

Illumina TruSight™ Software Suite Release Notes

v.2.5.0

October 2021

Introduction

TruSight™ Software Suite (TSS) is designed for translating genomic sequencing data in meaningful, interpretable results in rare disease cases. Highlights include:

COMPREHENSIVE, ULTRA-RAPID VARIANT CALLING

Use DRAGEN™ secondary analysis to call small variants, structural variants, mitochondrial variants, repeat expansions, runs of homozygosity, and SMN1/SMN2 variants.

SIMPLIFIED, CUSTOMIZABLE CASE MANAGEMENT

Manage cases from sample acquisition to report, assign cases to users, configure pipeline settings, and set quality control (QC) thresholds.

INTUITIVE, HIGH-POWERED INTERPRETATION AND REPORTING

Filter variants via gene lists, inheritance modes, custom annotations, and complex logic; flag, sort, and prioritize important variants; use customizable reporting templates.

SECURE, COMPLIANT ENVIRONMENT

TruSight Software Suite has been independently audited and certified for HIPAA compliance, ISO27001, and ISO13485. It is built to enable data privacy and compliance with the principles of GDPR.

These Release Notes detail the key features and changes to software components for the release of TruSight Software Suite v.2.5.0. For information on how to use the system, see the [TruSight Software Suite Online Help](#). TruSight Software Suite is a comprehensive solution for alignment, variant calling, variant annotation, filtering, interpretation, curation, and reporting, including features such as:

- Automatic secondary analysis with DRAGEN™ and annotation of:
 - Small Variants, CNVs, SVs, Mitochondrial variants, ROH, STRs, SMA
- Support for whole genome and whole exome sequencing; both from sequencing output file (FASTQ) and secondary analysis output (VCF)
- Sequencer and BaseSpace Sequence Hub Integration
- Case Dashboard and Test Management
- Turnaround time (TAT) management
- IGV Visualization
- Complex custom filters
- Custom flagging of variants
- Custom annotation
- SpliceAI & PrimateAI
- AI-based variant prioritization via Emedgene
- Auto-populated ACMG criteria
- Gene lists from phenotypes
- Storage of variant curation
- Visualization of aggregate data for genes or variants
- Customized report generation
- Multiple report
- Audit logging
- Command-line interface for uploading FASTQs
- API documentation

RELEASE v.2.5.0 HIGHLIGHTS

- Start from Analysis: available as a pipeline supporting DRAGEN analysis output from 3.8.4, 3.7.5, 3.7.7 (WGS and exome), for interpretation and report.
- Dashboard-level turnaround time monitoring: set and monitor turnaround time (TAT) in test definition.
- Auto-ACMG classification: advances in Interpretation workflow and reporting with Auto-populated ACMG variant tagging empowered by Emedegene algorithm.
- Support report on the incidental findings and generating multiple reports per case.

NEW FEATURES IN DETAIL

- System Level
 - Available pipeline for start from DRAGEN output for DRAGEN 3.7.5, 3.7.7, and 3.8.4 for both WGS and WES.
 - Turnaround time (TAT) setting and monitoring through the test definition. TAT starts when a case processed. Cases can be sorted and reviewed by TAT status.
 - Monitoring and auto retiring of failed steps in the analysis pipeline.
- Data Ingestion
 - The CLI will provide the ability to create, get, list and delete samples, and analyses. Individual files, and output directories can also be listed, and downloaded. The CLI requires Java 11. The CLI supports the use the '--configFile' flag anywhere in the command line.
 - The queuing structure for case ingestion has been updated to rotate between submitters to avoid scenarios where one large submission would lock up the queue.
- Test Management
 - Enables to create multiple report definition in test management and allowing for multiple reports per case to support incidental findings and other germline panel reporting on WGS/WES backbone.
 - Available version reference and link-out to the test definition in setting page.
 - Ability to retire a test; user will first be prompted if they are sure they want to retire the test.
 - Preview of gene list from Test Management settings.
 - Allow tracking of comments associated to a test definition.

- Case Management
 - Provide an "All" tab in the case list page for searching and filtering across all case statuses and sub-statuses.
 - Monitor the progress of case; If a case remains in processing for three days, the case will be marked as 'In Progress - Has Issues.'
 - Ability to manage editing of report after approval; reports in the case marked as 'Complete - Delivered.' can be edited. Reports for the case that pass the 'Complete - Delivered' status and marked as 'Complete - Closed.' cannot be edited.
 - Allowing admin to manage role-based ability to close cases with the 'CloseCaseEnabled' feature flag in TAC page.
 - Access to client information and ability to edit after the case has been created.
 - Provide A 'Resume Case' option in the case subject information page for 'In Progress - Processing' and 'In Progress - Has Issues' cases.
 - Streamline migration to a new version of the software; cases will remain in the status as they were prior to migration.
 - Improve case creation experience; after submitting a case with incomplete molecular data, an error message will not be provided and when creating a client, credentials are no longer a required field.
 - Ability to specify 'Expected Pedigree' and 'Age at Time of Testing' on the case subject information page.
 - Ability to edit case subject information for New and In Progress substates. Fields that impact the analysis pipeline, and reporting cannot be changed after a case is ready for interpretation.
 - Ability to exclude case subjects from the analysis pipeline. The excluded subject case information is retained.
 - Allows modification of the case display ID for New cases.
 - Allows replacing the samples before the case is ready for interpretation.
 - Improve in family-based analysis query (FBA); Unknown affected status is now supported when running FBA queries rather than treating these subjects as missing data.
 - Enables to re-run Emedgene to get update classifications when updating the indications of a case.

- Variant Grid / Filters
 - Export a view of the variant grid with quick filters applied (e.g., flags).

- Improved filter setting process with ability to add multiple filter groups in a single view that are OR'd together.
 - Allow user to lock and unlock views created during interpretation. When a view is locked, the filters are not able to be edited
 - Validate the name of the genes against HGNC-approved symbols when uploading a gene list or adding genes to a variant filter, and a discrepancy will be displayed to the user.
 - Improved variant ranking strategy by Emedgene to returned 10 variants hits where an obvious causal variant is not present.
 - The zygosity filter now supports applying criteria across the entire pedigree, including the support for the absence of a variant in other pedigree members.
 - Message to guide for additional filter setting in a situating where a recessive filter returns too many variants.
- Variant Details
 - Auto-populated ACMG criteria. Once the user selects an OMIM disease term while creating an association, the user will be able to use the auto-populate function to pull in ACMG tags as determined by Emedgene's algorithm.
 - The ACMG calculator has been embedded within the Variant Details for small variants, and evidence has been embedded within the Variant Details for non-small variants and Gene Details. Google Scholar has been moved to Resources in Variant Details and Links in Gene Details.
 - Improved variant comments tracking with genome-build aware variant ID.
 - Improved zygosity tagging for ROH and mitochondrial variants. "observed" for zygosity for ROH and heteroplasmic" / "homoplasmic for mitochondrial variant.
 - Ability to add or bulk upload preferred disease name for one or multiple ontology term and save it in variant detail UI page and KNS and use it in report.
 - Add ontology external ID after disease name when auto-complete disease in both KNS and variant detail page.
 - Ability to add ACMG criteria for small variant without the requirement of providing evidence.
 - Visibility to previously recorded/reported associations and the link to the variant and association in KNS.
 - Allows performing 'Get New Associations' during interpretation, without losing the interpretation page view.
 - Improved SMN1/2 variant details. UI visibility to SMN1 Allele Depth and SMN2 Allele Depth in variant page.

- Updated InheritedFrom logic to support rare scenarios in which the label could be more informative (e.g. Ambiguous/Conflict - when the variant is heterozygous in the proband and homozygous in both parents, the variant is ambiguously inherited and contrary to expected inheritance patterns).
- Link to the Clinvar VCV entry from variant detail page (Known Issue: in rare scenarios a variant may have multiple VCV entries).
- Case and Variant Visualization
 - Improved and customized IGV visualization; coverage and callability can be filtered. Exon-level coverage and callability can be assessed when exon coordinates are listed in the QC coverage and callability BED file.
- Curation and Knowledge Network
 - Flag when the same variant (small variants exact VID match) is in the process of curation for another case.
 - Customer will have a higher character limit for the curation notes section where they can put in their internal notes for the association.
 - Improved bulk upload result UI to allow additional filtration, performance improvement; make the disease name optional when the user trying to bulk upload an association (ontology node e.g. HPO and Ontology external ID is required).
 - Provide additional filtering in the bulk upload result UI to help the customer navigate the failed records easier.
 - Allow the user to create multiple association in the knowledge network; user can delete a disabled association and create duplicate associations if needed.
- Annotation
 - Improved mitochondrial variants details page and linked to gnomAD for variants annotated based on GRCh37 and GRCh38; gnomAD provides mitochondrial data only on the GRCh38 reference, however, the mitochondrial reference sequence hasn't changed between GRCh37 and GRCh38.
 - Added support for consequences that indicate overlap with CNV/SV consequences: exon_variant , intron_variant and transcript_variant.
 - Ability to limit OMIM disease overlap based on the presence of specific MOI annotations.
 - Support custom annotation of small variants with 'matchVariantsBy' set to either 'allele' or 'position'.
 - Enables the use of scores in custom annotation. The user can annotate variants with a numerical score, which can then be filtered on by using numerical comparisons.

- Report
 - Role-based permission to edit and approve a completed report. lab director and case manager can edit a completed report and only lab director can approve the edited report.
 - Allow the user to edit a completed versioned report. All the following fields can be edited: PHI and Indications, add/remove variants, summary and citations in the report page.
 - Add zygosity and VRF information of other subjects to the report for proband
 - Ability to add variant associations that have been added to and removed from the report more than once.
 - Report customization: prior to processing a case, optional reports section can be opted-in and opted-out of for each case subject. Optional reports are set in the test definition.
 - Reports will have a standardized name.
`<case_display_id>_<subject>_<_sample_id>_<report_name>_<version>.pdf`
`<case_display_id>.json`
 - Ability to preview the pdf view of a report template when setting up a report for a test definition.
 - Ability to generate a report to be proband-only or all subjects specified in the test definition; allowing reports to be opt-ed out of during case accessioning for each subject of a case. Reports for all subjects creates unique report for each subject of the pedigree.
- QC and Auditing
 - Access to QC metrics generated by DRAGEN in TSS. Individual metrics can be optionally added to the 'QC Threshold' section of the test definition.
 - Link to PLINK's identity by descent calculations for review and select PLINK metrics will be available for QC.
- APIs
 - Enable APIKeys for DRS and KNS API endpoints so the user can use the same APIKey and access all APIs in the system
 - APIs for tag creation, deletion, listing, and searching are publicly accessible.
 - Provide an API that clones a case as is. Modifications to the test definition through cloning is not supported in 2.5.
 - Access to case attachment and comment APIs.
 - Enables entering custom metadata at the case, sample, and subject level via APIs.
 - Provide an API to get KNS bulk upload file status.

- Release versions
 - TSS v.2.5.0 runs multiple DRAGEN versions for secondary analysis:
 - Whole genome RUGD Analysis v3.8.4
 - Whole exome v.3.8.4
 - Whole genome v.3.7.7
 - Whole exome v.3. 7.7
 - Whole genome v.3.5.7b
 - Whole genome v.3.7.5
 - Whole exome v.3.7.5
 - TSS v.2.5.0 uses Nirvana v.3.17 for annotation
 - TSS v.2.5.0 uses KNS-API v0.14.0 and KNS-UI v0.3.0 for curation

RESOLVED ISSUES

Defect repairs (bug fixes) from v2.0.2

- Default filters produce an error.
- Case "In progress" not terminated.
- Error on creating/editing case with sample 'Collections Dates' before 1970.
- Imported Test Definition filter does not show Custom Annotation Label filters in filter UI.
- Case Visualization (genome view) defaults to BAMs not SEG or BEDGRAPH tracks to show normalized coverage and B-allele plots.
- Joint GT of parents is based on the last child genotyped instead of all children in the pedigree file.
- In variants that overlap 2 or more genes, Ontology terms are not seen in the Overlap modal for some variants.
- The use of certain strings in SampleID (bam, vcf, seg, gff3, bed, etc.) cause unexpected IGV tracks to always be enabled.
- Creating new client gives error when values for fields not marked as required are not entered.
- Filters are not selected on export/ import of a test.
- References are not removed (or auto deselected) when a variant has been removed from the report.
- The Include/Exclude Dropdown is enabled/shown in the Variant Category Filter.
- Unable to add gene-level information only if the variant has multiple genes and one of the gene already added gene information.
- In IGV, the RefSeq gene track has ENSEMBL annotations.

KNOWN ISSUES

- Literature search result is not matched with Gene Details.
- For cases added to CaseLog, variants in some samples are missing.
- The link to STR alignment is not working in variant details.
- Incorrect toast notification when adding association to completed report.
- In default STR annotation threshold file - locus 'Spinocerebellar ataxia 17' is missing.
- New QC coverage BED file is ignored for "start from analysis" cases.

- labels in IGV track settings are distorted for long sample ID.
- ClinVar resource shows no genes for any phenotypes chosen in TSS variant filter window.
- Large variants are annotated with multiple QC regions.
- 100x fastq single sample case ingestion completes great than 6hrs.
- Inconsistent behavior for the "cancel curation" button.
- Active filter tab cannot be consistent after navigating back from case list page.
- Resume case is not working when case failed in VQS ingestion.
- Phenotype number in the subject header is not change after switching subject in OUI.
- TAT start is not set for case posted via API.
- Different SV variant counts for the same case from FASTQ
- In a recently ingested case, clicking "Duplicate" on a filter tab does not create a new tab.
- Filter View Duplication tab is not working when filter name exceeds character limit.
- User cannot return to the full gene list after closing gene details of a searched gene on gene details tab
- TAT: Time elapsed increment before the case has been processed instead of staying in day 0.
- Reset filter redirects to the new case tab.
- Incorrect sex ploidy in exome workflow. Workaround is to remove the sex ploidy check from exome test definitions.
- Autosomal and Allosomal Transcript Standard is not Conserved during test definition export

Open known issues from previous releases can be found in TruSight Software Suite Release Notes v.2.0.2 and earlier:

<https://support.illumina.com/downloads/trusight-software-suite-release-notes.html>