varsomeclinical

A CLINICAL CASE STUDY

Hereditary Cancer Panel Testing at Scale

A Diagnostic Yield Case Study with Lorgen

Lorgen
genética y proteómica

CONTENTS

Background

Lorgen is a clinical laboratory offering end-to-end hereditary cancer testing, spanning wet lab processing through to variant interpretation and reporting. Operating under IVDR, their bioinformatics pipeline is subject to the same certification requirements as the rest of their workflow, which means the software used for variant analysis cannot be a generic research tool. It must meet the regulatory standard for in vitro diagnostic software.

VarSome Clinical is IVDR-certified, and for Lorgen that was a prerequisite. Beyond certification, the platform needed to support ACMG-based variant classification at scale, phenotype-aware filtering, and integrated CNV analysis within a single workflow.

The Challenge

Hereditary cancer panel testing presents a specific set of interpretation challenges that don't resolve themselves through sequencing depth or panel breadth alone. Lorgen's workflow needed to:

- Classify variants consistently across a 113-gene panel covering multiple cancer types and inheritance contexts
- Manage VUS reporting in a way that preserved clinical utility without overwhelming referring clinicians with unactionable findings
- Extend analysis to copy number variants for cases where SNV/indel analysis returned no pathogenic finding
- Do all of this at scale, across a heterogeneous referral population spanning breast/ovarian, colorectal, gastric, and general cancer indications

Approach

Lorgen runs analysis in VarSome Clinical from FASTQ, using virtual gene panels: a single sequencing dataset interrogated against a defined gene list, without the need to re-sequence when panel definitions change. Across this cohort, the same 113-gene virtual panel was applied consistently, covering the high-penetrance hereditary cancer genes alongside a curated set of moderate-penetrance loci.

Variant classification follows the ACMG/AMP framework [1], with VarSome Clinical aggregating evidence automatically from gnomAD, ClinVar, LOVD, and specialist curated resources including ENIGMA for BRCA1/2 variants. For a cohort of this size, the consistency that comes from platform-driven classification matters — inter-analyst variability in manual curation is a known source of discordance, particularly at the pathogenic/VUS boundary [2].

VUS triage is where Lorgen's workflow makes a considered trade-off. Rather than reporting all VUS identified in the 113-gene panel, they apply a filtering rule: only “hot” VUS are reported; those in genes phenotypically relevant to the patient’s referral indication, showing an autosomal dominant inheritance pattern, and carrying supporting ACMG evidence codes (PM-level or above, with BP4 used to deprioritize benign-leaning variants). VarSome Clinical’s filter functionality makes this triage step tractable at scale. VUS in genes unrelated to the patient’s phenotype are not reported.

CNV analysis is triggered conditionally: only for cases where SNV/indel analysis has not already returned a pathogenic finding. Candidate pathogenic CNVs are confirmed by MLPA before reporting.

Results

Across 873 cases, 161 pathogenic or likely pathogenic variants were identified, yielding an overall diagnostic rate of 18.4%. 93 VUS were reported after phenotype-aware filtering.

Cancer Type	Cases	Pathogenic	VUS (filtered)	CNVs
Breast / ovarian	484	89	44	3
Colorectal	219	38	24	1
General cancer	150	33	16	0
Gastric	20	1	9	0
Total	**873**	161	93	4

The breast/ovarian cohort, at 484 cases, drove the largest share of pathogenic findings (89 of 161, approximately 55%), consistent with the well-established prevalence of BRCA1/2 pathogenic variants in this referral population. The colorectal cohort yielded 38 pathogenic findings across 219 cases, a yield of approximately 17%, reflecting the contribution of Lynch syndrome MMR gene variants. The gastric cohort is small (n=20) and the single pathogenic finding there should be interpreted with appropriate caution given the sample size; notably, the VUS count of 9 in that group is disproportionately high relative to yield, likely reflecting the limited evidence base for many variants in gastric cancer susceptibility genes.

CNVs contributed 4 confirmed pathogenic findings; cases that would have been reported as negative had the workflow been restricted to SNV/indel analysis.

"Before VarSome Clinical, curating ACMG evidence across a 113-gene panel meant manually cross-referencing gnomAD, ClinVar, LOVD, and specialist resources for every variant. Automated evidence aggregation and phenotype-aware VUS filtering have cut our interpretation time by around 40%, without compromising the rigor a panel of this size demands. That efficiency shows up directly in the reports: 93 clinically focused VUS instead of hundreds of unfiltered ones, so referring clinicians receive actionable findings rather than noise." - José Manuel Rubio Gómez, Lorgen

Clinical Impact

For the 161 patients who received a pathogenic finding, the result directly informs clinical management. BRCA1/2 pathogenic variant carriers are eligible for PARP inhibitor therapy across multiple solid tumor indications — olaparib, niraparib, and talazoparib are FDA-approved for germline BRCA1/2-mutated breast, ovarian, prostate, and pancreatic cancers [4]; in the breast/ovarian cohort specifically, this has direct implications for treatment selection. Confirmed hereditary cancer syndrome diagnoses, including Lynch syndrome, trigger cascade testing in first-degree relatives, enroll patients in early detection programs, and in the case of Lynch syndrome, initiate colonoscopic surveillance from age 20–25 years at intervals of one to two years [5].

The 619 patients who received a negative result are a clinically heterogeneous group. Hereditary factors are estimated to explain approximately 5–10% of all cancer cases [3], so the majority of negative results reflect the absence of a hereditary contribution within the tested gene set. However, a subset will have causative variants outside the panel, in non-coding regions, or in complex structural configurations that short-read NGS does not resolve. Clinician-directed follow-up (extended panels, MLPA, or array-based approaches) remains an option in cases where clinical suspicion persists despite a negative report.

How VarSome Clinical Supports Diagnostic Yield

The 18.4% pathogenic yield observed here is the product of biology, panel design, and interpretation decisions working together. VarSome Clinical contributes directly to the last of those:

Consistent ACMG classification at scale. Automated, multi-source evidence aggregation reduces the classification variability that arises in manual workflows. Variants at the VUS/LP boundary are classified against the same evidence base across every case in the cohort.

Phenotype-aware VUS filtering. VarSome Clinical's filtering functionality enabled Lorgen to operationalize their VUS triage rule (phenotype match, inheritance pattern, ACMG evidence tier) without manual case-by-case review. This keeps the reported VUS list clinically focused — 93 VUS were reported against a panel of 113 genes, reflecting the effect of phenotype-aware filtering on the raw variant count — and reduces downstream follow-up burden.

Integrated CNV analysis from FASTQ. Running CNV calling within the same platform as SNV/indel analysis, with conditional triggering, allowed Lorgen to capture 4 pathogenic structural findings that would otherwise have been missed. The MLPA confirmation step sits outside VarSome Clinical, but the platform flags the candidates for it.

IVDR certification. The ability to operate a certified end-to-end diagnostic workflow, wet lab through bioinformatics, required IVDR-compliant software. VarSome Clinical's certification was a prerequisite for Lorgen's own laboratory certification, not an optional feature.

Conclusion

Lorgen's 873-case cohort demonstrates a diagnostic yield of 18.4% across a multi-indication hereditary cancer testing service, a figure that reflects both the biology of hereditary cancer predisposition and the analytical choices made at the interpretation layer. Phenotype-aware VUS filtering, systematic ACMG evidence aggregation, and integrated CNV analysis each contribute to a result that is both clinically actionable and operationally sustainable at scale.

For laboratories building or refining hereditary cancer testing workflows under IVDR, the case illustrates that diagnostic yield is not determined at the sequencing step. It is determined by the rigor and consistency of variant interpretation and by the platform infrastructure that makes that rigor reproducible across hundreds of cases.

873 patient cases analysed using VarSome Clinical. Panels: Agilent CCP17 and Illumina TruSight Hereditary Cancer v2. 113-gene virtual panel applied consistently across the cohort.

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