

Illumina Connected Insights

Enabling NGS data
interpretation through report
generation for oncology
applications and beyond

- Streamlined to save time and increase confidence by consolidating knowledge sources and automating routine tertiary analysis workflows
- Integrated for fewer touchpoints from sample to report with automatic information flow, regardless of assay or instrument
- Powered for growth, enabling clinical research labs to keep pace with new knowledge, expand test menus, and scale for precision medicine

Introduction

Innovations in next-generation sequencing (NGS) technology have enabled deeper sequencing, higher throughputs, and more comprehensive assessment of variant classes and biomarker types. With these technological advances, precision medicine has been enabled on a whole new level. Genomics-powered insights are helping to identify underlying causes, optimize treatments, and create better outcomes for patients.

Genomics has many opportunities in precision medicine. NGS can sequence multiple genes to whole exomes or genomes, potentially revealing new underlying mechanisms of disease. While accessible bioinformatic innovations for secondary analysis have kept pace with the massive amounts of data generated by NGS methods, many labs still struggle with scaling tertiary analysis, including interpreting genetic variants to extract biologically relevant meaning. Additionally, oncology researchers need to associate identified variants with clinical information, eg, available treatment options and relevant clinical trials, and track information across multiple sources to stay current on the latest guidelines and drug approvals. This further increases the burden on lab personnel and makes variant interpretation a time-intensive, potentially manual process that requires numerous, repetitive steps and takes as long as seven hours per genome or with other comprehensive assay types.¹

Illumina Connected Insights helps labs address this data interpretation bottleneck as they bring NGS assays in house or scale existing workflows. This cloud-based, customizable platform enables tertiary analysis, from data upload to report generation, and streamlines the user experience through automatable user selections. Through application programming interface (API)-based calls, Connected Insights allows users to access variant information from > 45 sources for filtering and report generation. Connected Insights' functionality is designed to decrease the time and effort required to extract biological insights from genomic data while maximizing operational efficiency for routine, user-defined interpretation (Table 1).

Connected Insights is designed to serve multiple applications and areas of interest. In somatic oncology, Connected Insights can be configured to accept input data from a wide range of oncology assays, including solid tumor comprehensive genomic profiling (CGP) (from tissue or liquid biopsies), and hematological malignancy testing. The software supports variants frequently identified in DNA and RNA tumor samples such as single nucleotide variants (SNVs), insertions/deletions (indels), fusions, structural variants (SVs), and others, and accepts and enables user interpretation for genome-wide biomarkers such as tumor mutational burden (TMB), microsatellite instability (MSI), and genomic instability score (GIS) to assess homologous recombination deficiency (HRD). Connected Insights is built on a future-proofed framework that will expand into additional application areas, within oncology and other disease indications.

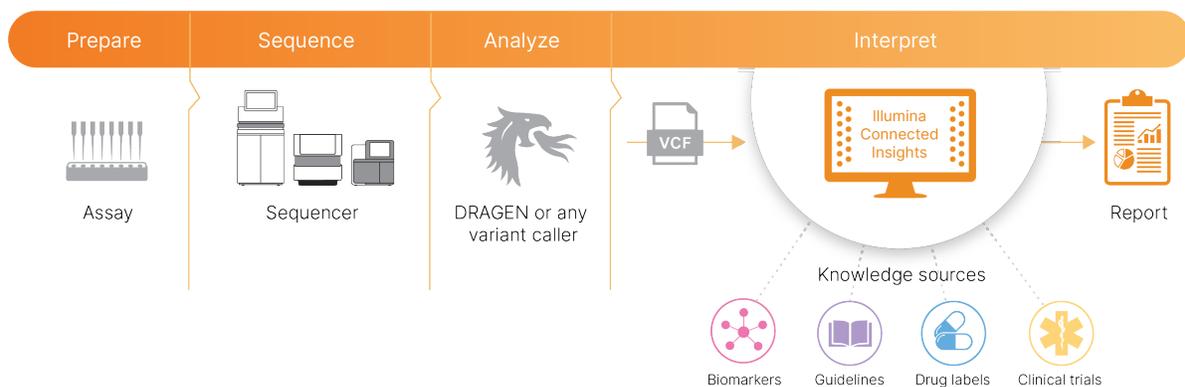


Figure 1: Connected Insights extends the NGS workflow—The software integrates with and extends NGS workflows, enabling variant interpretation and reporting across applications and areas of interest.

The software integrates with and extends existing NGS workflows (Figure 1), enabling labs to implement standardized, user-defined workflows to interpret disease-relevant variants rapidly, and generate reports summarizing findings in a structured format. With Connected Insights, labs have direct access to a network of external knowledge sources, which include regionally specific drug labels, guidelines, clinical trials, and peer-reviewed literature curated by experts. Connected Insights represents the final piece in the NGS workflow, enabling labs to streamline their tertiary analysis today, and scale operations for tomorrow.

Table 1: Features of Illumina Connected Insights

Feature	Specification
Platform compatibility	Broad spectrum of NGS instrument
Data input compatibility	VCF from DRAGEN software or any other secondary analysis solution with seamless data flow
Assay compatibility	Wide range of DNA or RNA assays with VCF output; supports solid tumor testing, liquid biopsy, hematological malignancy testing, panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS)
Variant classes	Small variants (SNVs, indels), copy number variants (CNVs), SVs, fusions, splice site variants
Pan-cancer biomarkers	TMB, MSI, HRD (GIS)
External knowledge sources	> 45 sources, including Clinical Knowledgebase (The Jackson Lab), COSMIC, and ClinVar
Comprehensive filtering	Includes variant frequency, quality scores, read depth, variant type, functional impact, clinical information, and others
Test definitions	Supports presets of key test parameters (eg, variant filters, report template) for convenient reuse and automation
Variant curation and storage	Automatically stores a lab's variant interpretations to facilitate future use
Customizable reporting	Enables generation of custom reports that can be optimized for different disease research areas

Abbreviations: TMB, tumor mutational burden; MSI, microsatellite instability; HRD, homologous recombination deficiency; GIS, genomic instability score

Streamlined operations

Multiple features streamline and optimize interpretation workflows and lab operations. Connected Insights is assay agnostic across applications and is available as a secure cloud solution. It is compatible with VCF files of DRAGEN™ Secondary Analysis, which may be deployed on-instrument on an Illumina NGS system, on premise on a DRAGEN Server, or in the cloud within Illumina Connected Analytics. It is also compatible with any third-party secondary analysis solution, enabling labs to quickly adopt and incorporate the software into their existing workflows.

Comprehensive knowledge base options all in one place

With API connections established by Connected Insights, labs have direct access to a network of > 45 external knowledge sources containing biologically and clinically relevant information to help assess a genomic alteration. These include [Clinical Knowledgebase](#) by The Jackson Lab (JAX CKB), [COSMIC](#), [ClinVar](#), the Online Mendelian Inheritance in Man ([OMIM](#)) catalog, variant frequency sources, functional impact resources, and other databases that are updated regularly (Table 1). By aggregating information from multiple sources into a single hub, Connected Insights eliminates the need for manual searches for variant information across disparate online resources, streamlining the interpretation process and saving valuable time. Users can choose their knowledge sources, view aggregated content for a given variant, and examine in-depth information on the variant associations, including publication IDs, guidelines, and other forms of evidence. The software can populate a standardized, succinct report template with relevant information automatically.

Regional content

By accessing the JAX CKB, Connected Insights provides access to comprehensive regional content, enabling labs to address local needs. These sources include:

- Regionally specific drug labels by the US Food & Drug Administration (US FDA), the European Medicines Agency (EMA), and the Therapeutic Goods Administration (TGA)
- Local clinical trials provided by clinicaltrials.gov
- Recommendations from the regional practice guidelines provided by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO, includes Pan-Asian guidelines)

In addition to the regional content, Connected Insights users can customize their variant interpretation and reporting to follow any regional tiering guideline, for example, the framework developed by ASCO/Association for Molecular Pathology (AMP),² the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT),³ and the [FDA approach](#). The biological classification used in some regions^{4,5} can also be utilized in addition to the tiering systems.

Automated workflows

Labs can easily configure and automate interpretation workflows in Connected Insights for additional efficiency gains. The software directly imports variant call format (VCF) files from any variant caller and enables convenient QC review to integrate into the user's analysis. Customized standard operating procedures (SOPs) can be implemented by creating sets of predefined filters to prioritize and explore variants by harnessing multiple knowledge sources, including the lab's historical variant curation. The entire workflow through custom report generation is configured once and then automated to increase your team's tertiary analysis speed, breadth, and confidence.

Lab-specific curation

Connected Insights features My Knowledge Base, a personalized, private repository for laboratory curated data, which includes information about variants already interpreted in the lab and details of their inclusion in past reports. My Knowledge Base is used throughout Connected Insights to inform about past decisions and to autopopulate the report. Effectively integrating the curated data and cumulative, expanding knowledge from the laboratory can reduce the burden of interpretation and curation for additional efficiency gains ([Figure 3](#)). My Knowledge Base allows users to:

- Upload past variant interpretations from the lab when adopting Connected Insights
- Clone and edit variant records created in the lab or by external sources
- Use any oncology tiering framework, including a fully custom one
- Use biological classification for oncogenic interpretation
- Interpret genome-wide biomarkers (TMB, MSI, and GIS)
- View a summary of past variants used including reports

Concise, customizable reports

Connected Insights provides powerful and flexible report generation capabilities to facilitate clear and concise variant reporting. Users can use the software to populate report sections by selecting variants for inclusion, along with their interpretation, references, and additional comments. Connected Insights also generates a report summary and preview, and facilitates sign-out by the lab director.

Users can choose to use a default report template or create and store multiple customized templates. In addition to changing report names and logo, frequent customizations include changes in the display of the sample and subject information, removal and update of report sections, translation to other languages, and other changes. This flexible system enables users to customize reports and accommodate requirements that are specific to different labs and areas of disease research. Reports can be exported in PDF or JSON format ([Figure 4](#)).

The screenshot displays the 'My Knowledge Base' section with a table of curated data. The table has columns for Latest Case Sign Off, Source, Level, HRD, Type, Classification, Direction, Therapy, Disease, and Actions. Three rows are visible, all with 'NA' as the latest case sign off and 'my KB' as the source. The first row is a Diagnostic Tier 1A for a Malignant tumor of ovary. The second is a Prognostic Tier 1A for a Malignant tumor of ovary. The third is a Therapeutic Tier 2C for Glyburide in a Malignant tumor of ovary. Below this is the 'Other Knowledge Bases' section, which shows two entries from 2023-01-18, both from 'CKB' source, representing Therapeutic Tier 1A Sensitive findings for Pancreatic adenocarcinoma and Ovarian cancer.

To the right, the 'Assertion 1' panel provides details for a specific assertion: Level (Nucleotide), HRD (Undetermined), Type (Therapeutic), Classification (Tier 2C), Direction (Responsive), Therapy (Glyburide), and Disease (Malignant tumor of ovary). It also includes a 'Create New Assertion' button.

Figure 3: Lab-specific curation in Connected Insights—A lab's repository of curated data can serve as a knowledge source for future cases, reducing the burden of interpretation and curation and resulting in additional efficiency gains.

The screenshot shows the 'Report' form on the left and a preview of the generated report on the right. The report is titled 'ILLUMINA DEFAULT REPORT' for case 'ILM-YUW-BQ6U' (Malignant tumor of ovary) dated January 20, 2023. It includes sections for Genomic biomarkers (TMB 12.6 mut/MB, BRCA2 Splice, BRCA1 Copy Number Loss, BRCA1 p.(Asp693Asn), MSI 3.6% unstable sites, BRCA1 p.(Prosf78Leu)), Case Information (Case ID, Workflow, Genome build, Hospital, Ordering Physician), Subject Information (Disease, Sex, Patient Name, Date Of Birth, MRN), and Findings (Nothing reported*). The report also lists therapies in subject and other diseases, and biomarkers like BRCA2 Splice, BRCA1 p.(Asp693Asn), and MSI 3.6% unstable sites.

Figure 4: Concise, customizable reports in Connected Insights—Powerful and flexible reporting capabilities within Connected Insights enable clear and concise variant interpretation reporting with preconfigured templates.

Interface optimized for lab efficiency

Connected Insights offers an intuitive, customizable user interface, designed with various features to help streamline tertiary analysis:

- Flexible variant filters (Figure 5) allow for development of comprehensive filtering strategies to rapidly isolate variants for review using dozens of parameters related to variants' biology, quality, frequency, functional impact, and clinical relevance; filters can be shared across teams, saved, and locked, streamlining analyses of future samples
- Past variant interpretations are prominently featured in the interface, allowing labs to save time and reuse the information for new samples
- The test definition feature provides an ability to set key parameters (eg, variant filters, report template, variant tiering, and tags) for each test conducted in the lab; the ability to control who can edit the presets allows for consistency and efficiency of lab's processes
- Team-based features, including variant tags, role-based permissions, logs, and workgroups, facilitate team coordination and collaboration, and enable team training and oversight to achieve even greater performance

Integrated solution

Connected Insights integrates with existing NGS workflows to streamline tertiary analysis and enable variant interpretation (Figure 1). While the software is compatible with the VCF output of any variant caller for maximum flexibility, labs can take advantage of a single vendor solution for their NGS workflow. Connected Insights is compatible with any Illumina sequencing system, and connects directly with the Illumina connected software ecosystem, designed to be a streamlined, holistic set of analysis and data management solutions that can be deployed out-of-the-box or customized to meet specific needs.

DRAGEN Secondary Analysis

Connected Insights can be configured to work with VCF data files output from any secondary analysis platform. With the option to connect to DRAGEN (Dynamic Read Analysis for GENomics) Secondary Analysis upstream of Connected Insights, labs of any size can take advantage of the proven performance and accuracy of variant calling across multiple variant types.

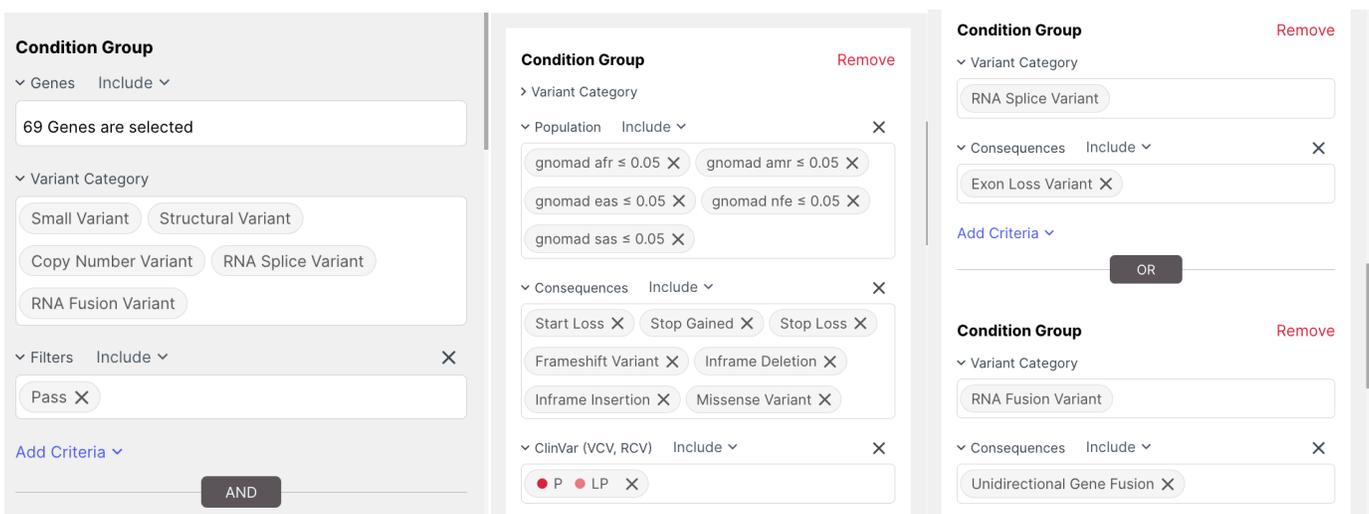


Figure 5: Comprehensive filters in Connected Insights—Comprehensive filter sets enables rapid isolation of key variants that are relevant to the current case.

ILLUMINA Connected Analytics

Connected Insights can integrate directly with Illumina Connected Analytics for consolidated data storage. Connected Analytics is a comprehensive, cloud-based bioinformatics platform that empowers researchers to manage and process large volumes of genomic data in a secure, scalable, and flexible environment. The software empowers labs performing deep data science across population cohorts and supports data sharing with collaborators on a secure platform compliant with international data privacy regulations. Future integrations will enable direct upload of VCF-level data from Connected Analytics to Connected Insights and automatic launch of user-defined interpretation.



Connected Analytics is a global platform that adheres to local data residency requirements. To learn more, read the [Security, privacy, and compliance with Illumina Connected Analytics technical note](#).

Powered for growth

Connected Insights enables labs to keep pace with evolving science and technology and scale operations to meet demand.

Trusted support and service partner

Illumina is committed to ensuring the user community is empowered to serve their mission and definition of growth. Illumina provides a world-class support team comprised of experienced scientists who are experts in library prep, sequencing, and analysis. Technical support is available via phone five days a week or access online support 24/7, worldwide and in multiple languages, with rapid response time near most major metropolitan areas.

Dedicated to your success, Illumina also provides customers with an Informatics Services team, bringing a staff of bioinformaticians, data scientists, and designers to help you customize and optimize your analysis workflow and minimize your development burden.

In addition to support, Illumina offers a complete professional services option to support customized implementation needs, upstream and downstream of Connected Insights.

Typical service projects span software implementation according to lab SOPs, past variant data aggregation and upload, data flow setup including laboratory information management system (LIMS) connectivity, electronic health/medical record integration (EHR/EMR), connecting collaborators with role-based permissions, and more. This service ensures that your resources remain focused on your mission critical work while leveraging the expertise of Illumina and partnered system integrators to efficiently connect and test your optimized data flow.

Security and compliance at the core

Security is of paramount importance when operating with genomics data for research, clinical therapeutics, and human diagnostics. Connected Insights employs various digital and administrative measures to meet even the most demanding data security requirements:

- Data uploaded from sequencing instruments are encrypted using the AES 256 standard and protected by transfer layer security (TLS) version 1.2 or newer
- Data within Connected Insights are hosted on Amazon Web Services (AWS) to maintain compliance with a wide variety of industry-accepted security standards by using AWS Well-Architected best practices⁶
- Authentication service is supported by SAML 2.0 to manage institutional users and passwords (optional)
- Audit reports support traceability of data provenance

Connected Insights also supports customers operating in regulated environments, who must comply with stringent requirements:

- Current data protection laws such as General Data Protection Regulation (GDPR)⁷ and Health Insurance Portability and Accountability Act (HIPAA)⁸
- Role-based management of PII/PHI data
- International Organization for Standardization (ISO) 27001⁹ information security management system*
- Guaranteed data residency to address local regulatory and compliance requirements

* Certification expected July 2023

Summary

Connected Insights streamlines tertiary analysis and variant interpretation workflows by connecting external knowledge sources via API calling and enabling highly tunable user-defined workflow automation. Connected Insights is designed to serve across multiple applications and areas of interest. While the software is compatible with the output of any secondary analysis variant caller, when integrated into the Illumina NGS workflow, users can take advantage of proven Illumina sequencing technology and the accuracy of secondary analysis with the DRAGEN platform. Connected Insights enables labs to streamline tertiary analysis today, and scale operations for tomorrow.

Learn more

[Illumina Connected Insights](#)

Ordering information

Available in select countries at launch.

For qualified inquiries, Illumina offers a supported evaluation experience, allowing customers to work with example cases available in Connected Insights or upload and evaluate their own cases within the software. Contact an Illumina sales representative for more information.



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M-GL-01399 v1.0

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