Paper Summary

<!--META_START-->

Title: Prospective Longitudinal ctDNA Workflow Reveals Clinically Actionable Alterations in Ovarian Canc

Authors: Jaana Oikkonen, Kaiyang Zhang, Liina Salminen, Ingrid Schulman, Kari Lavikka, Noora Anderss

DOI: https://doi.org/10.1200/PO.18.00343

Year: 2019

Publication Type: Journal

Discipline/Domain: Oncology / Precision Medicine

Subdomain/Topic: Circulating Tumor DNA (ctDNA) in High-Grade Serous Ovarian Cancer (HGSOC)

Eligibility: Eligible

Overall Relevance Score: 90

Operationalization Score: 95

Contains Definition of Actionability: Yes (implicit, clinically oriented)

Contains Systematic Features/Dimensions: Yes

Contains Explainability: Yes

Contains Interpretability: Yes

Contains Framework/Model: Yes (workflow pipeline)

Operationalization Present: Yes

Primary Methodology: Mixed Methods (prospective clinical cohort, bioinformatics pipeline)

Study Context: Clinical workflow for longitudinal ctDNA analysis to guide treatment in HGSOC

Geographic/Institutional Context: Turku University Hospital & University of Helsinki, Finland

Target Users/Stakeholders: Oncologists, molecular tumor boards, translational cancer researchers

Primary Contribution Type: Clinical proof-of-concept & open-source workflow

CL: Yes

CR: Yes

FE: Yes

TI: Yes

EX: Yes

GA: Yes

Reason if Not Eligible: N/A

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Title:

Prospective Longitudinal ctDNA Workflow Reveals Clinically Actionable Alterations in Ovarian Cancer

Authors:

Jaana Oikkonen, Kaiyang Zhang, Liina Salminen, Ingrid Schulman, Kari Lavikka, Noora Andersson, Erika

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Year:

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Publication Type:

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Discipline/Domain:

Oncology / Precision Medicine

Subdomain/Topic:

ctDNA analysis in high-grade serous ovarian cancer (HGSOC)

Contextual Background:

The study addresses the challenge of guiding treatment in metastatic solid cancers, particularly HGSOC,

Geographic/Institutional Context:

University of Helsinki & Turku University Hospital, Finland

Target Users/Stakeholders:

Oncologists, molecular tumor boards, translational researchers, precision medicine programs

Primary Methodology:

Mixed methods — prospective clinical cohort of 12 HGSOC patients (78 plasma samples, 21 tissue samp

Primary Contribution Type:

Clinical proof-of-concept and open-source workflow for actionable ctDNA detection

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General Summary of the Paper

This study presents a clinical and bioinformatics workflow for detecting clinically actionable alterations in

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Eligibility

Eligible for inclusion: **Yes**

How Actionability is Understood

Implicitly defined as the presence of genomic alterations in ctDNA that can be linked to existing therapies

> “Potentially clinically actionable alterations were validated… classified as most prominent (ESCAT… Sc

> “The provided approach allows the selection of treatment options that target subclones that persist duri

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What Makes Something Actionable

- Direct association with existing or investigational therapies
- Sufficient evidence of clinical relevance (ESCAT ranking)
- Persistence in tumor subclones during treatment
- Validation in tumor tissue (IHC/ISH)
- Concordance with patient’s mutational profile and disease context

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How Actionability is Achieved / Operationalized

- **Framework/Approach Name(s):** Clinical ctDNA workflow integrating sequencing, bioinformatics pipel
- **Methods/Levers:** >500-gene targeted panel sequencing, variant/CNA calling, filtering, prioritization v
- **Operational Steps / Workflow:** Longitudinal plasma sampling → sequencing → bioinformatics filterin
- **Data & Measures:** VAF dynamics, mutation counts, CNA ratios, CA-125 levels
- **Implementation Context:** Prospective monitoring before, during, after chemotherapy in HGSOC

> “Longitudinal ctDNA sampling can be used to detect response… and identify clinically applicable mutat

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Dimensions and Attributes of Actionability (Authors’ Perspective)

- **CL (Clarity):** Yes — clear link between detected alteration and therapeutic relevance (ESCAT criteria
- **CR (Contextual Relevance):** Yes — therapy matching based on patient-specific ctDNA profile.
- **FE (Feasibility):** Yes — minimally invasive sampling, open-source tools.
- **TI (Timeliness):** Yes — early detection of poor responders after 1–2 chemo cycles.
- **EX (Explainability):** Yes — biological pathway context and evidence level for each alteration.
- **GA (Goal Alignment):** Yes — aligns with goal of improving survival in HGSOC by targeting resistant
- **Other Dimensions Named by Authors:** Concordance with tumor tissue; evidence-based prioritization

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Theoretical or Conceptual Foundations

- ESCAT (ESMO Scale for Clinical Actionability of Molecular Targets)
- Concepts from precision oncology: mTOR, HR deficiency, EGFR pathway targeting
- Longitudinal biomarker monitoring

Indicators or Metrics for Actionability

- Variant Allele Frequency (VAF) trends
- CNA ratios
- CA-125 tumor marker correlation
- ESCAT evidence tier assignment

Barriers and Enablers to Actionability

- **Barriers:** Low VAF subclonal mutations, ctDNA heterogeneity, validation requirements, therapy avail
- **Enablers:** Open-source pipeline, integration with knowledgebase, high plasma-tumor concordance, r

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Relation to Existing Literature

Builds on prior ctDNA monitoring studies (e.g., TP53 tracking in HGSOC) but extends to broad-panel acti

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Summary

This paper delivers a robust, clinically relevant framework for using longitudinal ctDNA profiling to guide t

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Scores

- **Overall Relevance Score:** 90 — Clear conceptualization of clinical actionability and explicit criteria fo
- **Operationalization Score:** 95 — Comprehensive, step-by-step clinical workflow integrating sampling,

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Supporting Quotes from the Paper

- “We identified high-confidence, potentially clinically actionable mutations or CNAs in seven patients (58
- “The provided approach allows the selection of treatment options that target subclones that persist durin
- “Treatment… was changed on the basis of detection of ERBB2 amplification… followed by significant tu
- “Longitudinal ctDNA sampling can be used… to identify poor-responding patients after first cycles of che

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Actionability References to Other Papers

- ESCAT framework: Mateo et al., 2018
- TP53 monitoring in HGSOC: Parkinson et al., 2016
- Pathway-specific targeting references for mTOR, HR deficiency, EGFR, CDK alterations