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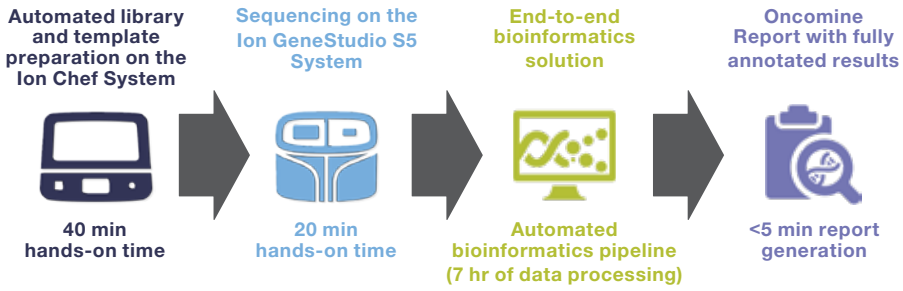
Comprehensive genomic profiling without compromises

The new, enhanced Oncomine Comprehensive Assay Plus

- **Single-gene biomarkers—**detect all types of single-gene variants, such as single-nucleotide variants (SNVs), insertions and deletions (indels), novel and known fusions, splice variants, and copy number variants (CNVs), including both copy number gains and losses
- **Multiple-gene biomarkers—**study potential response to immunotherapies with measurement of tumor mutational burden (TMB), predisposition to genetic hypermutability by comparing microsatellite instability (MSI) regions, and analyze mutational signatures for insights into etiological factors in tumorigenesis
- **Homologous recombination repair deficiency (HRD) research—**detect both gene-level and sample-level loss of heterozygosity (LOH) to assess genomic instability and mutations in 42 key genes in the homologous recombination repair (HRR) pathway
- **Low input requirements—**formalin-fixed, paraffin-embedded (FFPE) sample inputs of 20 ng DNA or RNA are sufficient to profile over 500 genes, helping ensure more samples can be analyzed
- **High testing success—**high sequencing success rates (up to 95%) combined with low QNS (quantity not sufficient) results, help ensure more samples are successfully tested
- **Bioinformatics solution—**streamlined bioinformatics analysis pipeline is optimized for the Ion Torrent™ Oncomine™ Comprehensive Assay Plus and packaged in a user-friendly experience with Oncomine Report and fully annotated results
- **Highly automated workflow—**with ~1 hr of hands-on time, supporting lab efficiency as well as helping to reduce possible errors due to handling

End-to-end solutions



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New: FusionSync technology

Key considerations for optimal fusion detection

- Fusion detection from low-input samples
- Detection of low level of fusion transcripts
- Ability to detect novel fusions for driver genes

With the Ion Torrent™ FusionSync™ technology, the Oncomine Comprehensive Assay Plus now covers >1,300 isoforms across 49 fusion drivers, enabling highly sensitive and robust detection of known fusions and novel combinations of known fusion partners at low levels of a tumor-specific fusion transcript in a background of normal RNA and with minimal input down to 20 ng. Simultaneously, the exon-tiling imbalance approach is now enabling this assay to detect novel fusions with key fusion driver genes such as *ALK, FGFR2, NTRK1, NTRK2, NTRK3,* and *RET* (Figure 1). For each driver gene in which a fusion is detected, the software also predicts the position of the fusion breakpoint relative to the kinase domain with high confidence. This is critical, as an intact kinase domain is essential for the pathogenicity of a fusion event.

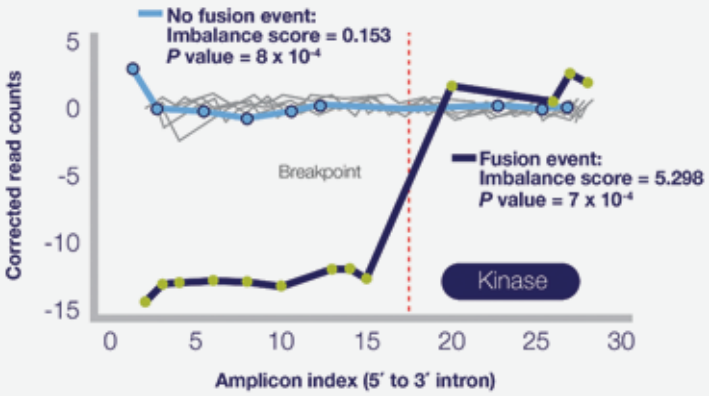


Figure 1. Detecting a novel fusion via an exon-tiling imbalance approach. Internal R&D data.

- Software measures the intragenic 3' to 5' expression ratio for each gene and compares the ratio to the baseline (normal sample).
- Genes that do not undergo a fusion event are expected to have a 3' to 5' expression ratio similar to the baseline.
- Genes that undergo a fusion event typically have a 3' to 5' expression ratio greater than the baseline.

New: Homologous recombination repair deficiency (HRD) research

HRD is becoming an important biomarker in precision oncology clinical research. Under normal conditions, errors during homologous recombination are repaired in the HRR pathway (Figure 2). Errors in the HRR pathway, such as loss-of-function or deleterious mutations in the associated genes, lead to higher levels of genomic instability. The Oncomine Comprehensive Assay Plus is a single assay for all HRR gene mutations as well as for measuring genomic instability by assessing (LOH) at both the gene level and sample level, and identifying mutational signatures.

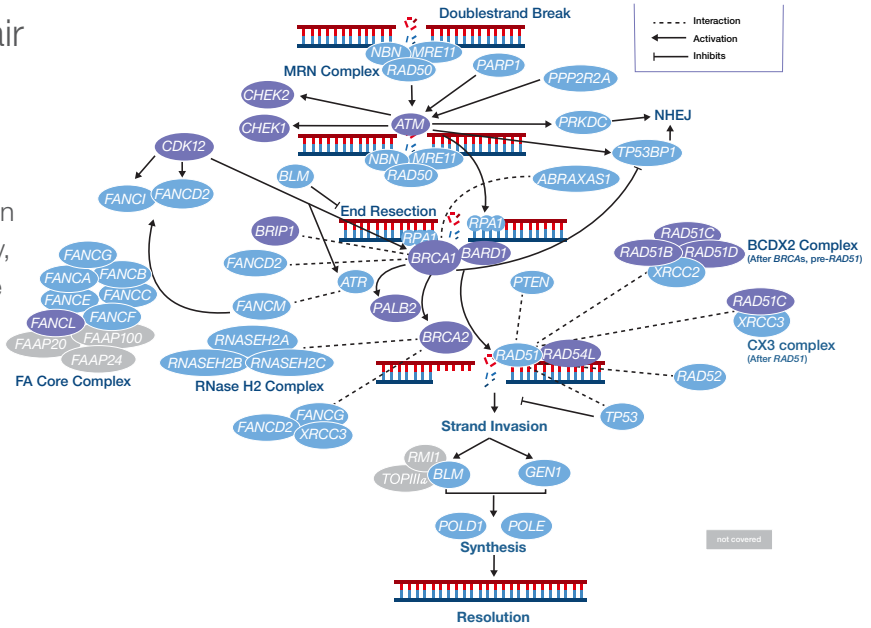


Figure 2. HRR pathway. Non-grey genes are covered in the Oncomine Comprehensive Assay Plus. Purple genes were included in clinical trials with prostate cancer clinical research samples.

Mutation detection of HRR pathway genes

The significant role of HRR genes in maintaining genome stability and tumor suppression has been studied extensively, especially in the *BRCA1* and *BRCA2* genes. In recent years, it has been demonstrated that alterations in the 'BRCAness' pathway, including HRR genes, may increase the risk of developing tumors. The status of HRR genes is now considered a new potential biomarker for precision oncology. Figure 3A shows the HRR genes covered in this assay.

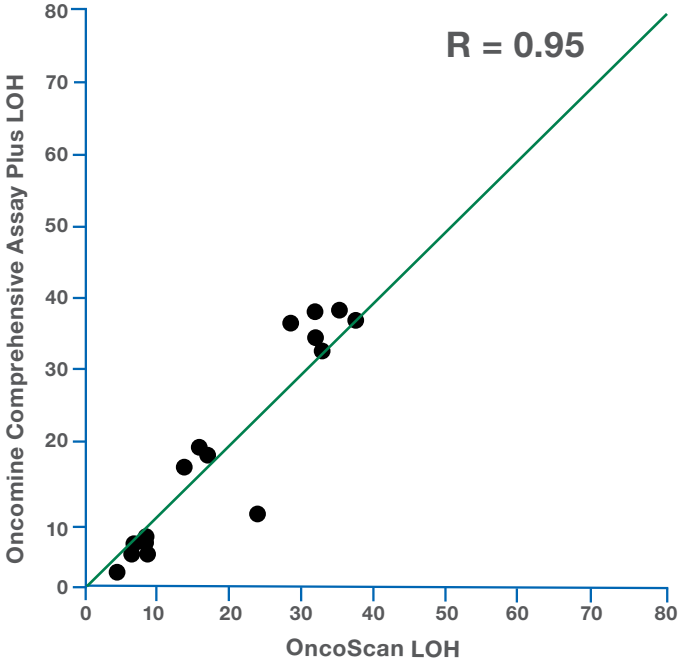
Genomic instability measurement

The Oncomine Comprehensive Assay Plus measures genomic instability with both gene-level and sample-level LOH with high accuracy. Figure 3 demonstrates the LOH assessment at both sample level and gene level compared with Applied Biosystems™ OncoScan™ CNV Assay as an orthogonal test using the same FFPE samples.

A. 42 HRR pathway genes are covered by the Oncomine Comprehensive Assay Plus

ABRAXAS1	*ATM*	*ATR*	*BARD1*	*BLM*	*BRCA1*	*BRCA2*	*BRIP1*	*CDK12*	*CHEK1*	*CHEK2*	*FANCA*
FANCC	*FANCD2*	*FANCE*	*FANCF*	*FANCG*	*FANCI*	*FANCL*	*FANCM*	*MRE11*	*NBN*	*PALB2*	*PARP1*
POLD1	*POLE*	*PPP2R2A*	*PTEN*	*RAD51*	*RAD51B*	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RNASE2A*	*RNASE2B*
RNASE2C	*RPA1*	*TP53*	*XRCC2*	*XRCC3*							

B. Sample-level %LOH comparison



C. Gene-level LOH accuracy

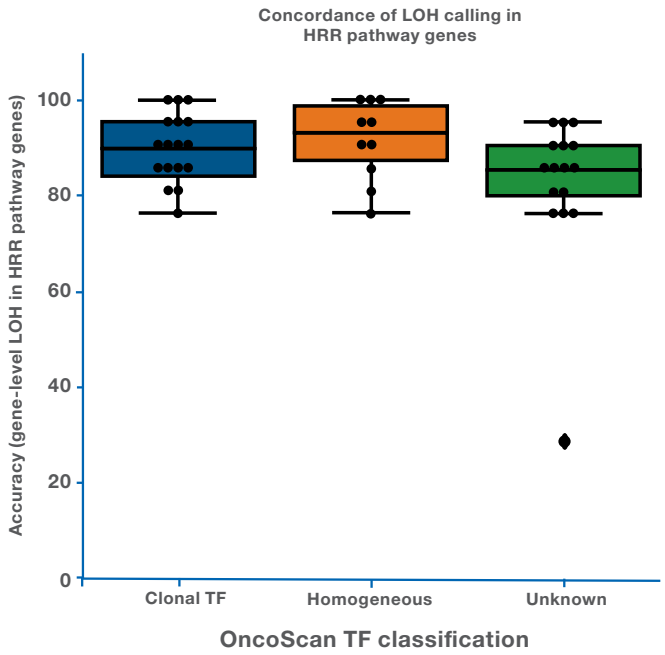


Figure 3. HRR pathway research with Oncomine Comprehensive Assay Plus. (A) 42 HRR pathway genes covered in the Oncomine Comprehensive Assay Plus. (B) Oncomine Comprehensive Assay Plus sample-level percent LOH estimates (y-axis) correlate favorably with the orthogonal test (x-axis), the OncoScan assay, on the same FFPE samples. Test sample set consists of FFPE samples from various solid-tumor tissue types. Pearson correlation (R) is shown as measure of association. (C) Gene-level LOH accuracy comparing 21 genes in the HRR pathway (concordance defined as proportion of these 21 genes that have LOH in both OncoScan assay and Oncomine Comprehensive Assay Plus), with 89% mean accuracy across clonal samples). Internal R&D data.

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New: Bioinformatics solution enabling visualization of mutational signatures

Mutational signatures are an important tool for precision oncology research, providing insights into the biological mechanisms involved in carcinogenesis (e.g., UV damage, deficiency in DNA repair).

The Oncomine Comprehensive Assay Plus provides you with a comprehensive genomic profile, and as part of the streamlined bioinformatics workflow, the mutational signature plot is automatically generated and does not require additional analysis with third-party software. Figure 4 shows an example of a clinical research FFPE sample analyzed with the Oncomine Comprehensive Assay Plus. This sample exhibited the Signature 3 from COSMIC Mutational Signatures Version 2, which is related to HRR pathway deficiency.

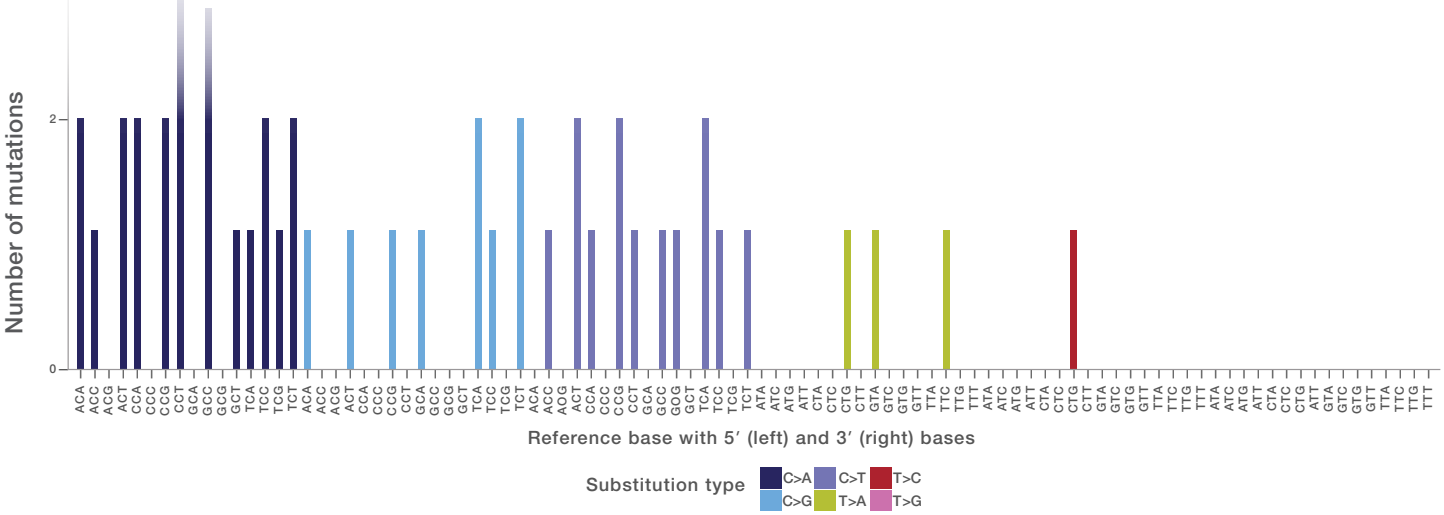

Figure 4. *BRCA1* and *BRCA2* mutations detected in a clinical research sample. This signature matches Signature 3 from COSMIC Mutational Signatures Version 2. Signature 3 is strongly associated with germline and somatic *BRCA1* and *BRCA2* mutations in breast, pancreatic, and ovarian cancers. In pancreatic cancer, responders to platinum therapy usually exhibit Signature 3 mutations.

Oncomine Comprehensive Assay Plus performance across single-biomarker variant types

Using commercially available reference controls and clinical research FFPE samples, assay sensitivity and specificity ranged from 93% to 100%, with averages of 97.0% sensitivity and 98.3% across all variants. Superior performance with CNV detection is noted below in bold.

Table 1. Internal R&D data.

Variant type	Sensitivity	Specificity
SNVs	98.9%	99.7%
Indels	**100%**	96.6%
CNV gain	**100%**	**100%**
CNV loss	93%	**100%**
Fusions	95.4%	95.4%

For more information about Oncomine NGS solutions, go to **oncomine.com**

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