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OneGenomics by

Optimum Data Analytics Pvt Ltd

AI-Enabled DNA Sequencing Interpretation for Biomarker-Stratified Oncology Clinical Trials

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Manual Variant Analysis Delays Trial Enrolment

Biomarker-based enrolment rose from 15% of oncology trials in 2000 to 55% in 2018, yet translating sequencing data into reproducible, documented patient eligibility decisions remains manual and expert-dependent.

Manual, Resource-Intensive Process

Evidence is manually aggregated from fragmented genomic and scientific literature sources, requiring experts to assess clinical significance, reconcile conflicting findings, and curate each report individually.

Inconsistent, Non-Reproducible Outputs

Reports vary in format and traceability across analysts and sites, making it hard to standardize biomarker-based eligibility decisions.

Ungoverned AI Risk

Relying solely on direct AI outputs for clinical interpretation introduces hallucination, poor traceability, and limited auditability.

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From An Annotated VCF To A Signed-off Clinical Report

1

Variant Filtration

Filtering cancer genes by relevance, quality metrics, transcript selection, functional impact & population frequency.

2

Variant Normalization

Standardization using ClinGen CAIDs and GA4GH VRS identifiers enables cross-reference and retrieval of variant evidence across knowledge sources.

3

Evidence Retrieval

Aggregation of variants' information from ClinVar, CIViC, PubMed/PMC, Open Targets, openFDA, Ensembl VEP & more.

4

Tiering & Conflict Detection

Classifying the variants via AMP/ASCO/CAP; route unresolved conflicts to human reviewers.

5

AI-Assisted Report Generation

LLM collates retrieved genomic evidence into cited summaries for validation and traceability.

6

FHIR Assembly & Sign-off

Assembling an HL7 FHIR-compliant report and releasing it only after expert review and approval.

Clinical Report Generation From Genomic Variants

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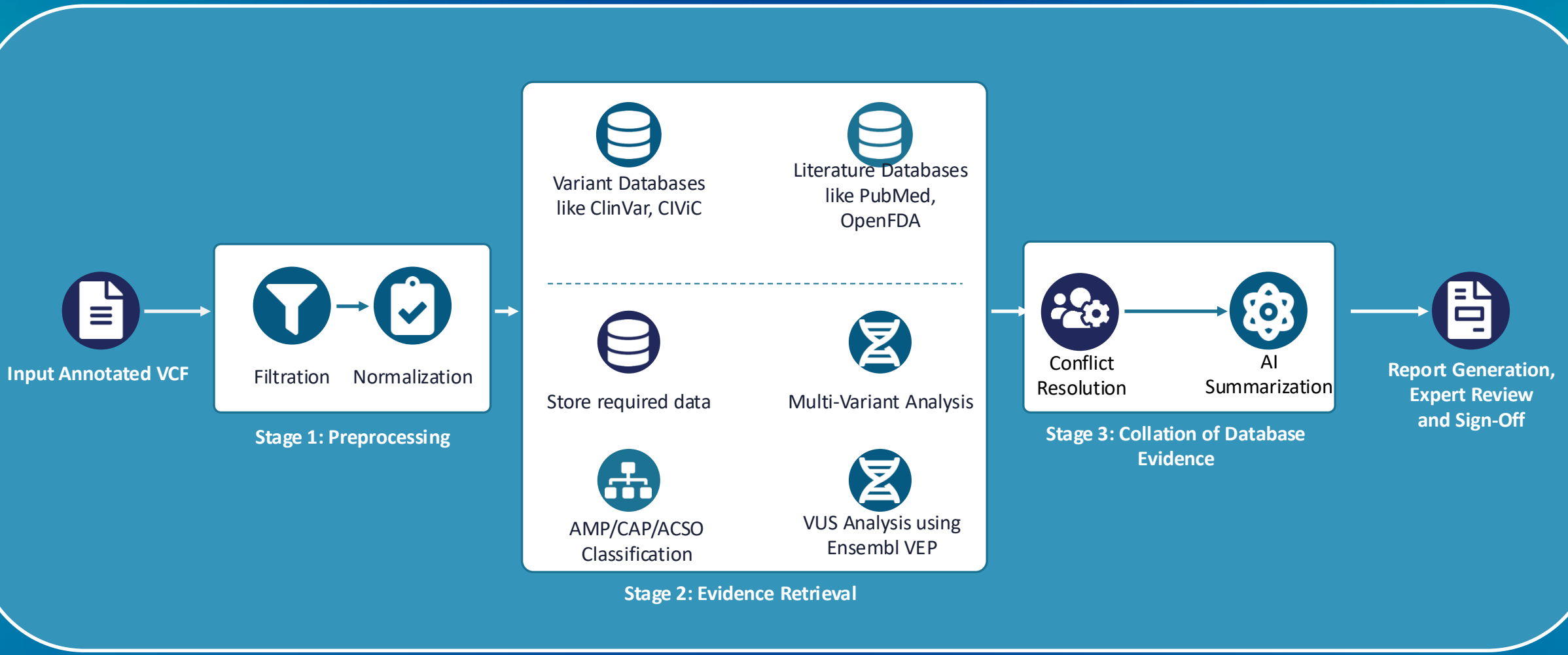

HL7 FHIR Compliance Output – Variant Information

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OneGenomics Somatic Panel – Tumor-Only *(Final Result)*

Test Information
Name: OneGenomics Solid Tumor Somatic Profile
Assay Mode: Tumor-only (Mode A)

Indication for Testing
Tumor Type: Breast Carcinoma (ductal)

Tumor Specimen
Facility: Optimum Data Analytics Genomics Laboratory
ID: 895544
Source: Breast, Left
Collected: 03/12/2026
Received: 03/14/2026
Tumor: 85%

Signed Off
Signing Pathologist: Kulkarni, Meera MD
Laboratory Medical Director:
Iyer, Raghav MD, PhD
Date Signed: 03/27/2026

Accession ID: 23-0000345

Matched normal specimen: Not submitted. This is a tumor-only assay; germline status of reported variants was not determined by paired normal sequencing. See Limitations.

Genetic Analysis Overall Interpretation

Sequencing of this breast carcinoma specimen identified 28 protein-altering variants passing quality filters, of which 23 were resolved to a MANE Select transcript and 5 were routed to human review for absence of MANE annotation.[Assay][Ensembl VEP] One variant, **TP53 p.Arg175His**, is classified in ClinVar as Pathogenic on the germline axis (reviewed by expert panel, Li-Fraumeni syndrome), Oncogenic on the somatic oncogenicity axis, and carries a somatic clinical impact classification of **Tier I – Strong**.[ClinVar 12374] The allele is registered in the ClinGen Allele Registry as CA000251 and corresponds to ClinVar Variation ID 12374.[ClinGen CA000251] It is present at 98.25% variant allele fraction against an estimated 85% tumour content, consistent with a clonal alteration accompanied by loss of the wild-type allele.[Assay] CIViC holds 13 evidence items for this specific residue change, including a breast cancer prognostic association with poorer overall survival relative to TP53 wild-type.[CIViC EID389][PubMed 16489069] A **BRCA2 p.Glu1593*** truncating variant was detected at 34.78% VAF; no ClinVar record exists for this allele, so no germline, oncogenicity or clinical impact classification is available.[Assay][ClinVar BRCA2 gene][COSMIC COSM13843] **FGFR1 p.Ser125Leu** was detected at 100% VAF and is classified in ClinVar as Uncertain significance with developmental rather than oncological trait associations.[ClinVar 376297] In-silico support for that variant is discordant, with SIFT calling it deleterious at low confidence and PolyPhen-2 calling it benign.[Ensembl VEP] Functional enrichment of the mutated gene set is most significant for Pathways in cancer (hsa05200, DAVID EASE 0.012) and Platinum drug resistance (hsa01524, EASE 0.017).[DAVID hsa05200][KEGG hsa05200][KEGG hsa01524] No variant reported here constitutes a treatment recommendation; all therapeutic content is evidence association only and requires clinical correlation.[Assay]

Clinically Significant/ Actionable Variants

Gene	Variant	Evidence	VAF
TP53 ENSG00000141510	p.Arg175His (R175H) NM_000546.6:c.524G>A NC_000017.11:g.7675088C>T ENST00000269305.9 rs28934578 · CA000251 · COSM10648 **Molecular consequence:** missense_variant	**ClinVar clinical impact: Tier I – Strong**[ClinVar 12374] **Oncogenicity classification:** Oncogenic[ClinVar 12374] **Germline classification:** Pathogenic[ClinVar 12374]	**98.25%** Clonal; consistent with LOH
BRCA2 ENSG00000139618	p.Glu1593* (E1593*) NC_000013.11:g.32339132G>T ENST00000380152.8 CA387783191 · COSM13843 **Molecular consequence:** stop_gained (VEP impact HIGH)	**ClinVar clinical impact:** Not asserted **Oncogenicity classification:** Not asserted **Germline classification:** Not asserted	**34.78%** Subclonal or germline-with-normal-admixture; ambiguous in tumor-only
FGFR1 ENSG00000077782	p.Ser125Leu (S125L) NM_023110.3:c.374C>T NC_000008.11:g.38428420G>A ENST00000447712.7 rs121913473 · CA4718768 · COSM601	**ClinVar clinical impact:** Not asserted **Oncogenicity classification:** Not asserted **Germline classification:** Uncertain significance[ClinVar 376297]	**100.00%** Homozygous / hemizygous call

HL7 FHIR Compliance Output – Drug Response

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Therapeutic Implications

Entries below are **evidence associations, not prescriptions**. Category reflects the strength and transferability of the underlying evidence to this tumor type. Drugs whose label biomarker is not matched by this specimen's genotype are marked accordingly.

Category	Drug	Implication	Summary
Multi-kinase inhibitor + HDAC inhibitor	Pazopanib + Vorinostat (combination)	TP53 R175H – Sensitivity / response	In a phase I trial of pazopanib plus vorinostat in 36 patients with advanced solid tumours, presence of a TP53 hotspot mutation was associated with a higher rate of stable disease of six months or longer or partial response, and with longer median progression-free and overall survival, than in patients without a hotspot mutation.[CIViC EID7540][PubMed 25669829] The effect was most evident in the sarcoma subset, and CIViC assigns this evidence level C with a rating of 2 in a sarcoma disease context.[CIViC EID7540] The population studied was not breast carcinoma, which limits transferability to this case.[CIViC EID7540] Vorinostat is FDA-labelled for cutaneous T-cell lymphoma, with labelled warnings covering pulmonary embolism, deep vein thrombosis, myelosuppression, gastrointestinal toxicity and hyperglycaemia, and a labelled interaction requiring more frequent INR monitoring with coumarin derivatives.[openFDA ZOLINZA (vorinostat)] Pazopanib is recorded in Open Targets against FGFR1 with breast cancer among its associated disease terms, but neither agent carries TP53 mutation status as a labelled selection biomarker, and the combination itself is not FDA-approved.[Open Targets pazopanib] [openFDA pazopanib]
Anthracycline (topoisomerase II inhibitor)	Doxorubicin	TP53 R175H – Sensitivity / response	In a genetically engineered mouse model, mammary tumours carrying the R172H allele, which is homologous to human R175H, were more responsive to doxorubicin than mammary tumours with wild-type Trp53.[CIViC EID319][PubMed 22698404] CIViC assigns this evidence level D (preclinical) with a rating of 3, in a breast cancer disease context.[CIViC EID319] This is animal-model evidence only and has not been validated prospectively in patients.[CIViC EID319] Doxorubicin is FDA-approved in breast cancer on histology and stage, not on TP53 status, and its label carries a boxed warning for cardiomyopathy, secondary malignancy, extravasation and severe myelosuppression.[openFDA doxorubicin] The label further states that the drug can cause fetal harm and advises effective contraception during and for six months after treatment.[openFDA doxorubicin: use in specific populations]
Cytotoxic chemotherapy combination	EAP protocol (etoposide, doxorubicin, cisplatin)	TP53 mutation – Sensitivity / response	Among 25 patients with advanced gastric cancer, TP53 mutations were detected in 32% of primary tumours and were associated with improved response to preoperative treatment with a modified EAP regimen of doxorubicin, etoposide and cisplatin.[CIViC EID2310][PubMed 14514923] CIViC assigns this evidence level C in a stomach carcinoma disease context.[CIViC EID2310] The association is reported at the level of TP53 mutation status generally rather than the R175H allele specifically, and the tumour type is gastric rather than breast; both reduce applicability here.[CIViC EID2310]
MDM2 inhibitor	MDM2 inhibitors (e.g. AMGMDS3 class)	TP53 R175H – **Resistance**	Across a panel of cancer cell lines, sensitivity to the MDM2 inhibitor AMGMDS3 was confined to lines with unaltered TP53, and none of 115 lines carrying a TP53 mutation with absence of the wild-type allele were sensitive.[CIViC EID4880][PubMed 25730903] R175H specifically was present in six insensitive lines, and the finding is recorded in two independent CIViC evidence items at level D, rating 3.[CIViC EID4880][CIViC EID10074] Mechanistically this is expected, since MDM2 inhibition acts by releasing functional p53, which a loss-of-function allele cannot supply; yeast transactivation assays confirm loss of transcriptional activity for this allele.[CIViC EID7106][PubMed 27589690] Given the 98.25% VAF observed here, consistent with loss of the wild-type allele, MDM2-directed strategies are predicted to be ineffective in this tumour.[Assay]
FGFR inhibitor	Pemigatinib, Futibatinib, Erdafitinib	FGFR1 S125L – No implication drawn	These FGFR inhibitors were retrieved on the basis of gene-level association with FGFR1 in Open Targets and openFDA.[Open Targets FGFR1] Pemigatinib and futibatinib are labelled for cholangiocarcinoma with an FGFR2 fusion or rearrangement, and erdafitinib for urothelial carcinoma with susceptible FGFR3 alterations; each requires a companion-diagnostic biomarker that this specimen does not carry.[openFDA pemigatinib][openFDA futibatinib][openFDA erdafitinib] The variant detected here is an FGFR1 missense change classified in ClinVar as Uncertain significance, with trait associations to hypogonadotropic hypogonadism 2 and Pfeiffer syndrome rather than to any malignancy.[ClinVar 376297] In-silico support is discordant, with SIFT 0.00 deleterious at low confidence against PolyPhen-2 0.025 benign, and there is no evidence of receptor activation.[Ensembl VEP] This row is included so that the absence of an FGFR-directed option is an explicit, auditable finding rather than a silent omission.[Assay] Open Targets does not return a maximum clinical stage value for these agents in the current evidence snapshot, so development stage is not asserted here.[Open Targets pemigatinib]
PARP inhibitor	PARP inhibitor class (olaparib, talazoparib)	BRCA2 E1593* – Potential sensitivity, not established	PARP inhibitor approval in breast cancer is conditioned on a deleterious or suspected-deleterious *germline* BRCA mutation confirmed by an approved companion diagnostic.[openFDA olaparib][openFDA talazoparib] The truncating BRCA2 variant detected here is mechanistically consistent with loss of function, since the stop codon falls upstream of the RAD51-binding and DNA-binding regions of the protein.[Ensembl VEP] No ClinVar record exists for this allele, so no germline or oncogenicity classification is available.[ClinVar BRCA2 gene] The allele is catalogued in COSMIC and registered in the ClinGen Allele Registry as CA387783191.[COSMIC COSM13843][ClinGen CA387783191] This is a tumour-only assay, germline origin has not been established, and no companion diagnostic has been run, so no therapeutic implication is asserted.[Assay]

Deterministic Analysis, Bounded AI, Standards

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Combining deterministic genomic analysis with controlled AI narratives, OneGenomics helps organizations scale precision oncology while preserving compliance, traceability, and reviewer confidence.

Reduces Manual Effort

Cuts manual work in tertiary analysis and clinical report preparation, accelerating delivery of reports.

Multi-Source Evidence

Integrates genomic, clinical, literature & drug databases in one pass - ClinVar, CIViC, PubMed, Open Targets, consistently for every case.

Standards-Based Interoperability

Built on HL7 FHIR Genomics Reporting for downstream integration and consistent aggregation across multi-site trials.

Transparent & Auditable

Deterministic guardrails keep the AI architecture traceable, with AI-generated outputs backed by citations that are validated against their source records.

Bounded AI

AI is restricted to narrative generation only, never clinical judgment, enabling safe adoption in clinical genomics.

Scalable Workflows

Supports multi-variant analysis and integration with data in Databricks, improving reviewer productivity as programs scale.

Validation & Future Scope

OneGenomics pairs rigorous, partner-backed validation with a deliberate roadmap - extending accuracy today while expanding scope, evidence, and protection for tomorrow.

Validation

- In discussions with oncology labs/practices for data and design partnerships to validate the workflow against real-world case data.
- Benchmarking against manual report generation - comparing AI-generated reports to manual-drafted ones on the same cases, based on both time-to-report and agreement rate.

Future Scope

- Extend to multi-omics data (RNA-seq, proteomics) along with DNA sequencing and process multiple annotated VCF inputs simultaneously.
- Expand evidence base coverage to additional trial-matching criteria sources (e.g., ClinicalTrials.gov eligibility parsing).
- Advance the filed patent application toward grant approval.

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