25. Liquid Biopsy — From WGS Signal to Clinical Translation
1 unit, Adam Widman, March 20, 2026

Purpose of the session

- Liquid biopsy as a *measurement problem* under extreme noise
- Why genome-wide approaches + AI are reshaping clinical feasibility
- How methodological choices constrain clinical claims

Key questions to keep in mind

- What limits sensitivity *in principle* vs *in practice*?

---

1. Biological & Clinical Foundations of Liquid Biopsy

Review reference:

- *Alix-Panabières & Pantel, 2024/2025 review* (*Cancer Cell*)

Clinical implementation settings

- Minimal residual disease (MRD)
- Treatment response monitoring
- Resistance mutation detection
- Early detection / screening (high-risk vs population)
- Therapy selection

---

2. Genome-Wide ctDNA Measurement with WGS

Background reference:

- *Zviran et al., Nature Medicine 2020*

Why WGS?

- Limits of targeted panels at ultra-low tumor fraction
- Mutation integration across the genome
- Signal accumulation vs locus-specific detection

Key technical ideas

- Patient-specific mutation catalogs
- Aggregation across thousands of loci
- Tradeoffs: sequencing depth vs breadth vs cost

---

3. AI & Machine Learning in Liquid Biopsy

Primary reference:

- *Widman et al., 2024* (PubMed 38877116)

What AI actually does here

- Signal enrichment vs classification
- Learning fragment-level or locus-level structure

Key methodological ideas

- Designing ML structures to fit biological data
- Expanding copy number variant signal inference
- Tumor-informed vs tumor-agnostic models

Discussion

- Is AI solving a biological problem or a statistical one?
- What are the failure modes (batch effects, leakage, confounding)?
- How do we validate AI-based ctDNA methods clinically?

---

4. Discussion- ppmSeq for improved WGS detection

Primary reference:

- *BioRxiv preprint 2025.08.11.669689v1*

Critical reading lens

- What is the true innovation vs recombination?
- Internal validation vs external generalization
- Claims about sensitivity, specificity, or clinical readiness