better inform your research studies with a selection of augmented assays powered by our ACE Technology. ACE Technology is the foundation upon which our ACE Research Exome/Transcriptome and ACE Extended Cancer Panels are built. By optimizing each step from nucleic acid extraction through to data delivery, we ensure that our partners get the most comprehensive and accurate genomic information possible.

Nucleic acid extraction and sample preparation

Personalis has developed protocols to overcome the challenges of working with difficult samples, including formalin-fixed paraffin-embedded (FFPE) specimens. Additionally, we simultaneously extract both DNA and RNA from the same sample in a sparing manner.

Sequencing

Gaps or inconsistent coverage can result in missed content. Personalis ACE Technology augments sequencing gaps for more complete coverage.



Alignment and variant discovery

Our advanced bioinformatics pipelines are optimized for accuracy and performance, resulting in superior sequence alignments and variant calls.

Variant annotation

We've implemented comprehensive annotation to overcome both mapping/nomenclature issues, and to overcome errors and inconsistencies in database curation.

Data deliverables

Data is available both as raw data files (e.g., FASTQ, BAM files) as well as reporting on biomedically-relevant genes, and is delivered with QC and statistical summary reports.

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ACE Assays

ACE Research Exome

Leveraging our patented ACE Technology, the ACE Research Exome outperforms conventional exome assays by augmenting coverage across intronic and difficult-to-sequence (high-GC content) regions, ensuring the capture of variants that would be otherwise missed (Figure 1).

The ACE Technology enables us to provide improved coverage of ~8,000 coding genes, as well as increased sensitivity to detect known and novel germline and somatic single-nucleotide variants (SNVs), insertions/deletions (indels), and copy number alterations (CNAs). This increased performance results in the delivery of higher quality genomic data and more comprehensive resolution into a drug candidate's mechanism of action and associated resistance mechanisms.

Figure 1

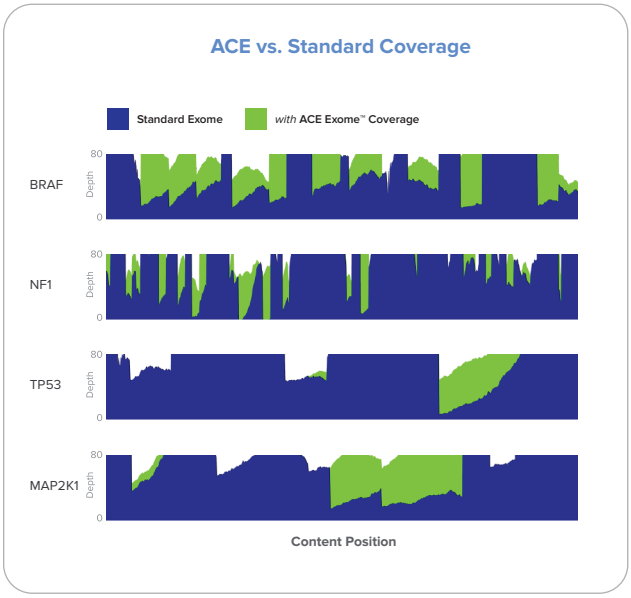

Figure 1: Example exon coverage and depth for select genes using the ACE Research Exome vs. standard exome sequencing. The blue regions show coverage and depth across the length of each gene from a standard, commercially-available assay. The green regions illustrate ACE augmentation of regions of the gene which are poorly covered by the standard offering. Personalis returns both the green and blue regions.

Technical Details

Genes Covered	~20,000
Genes Augmented (with ACE Technology)	~8,000 biomedically-important genes, including >1,400 cancer-related genes
Sequencing Information	Standard configuration: ~120X mean coverage Read length: 2x150bp Instrumentation: Illumina NovaSeq
Cancer Analysis Configuration	Paired tumor/normal or tumor only
Species	Human

ACE Research Transcriptome

Transcriptome sequencing provides complementary information for your research studies, including data on gene expression levels, fusion events, variants in expressed genes, and RNA allelic fraction, as well as providing insights into functional pathways and the regulatory networks in biological systems. RNA-seq is commonly utilized in drug discovery for the identification of drug-related genes; further aiding in the elucidation of a given drug's mechanism of action. This is enabled via the investigation of drug-induced, genome-wide gene expression alterations which, in turn, can determine the transcriptional impact of drug candidates and can help in accelerating the target identification process.

Optimized for FFPE

Many clinical studies depend on tissue archives that have been fixed using FFPE procedures. This preservation process makes it difficult to obtain a pure sample and often leads to RNA degradation, which impacts the ability of traditional RNA-seq methodologies like poly-A-selection and ribosomal RNA (rRNA)-depletion to generate accurate or usable results. To overcome this challenge, Personalis has developed an exome-capture transcriptome protocol based on our ACE Technology that enables us to produce high-quality transcriptome sequencing results from challenging samples. Additionally, our sample preparation process allows RNA to be co-extracted from the same tissue sample used for exome sequencing, thus maximizing the data generated from limited samples.

Our enrichment protocol directly selects for transcripts using the optimized ACE capture probes, specifically targeting regions of interest and eliminating background noise. We've demonstrated that with the use of the ACE Research Transcriptome protocol, >90% of the bases are mapped within the coding and untranslated regions (UTRs) of the RNA (Figure 2). Thus, the ACE approach results in high-quality data and low off-target reads.

Figure 2

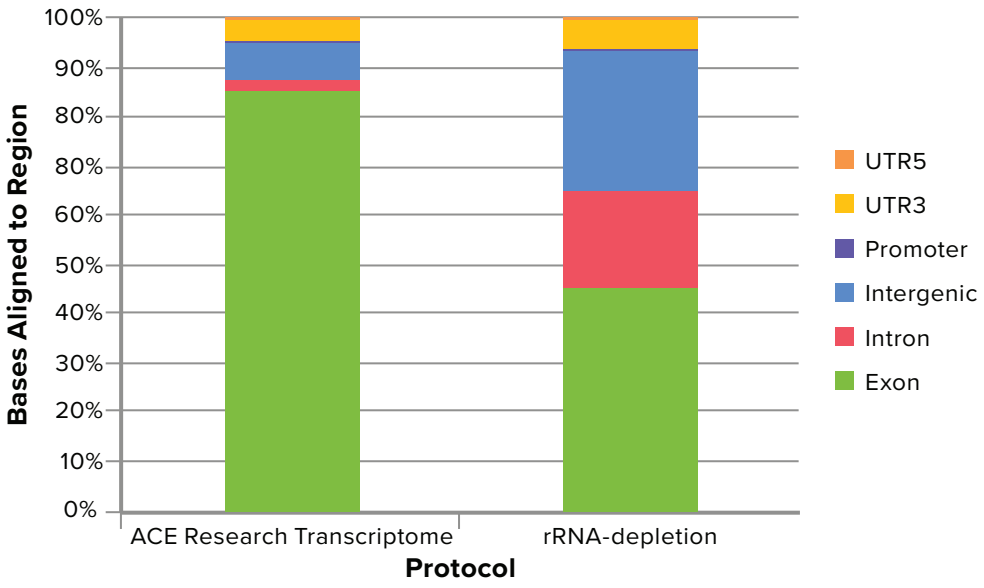

Figure 2: ACE Research Transcriptome focuses on regions of high interest.

Accurate gene expression data

Using paired FFPE and matched adjacent fresh frozen tissues, we found high correlation of normalized (TPM) gene expression (Figure 3) across various tumor types. This data demonstrates the ACE Research Transcriptome is an accurate and reliable method for characterizing gene expression in even challenging materials such as FFPE.

Figure 3

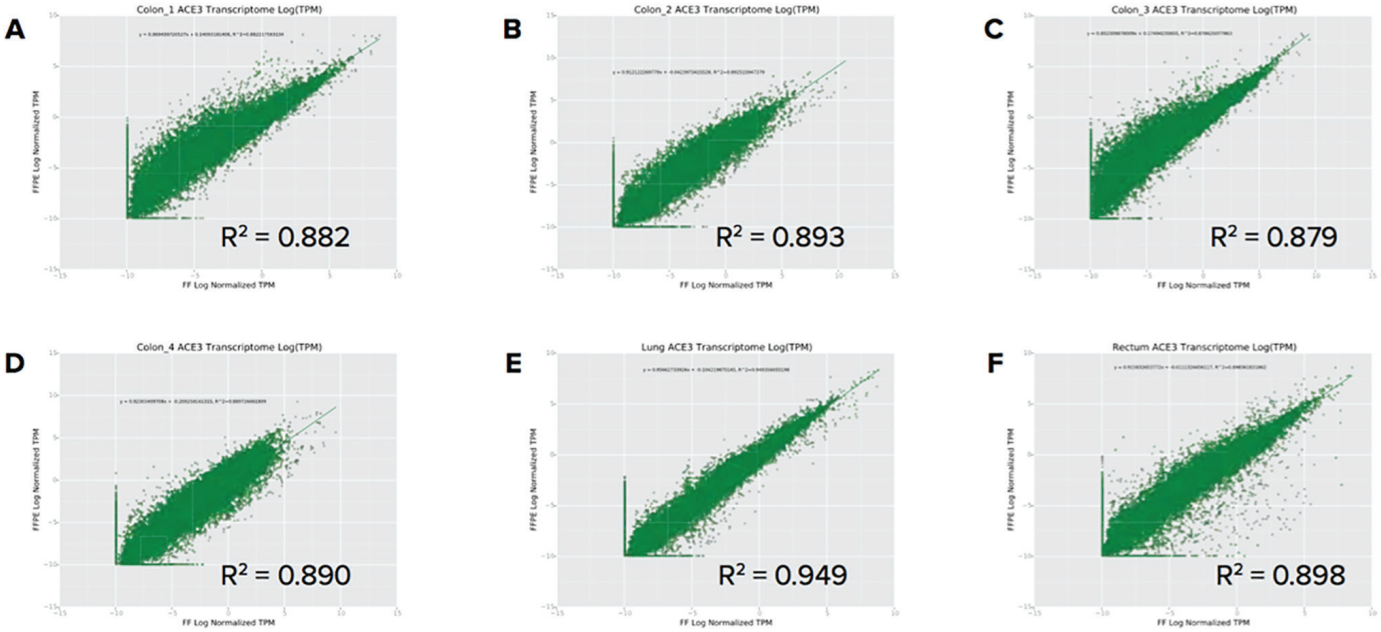

Figure 3: Correlation plots of $\log_2$ transcripts per million (TPM) between matched FF (x-axis) and FFPE (y-axis) pairs in A-D) colon, E) lung, and F) rectal tumor samples.

Technical Details

Genes Covered	~20,000
Genes Augmented	~8,000 biomedically-important genes, of which >1,400 are cancer-relevant
Sequencing Information	Standard configuration: 25M or 50M paired-end (50M or 100M total) reads Read length: 2x150bp Instrumentation: Illumina NovaSeq
Cancer Analysis Configuration	Tumor only
Species	Human

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ACE Extended Cancer Panel for DNA

Covering more than 1,400 cancer genes, the ACE Extended Cancer Panel for DNA includes a core set of clinically-actionable[1] genes, all genes in the Cancer Gene Census, genes from TCGA reports, and those within canonical cancer pathways proposed by leading academic groups.

By once again leveraging our ACE Technology, the panel's performance has been enhanced over that of standard approaches by augmenting and repairing coverage gaps. This is accomplished by performing separate targeted capture under optimized sample preparation conditions and combining data from these individual preps into a single high-quality sequencing dataset. This results in more complete coverage and the highly sensitive and specific identification of known and novel SNVs, indels, and CNAs.

Technical Details

Genes Covered	>1,400
Genes Augmented	>1,400
Sequencing Information	Standard configuration: >500X (tumor)/>100X (normal) mean coverage Read length: 2x150bp Instrumentation: Illumina NovaSeq
Assay Sensitivity	>99%
Assay Specificity	>99%
Cancer Analysis Configuration	Paired tumor/normal or tumor only
Species	Human

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ACE Extended Cancer Panel for RNA

The ACE Extended Cancer Panel for RNA targets the same genomic footprint (>1,400 cancer-related genes) as the ACE Extended Cancer Panel for DNA, and provides unparalleled detection of unique variant types that are more difficult to identify with DNA sequencing analysis alone. The assay provides information including gene expression levels, gene fusions, SNVs, and indels for all targeted genes. Crucially, the panel enables extensive gene fusion discovery of both clinically-actionable[2] fusions involving critical genes such as ALK, ROS1, and RET, as well as the detection of novel fusions involving other genes that might be missed by NGS panels that either target a smaller number of genes or that don't provide RNA information.

Personalis' targeted approach to RNA sequencing provides researchers with higher quality RNA results compared to those achieved by conventional RNA-seq practices. We accomplish this by excluding intronic RNA from unspliced transcripts and by using a capture method that can isolate degraded RNA more effectively than other methods. This results in high-quality RNA reads with minimized background.

Technical Details

Genes Covered	>1,400
Genes Augmented	>1,400
Sequencing Information	Standard configuration: 8M paired-end (16M total) reads Read length: 2x150bp Instrumentation: Illumina NovaSeq
Cancer Analysis Configuration	Tumor only
Species	Human

[1,2] Genes referred to here as being clinically-actionable reflects the fact that the efficacy of cancer drugs, FDA approved or in clinical trials, are thought to be modulated by variants in these genes. This does not imply that this panel is for clinical use — it is a Research Use Only service.

ACE Analytics

DNA Analysis

The ACE DNA Analysis Pipeline performs high-accuracy alignment and variant calling for both germline and (where applicable) somatic variants. Variant types including SNVs, indels, and CNAs are reported. All of these variants are annotated against databases of known variants collated into reports. In addition, filtered and refined reports are generated for ease of use. Finally, QC reports delineating sequencing metrics as well as germline and somatic analysis summary statistics are included.

RNA Analysis

The ACE RNA Analysis Pipeline performs a high-accuracy gapped alignment and variant calling. This Personalis pipeline is capable of detecting a wide variety of important variants from RNA sequencing data including SNVs and indels, as well as gene fusion[3] events which can be difficult to detect with DNA analysis alone. RNA read depths can also be used to digitally quantify relative gene expression. To further empower researchers, our pipeline thoroughly annotates variants using a wide variety of sources, including information covering many important germline and somatic features. For cancer analysis, comparison of variants identified in RNA vs. DNA, from the same sample, enables the determination of which DNA variants are actually expressed, and at what level, in tumor samples. As with the DNA analysis, detailed reports are provided for each variant class, easing accessibility.

[3] Fusions referred to here as being clinically-actionable reflects the fact that the efficacy of cancer drugs, FDA approved or in clinical trials, are thought to be modulated by occurrence of these fusions. This service is intended for Research Use Only and not for use in diagnostic procedures.

Bioinformatics deliverables

DNA Analysis

- Raw data files: FASTQ, BAM
- Germline & somatic small variant (SNVs, indels) analysis and report: VCF file
- Germline & somatic CNA reports and plots
- LOH reports and plots (exome only)
- Variant annotation: VAR file
- Filtering and annotation of variants by cancer relevance and frequency
- Quality Control report and Statistical Summary report

RNA Analysis

- Raw data files: FASTQ, BAM
- Variant (SNVs, indels) analysis and report: VCF file
- Gene variant analysis (with additional filtering by cancer relevance, where applicable)
- Fusion gene analysis and report
- Gene-based expression results
- Quality Control report and Statistical Summary report

Standard Assays

Whole Genome

In recent years, the declining cost of NGS has resulted in the increased use of broad genomic characterization approaches, including whole genome sequencing (WGS), for various research applications. Historically, the role of WGS in drug development has largely been limited to the analysis of genetic variations across the genomes of similarly-affected individuals to enable the identification of disease-associated germline variants. However, the reduction in the cost of contemporary sequencing approaches has coincided with researchers' need for more comprehensive molecular information in the disease areas of cardiology, endocrinology, rare disease, autoimmune disorders, and ever-increasingly, cancer.

WGS is an attractive option for many researchers due to its ability to provide insights into non-coding variation as well as it's unrivaled resolution of genome-wide structural variations, rearrangements, and exon duplications, the impact of which are becoming more pronounced in many disease states, especially cancer. While the use of WGS in the study of cancer genomes to date has been largely stymied by the prohibitive cost, the complexity and scale of WGS bioinformatics analysis has also been a deterrent to many researchers. However, with improved computational methods for comprehensive analysis and the increasing affordability of sequencing, there's never been a better time to integrate a WGS strategy into your early drug development studies.

Personalis is one of the largest processors of human whole genome sequences in the world today and is your ideal partner for any WGS project across disease areas.

Technical Details

Genes Covered	All coding and non-coding regions
Sequencing Information	Standard configuration: 30X or 60X mean coverage Read length: 2x150bp Instrumentation: Illumina NovaSeq
Species	Human

Whole Transcriptome

As mentioned in the ACE Research Transcriptome section above, RNA-seq can be utilized in many ways at the early stages of drug discovery and preclinical development. While we encourage the use of the ACE Research Transcriptome in the majority of RNA-seq-related projects due to the benefits afforded by the use of the ACE Technology, we also provide whole transcriptome services that utilize ribosomal RNA (rRNA)-depletion or polyadenylated (poly-A)-selection methodologies for the profiling of intact (non-degraded) RNA starting material, where applicable.

By offering both poly-A-selection and rRNA-depletion methodologies for whole transcriptome profiling, in addition to our exome-capture-based ACE Research Transcriptome assay, our suite of RNA-seq assays gives us the flexibility to cater to the needs of our customers across many application areas in early drug development.

Technical Details

Genes Covered	>20,000
Sequencing Information	Standard configuration: 25M or 50M paired-end (50M or 100M total) reads Read length: 2x100bp Instrumentation: Illumina NovaSeq
Species	Human Mouse

miRNA-Seq

Micro RNAs (miRNAs) are a small non-coding type of RNA molecule (18-40 nucleotides in length) that play a functional role in the regulation of RNA silencing and post-transcriptional gene expression. These molecules are heavily involved in the regulation of a wide-range of biological and pathological processes. It has been shown that miRNAs influence the activity of genes related to cell proliferation, cell cycle modulation, and apoptosis, while they also play a critical role in the absorption, distribution, metabolism, and excretion of chemotherapeutic agents and their metabolites. Thus, miRNAs have been widely implicated in the development of resistance to chemotherapies in many different tumor types.

miRNA-seq enables the investigation of the function of small RNAs and the evaluation of regulatory networks of miRNAs, their target genes, and whether any of these genes may be important in the acquisition of drug resistance.

Technical Details

Sequencing Information	Standard configuration: 10M single-end reads Read length: 1x75bp Instrumentation: Illumina HiSeq
Species	Human

Analytics

Personalis can provide a broad range of analytical capabilities in order to ensure the delivery of the data derived from our standard sequencing assays in a format that makes sense for individual projects. For more information on our analytical capabilities, contact your local Business Development Manager or contact us at the email address shown below.

Supporting Drug Development Innovation

Our Pharma Research Solutions are designed to provide you with the most complete and accurate genomic data possible for your research studies. To learn more about how we can partner together to advance therapy development, contact us at **info@personalis.com**.

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