Cell-free circulating tumor DNA profiling in cancer management

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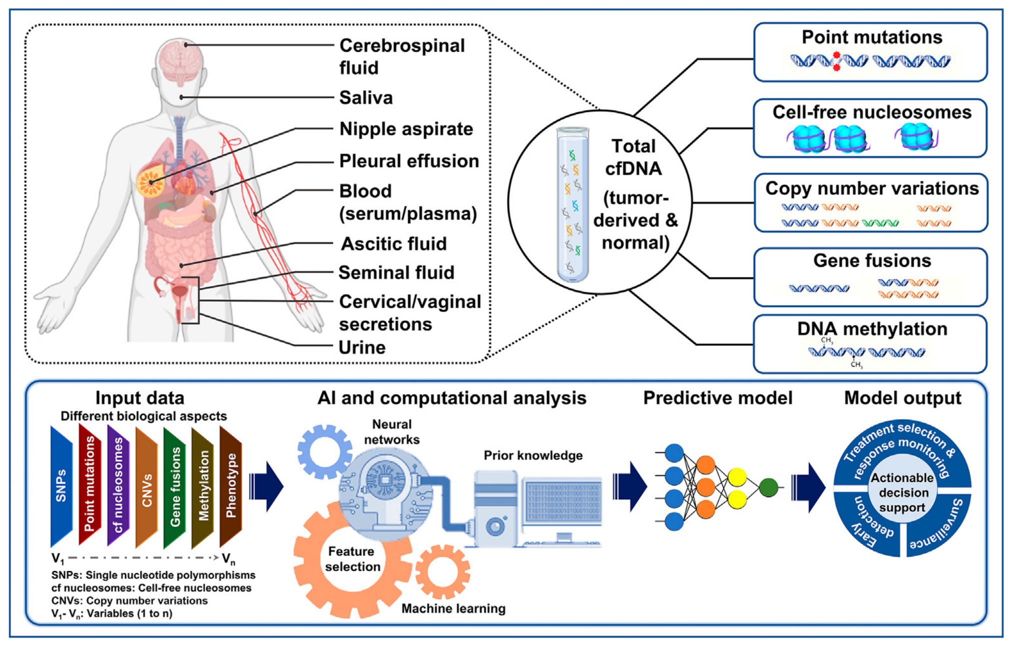
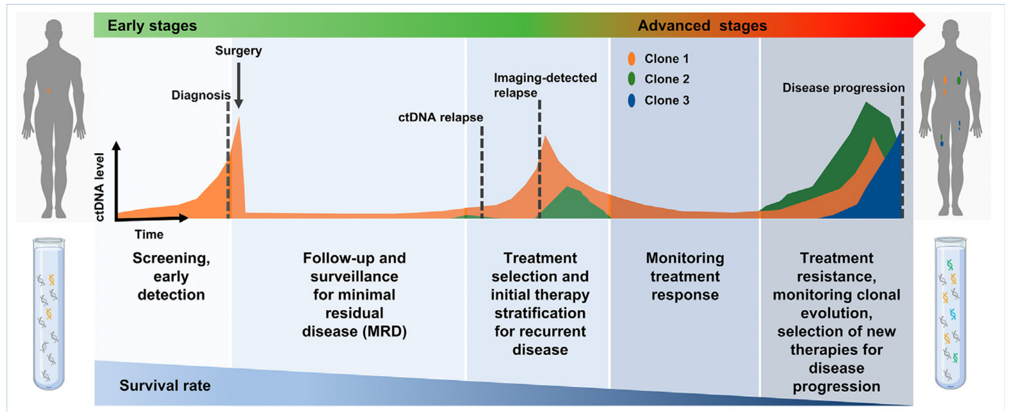


Trends in Molecular Medicine

The tumor-derived fraction of circulating cell-free DNA (cfDNA) in various body fluids, known as circulating tumor DNA (ctDNA), can serve as a minimally invasive tumor biomarker. Artificial intelligence (AI) using next-generation sequencing data promises to revolutionize assay performance and its integration into the clinical workflow to advance precision medicine. AI and machine learning-based ctDNA profiling, including epigenetic profiling, may assist early-stage detection and prediction of cancer progression, helping to guide treatment decisions.



Trends in Molecular Medicine

Profiling of ctDNA may enable large-scale screening of healthy or at-risk population groups for early detection of cancers. Serial ctDNA sequencing, which tracks tumor heterogeneity and evolutionary dynamics, may assess disease progression and may be used for treatment selection and monitoring of response in patients with advanced disease. Note that detection of ctDNA relapse occurs earlier than imaging-detected relapse.

ADVANTAGES:

Real-time detection of tumor burden and minimal residual disease (MRD), reflecting cancer growth and spread.

Representation of spatial and temporal tumor heterogeneity.

ctDNA levels as early indicator of disease recurrence (ctDNA relapse) may predate imaging findings of distant metastasis.

Concordance between tissue and ctDNA profiling.

Personalized treatment to select and monitor response to therapy based on ctDNA (e.g., *PIK3CA*, breast cancer; *EGFR* T790M, non-small cell lung cancer; *BRAF* V600E/K, melanoma).

CHALLENGES:

Highly fragmented DNA, short half-life, low overall yield.

Preanalytical and analytical factors can influence standardization and quality of cfDNA extraction and ctDNA analysis.

Sequencing techniques/protocols can impact identification of alterations.

Clonal hematopoiesis of indeterminate potential may misdiagnose patients over age 50 years with low variant allele frequency ctDNAs unless paired with peripheral leukocyte DNA analyses.

Demonstrating clinical utility (e.g., improvement in overall survival) of dynamic ctDNA monitoring for detection and treatment of early relapse and late-stage progression.

APPLICATIONS:

Cancer detection/early diagnosis.

MRD surveillance.

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Declaration of interests

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Resources

[i]www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

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Treatment selection/monitoring response.

Tracing tissue origin of ctDNA.

FDA-approved single and multigene assays used as companion diagnostics for breast, lung, ovarian, pancreatic, and prostate cancer[i].

Non-FDA-approved cfDNA-based tests marketed as laboratory developed tests.

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