Illumina TruSight™ Software Suite Release Notes

v.2.6.0

February 2022

Introduction

TruSight™ Software Suite (TSS) is designed for translating genomic sequencing data into 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.2.6.0. 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 reports
- Audit logging
- Command-line interface for uploading FASTQs
- Improved API documentation

RELEASE v.2.6.0 HIGHLIGHTS

- UI improvement: maximum screen space to view variant information and interaction with variant grid, UI access to client management functionality.
- Test Management Improvement: build and save ad hoc filters during interpretation for each case, flags and column configuration (i.e., selection, order, sort) will be saved with the filter.
- Enhanced Annotation: filter on the preferred transcript, case-specific custom annotations, ACMG support for CNV variant in Knowledge Network Service (KNS).

NEW FEATURES IN DETAIL

- Test Management
    - Filters can be saved during interpretation to test management. Compatibility of the filter (e.g., genome build, custom annotations) will be displayed when saving, as applicable. This can assist with test development, as filters can be created with real data during interpretation, saved, and added to tests without having to duplicate them. Additionally, any compatible filter can be loaded from test management to the variant grid on demand.
    - Ability to retire a test although there are active cases; The user will be warned when retiring a test if a test is utilized in any active cases.
    - Gene list validation improvement (transcript library and reference genome checks)

- Case, Sample and Client Management
    - Ability to add a description of "Other" subject in subheader and interpretation; When a family member is set to Other during case creation, Relationship details will be displayed in place of Other throughout interpretation, including pedigree cards, zygosity filters, columns, and metrics.
    - Ability to transition cases from New to Complete - Closed for archival purposes only. Secondary analysis results, reports, and the variant index will not be created or available for review. Turnaround time (TAT) start date, length, and completed date can be associated to the case via the APIs (1) POST /crs/api/v1/cases, and (2) POST /crs/api/v1/cases/{caseId}/complete.
    - Improved case management by restricting the user's ability via API to process cases that have the following substates - processing, and read for interpretation or cases that have a complete state
    - The samples interface provides a sample-centric view of data in the workgroup; high-level summary of samples, filter, and search for sample(s), delete sample(s), view sample metadata, view cases linked to samples.

- Improved client management: the clients interface provides a central location to view, create, edit, and archive clients in the workgroup.

- Interpretation, Filters, Variant Grid, and Variant Details
  - Family-based Analysis Improvements; the user can now filter on Inherited From, and virtual variants can now be returned as part of Recessive MOI filters.
  - Ability to include filtering on flags as part of a saved filter.
  - Allow users to associate column and sort settings to saved filters in test definition; Added sorting functionality for Category, FILTER, Quality, pLI, SpliceAI, PrimateAI, ClinVar, MyKB, Genetic Findings.
  - Consolidate Prediction Scores for Interpretation; SpliceAI / PrimateAI data will be shown on the transcript details view (instead of on the Variant and Gene Details page).
  - Variant Details has an improved resizable popover to provide maximum screen space to view content in and for easier interaction with the variant grid.

- Curation and Knowledge Network
  - Additional CaseLog information will be provided if the user chooses to curate in KNS.
  - Ability to save evidence criteria and evidence score for CNVs in KNS.
  - The system will identify duplicated large variants and gene associations that are sent for curation.
  - Utilize reciprocal overlap for large variant matching with KNS for LB/B associations; When matching associations from KNS, the system will now utilize different overlap logic depending on the pathogenicity of the association:
    - If the association is P/LP/VUS, the system will use annotation overlap - more permissive
    - If the association is LB/B, the system will use reciprocal overlap - more restrictive

- Analysis Pipelines and Annotation
  - Available DRAGEN 3.9.5 analysis pipelines:
    - Whole Genome RUGD Analysis with DRAGEN 3.9.5, GRCh37, hg38/ GRCh38
    - Whole Genome RUGD Analysis with DRAGEN 3.9.5 (Graph Genome), hg38 (alt-masked)
    - Exome Analysis with DRAGEN 3.9.5, GRCh37, hg38/ GRCh38
  - DRAGEN. 3.5.7b has been removed from the analysis pipeline menu. Tests using DRAGEN. 3.5.7b should be retired since they cannot be edited or imported. Cases utilizing DRAGEN 3.5.7b will continue to function in the system.

  - Support DRAGEN 3.9 SMN Caller SMN1 Copy Number, SMN2 Copy Number, and Carrier status are exposed to the user in the variant details and report.
  - Ability to attach custom annotations that are case-specific during case accessioning: the user can upload a case-specific custom annotation during case accessioning, the custom annotation is validated on upload, and the user may view case-specific custom annotations in the grid and create ad-hoc filters targeting case-specific custom annotation data.
  - Non-coding transcript consequences will not be shown as overlapping the gene in the gene details view of small variants.
  - Ability to add and filter on preferred transcripts.
  - Improvement in Start from Analysis workflow; settings for Start from Analysis tests is not required including analysis files, The analysis type needs to be specified in the manifest.
- Report
  - Add order for variants in report Edit mode so that it could reflect the user expected order in PDF
  - Additional variant related information will be available for reporting
  - Timestamp on the report is off by 8 hrs
  - the correct relationship of "other" will show up correctly in the report
- QC and Auditing
  - DRAGEN metrics are aggregated into a single file, <case ID>.aggregated_metrics.csv.
- APIs
  - Expose the API to activate/ inactivate cases.
  - Optimized variant query API response.
  - Ability to access Swagger URLs pages and APIs.
  - Expose the API used to check the status of a case.
  - Expose API to ingest cases into CaseLog.
  - Expose the API to inactivate and activate a case index.
  - Ability to delete a case with an API call.
- Release versions
  - TSS v.2.6.0 runs multiple DRAGEN versions for secondary analysis: 3.7.5 WGS, 3.7.5 Exome, 3.7.7 WGS, 3.7.7 Exome, 3.8.4 WGS, 3.8.4 WGS with

hg38/GRCh38 Graph Reference Genome (alt-aware), 3.8.4
Exome, 3.8.9 WGS, 3.8.9 WGS with hg38/GRCh38 Graph Reference Genome (alt-aware), 3.8.9 Exome, 3.9.5 WGS, 3.9.5 WGS with hg38/GRCh38 Graph Reference Genome (alt-masked), 3.9.5 Exome.

- WGS and exome analysis pipelines use hg38/ GRCg38 or GRh37 reference genomes without HLA contigs unless indicated otherwise.

- TSS v.2.6.0 uses Nirvana v.3.17 for annotation
- TSS v.2.6.0 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 a new client gives an 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 genes already added gene information.
- In IGV, the RefSeq gene track has ENSEMBL annotations.
- For any cases added to CaseLog after the fix, all samples in a case will show up in the list of samples for a given variant. Note: if you observe a discrepancy for cases previously added to CaseLog, please contact the support team to help update these cases in CaseLog.

KNOWN ISSUES

- Literature search result is not matched with Gene Details.
- The link to STR alignment is not working in variant details.
- Incorrect toast notification when adding association to a 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 the 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 the case list page.
- Resume case is not working when case failed in VQS ingestion.
- Phenotype number in the subject header is not changed 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 the character limit.
- User cannot return to the full gene list after closing gene details of a searched gene on the 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. The workaround is to remove the sex ploidy check from exome test definitions.
- Autosomal and Allosomal Transcript Standard are not Conserved during test definition export.
- Expose RN (ALT field) for legacy cases with STRs in the Change column
- Unexpected change in DRAGEN 3.9.5/ 3.7.5 /3.8.4 results for a FASTQ case
- Archived clients can be edited.
- Case-specific custom annotation associated filter should not be selected in test definition.
- PLINK error terminates the pipeline when VCFs is empty
- CMP: The SFA case still can be saved and ingest success with the wrong relationship
- Gene Evidence is missed after editing it.
- Some long deletions called by the SV caller are inappropriately categorized as small variants instead of SV

- Columns are not consistent in saved filter view which cases ingested with different case datasets.
- ClinGen link out in Gene detail page not working correctly. (Placeholder: this one will be resolved when TSS 2.6.0 is deployed to production. We will remove this one from final Release Note)
- SampleIDs are case sensitive in the case create form but are not the sample UI.
- Variant search function on caselog tab does not work
- Column Sorting was not maintained after migration.

Open known issues from previous releases can be found in TruSight Software Suite Release Notes v.2.5.0 and earlier:

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