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VIVEKANANDHA MEDICAL CARE HOSPITAL
ALLIED HEALTH SCIENCE

SPOT LIGHT

THE STUDENTS MAGAZINE

THEME :
LIQUID BIOPSY

This month's edition curated by
The Bright Minds of
BSc.Medical Laboratory Technology
Students

Preface

** Several months ago, Glenda learned that she had a suspicious mass of tissue in her left lung.*

** Her doctor surgically removed a small piece of the tissue for analysis and, after looking at it under the microscope, confirmed that it was cancerous.*

** The question that Glenda and her doctor then asked was which of the available treatments was best for her particular cancer?*

** Not enough tissue was left for more specific tests that might help answer this question.*

** Glenda was faced with having to undergo another surgery to get more of the cancerous tissue, but she was not happy at the prospect of another surgery and her doctor was worried that the tumor was in a sensitive location. Fortunately, medical advances have led to an alternative type of test that may be useful for Glenda and her doctor:* ***THE LIQUID***

INTRODUCTION

Liquid biopsy is a non-invasive diagnostic technique that detects cancer biomarkers, such as circulating tumor DNA, in bodily fluids like blood. It enables early cancer detection, treatment monitoring, and real-time tracking of tumor progression.

HISTORY

The term 'liquid biopsy was coined in 2010 by Catherine Alix Panabieres and Klaus Pabel. However, the concept of liquid biopsy can be traced back to earlier studies that found links between tumor cells and blood.

CTCS were isolated from blood and shown to coordinate with pathologic staging, Liquid biopsy development.

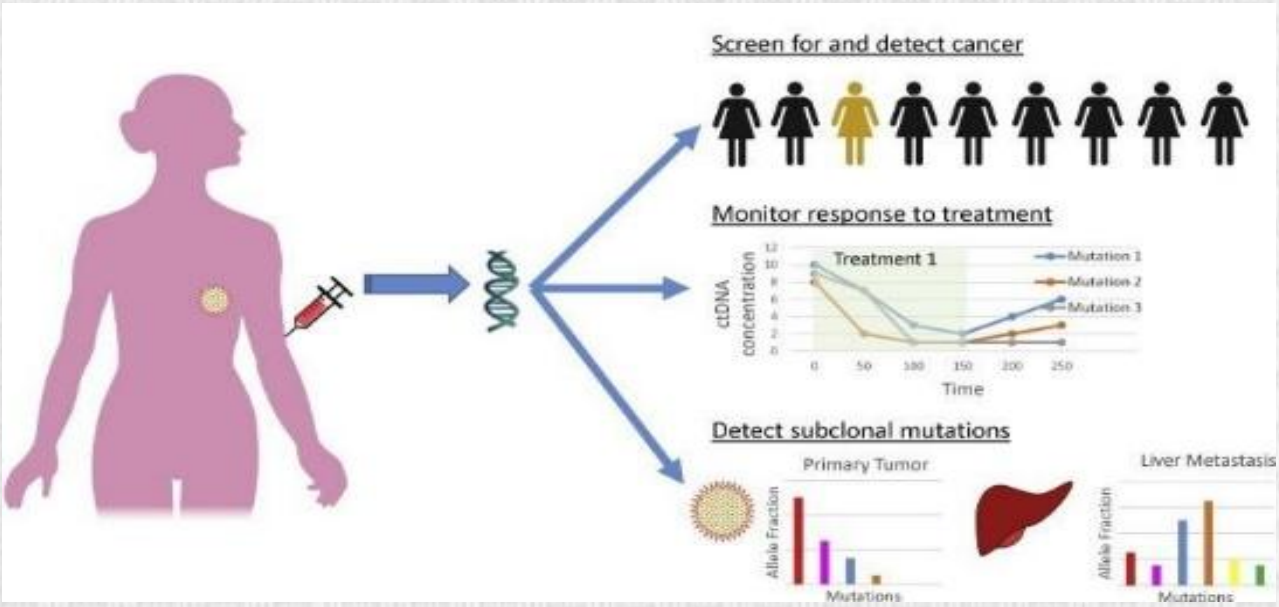
Leon et al, found that people with tumors had higher levels of plasma free DNA than healthy people.

PCR was used to identify a KRAS mutation in pancreatic cancer patients Hood.

The term liquid biopsy was wined and the concept was introduced for circulating tumor cells (CTCs)

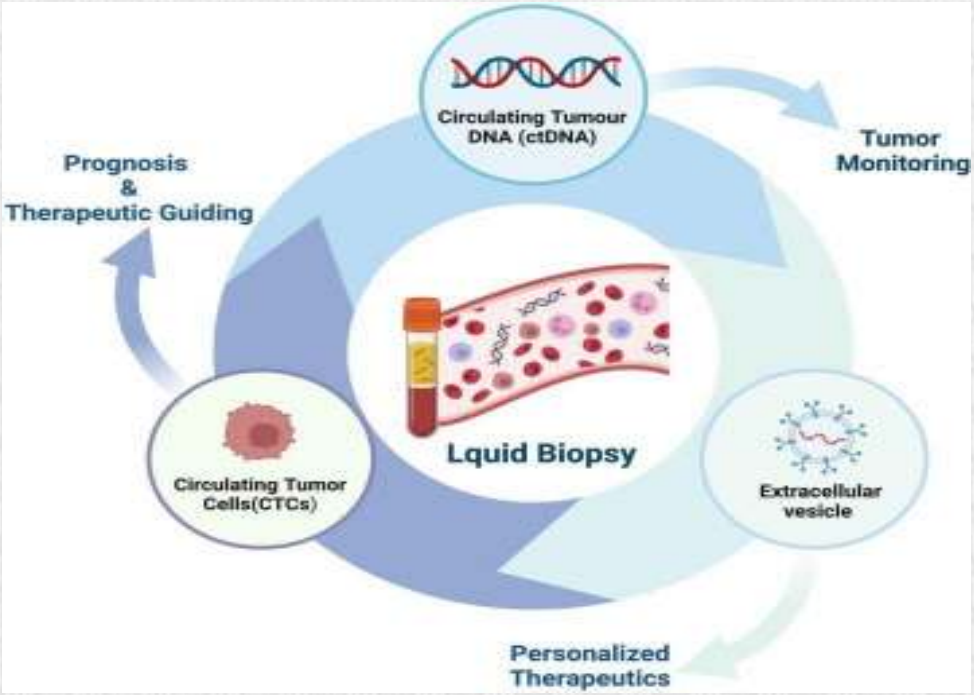
Early-mid 2000s!

It was shown that cancer patients have highest levels of CTCS than healthy people.



Development

Why have Liquid Biopsies Recently Become So Popular in Cancer?



** Liquid biopsies have recently gained attention in cancer research and treatment due to advancements in detection technology and a deeper understanding of cancer biology.*

** Improved techniques now allow researchers to detect tiny amounts of cancer cells in blood, even when outnumbered by normal cells, which was previously impossible.*

** Additionally, liquid biopsies provide a less invasive way to track cancer mutations over time, unlike traditional solid tumor sampling.*

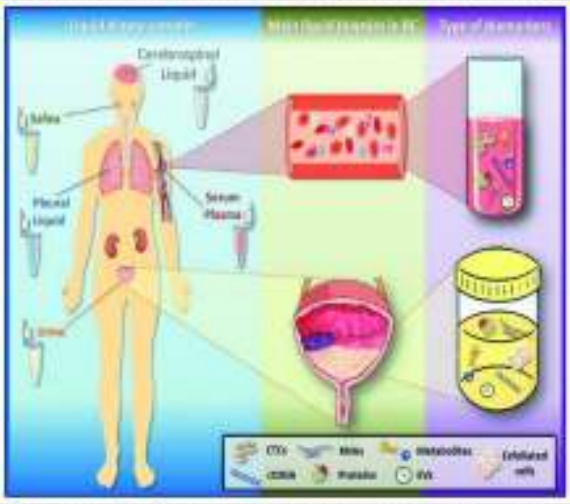
**This is crucial since mutations driving cancer can vary within a tumor and change in response to treatment, helping tailor treatment plans and advancing cancer research*

What do Liquid Biopsies Detect?

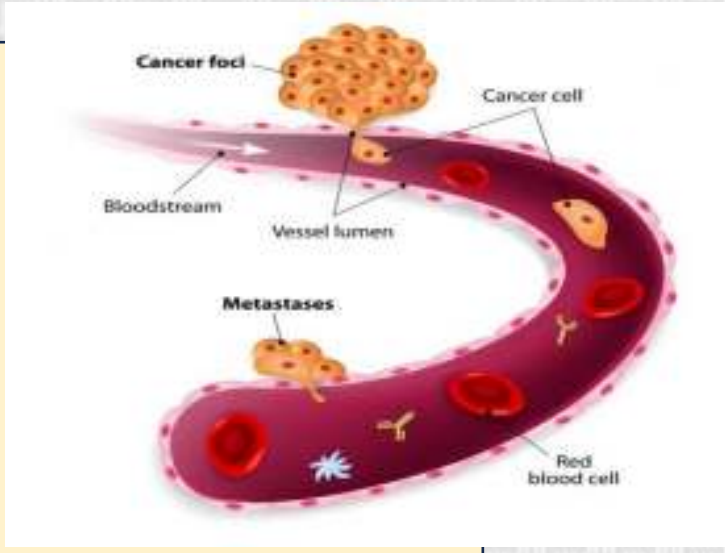
(A) Liquid Biopsies Detect Biomarkers

* Liquid biopsies don't detect solid tumors directly but instead identify biomarkers in bodily fluids that provide information about the tumor.

* Liquid biopsies, the focus is on tumor released biomarkers, such as circulating tumor cells, circulating tumor DNA, RNA, and exosomes.



(B) Circulating Tumor Cells



* Circulating tumor cells (CTCs) are cancer cells shed from tumors into the bloodstream, potentially leading to metastases.

* They are usually introduced into the blood through tumor growth or mechanical disruption, such as surgery.

* Most CTCs are destroyed by the immune system, blood flow, or lack of tissue attachment, with only about 1 in 10,000 surviving and forming new tumors.

* However, as cancer advances and weakens the body's Defenses, CTC levels in the blood increase, reflecting disease progression.

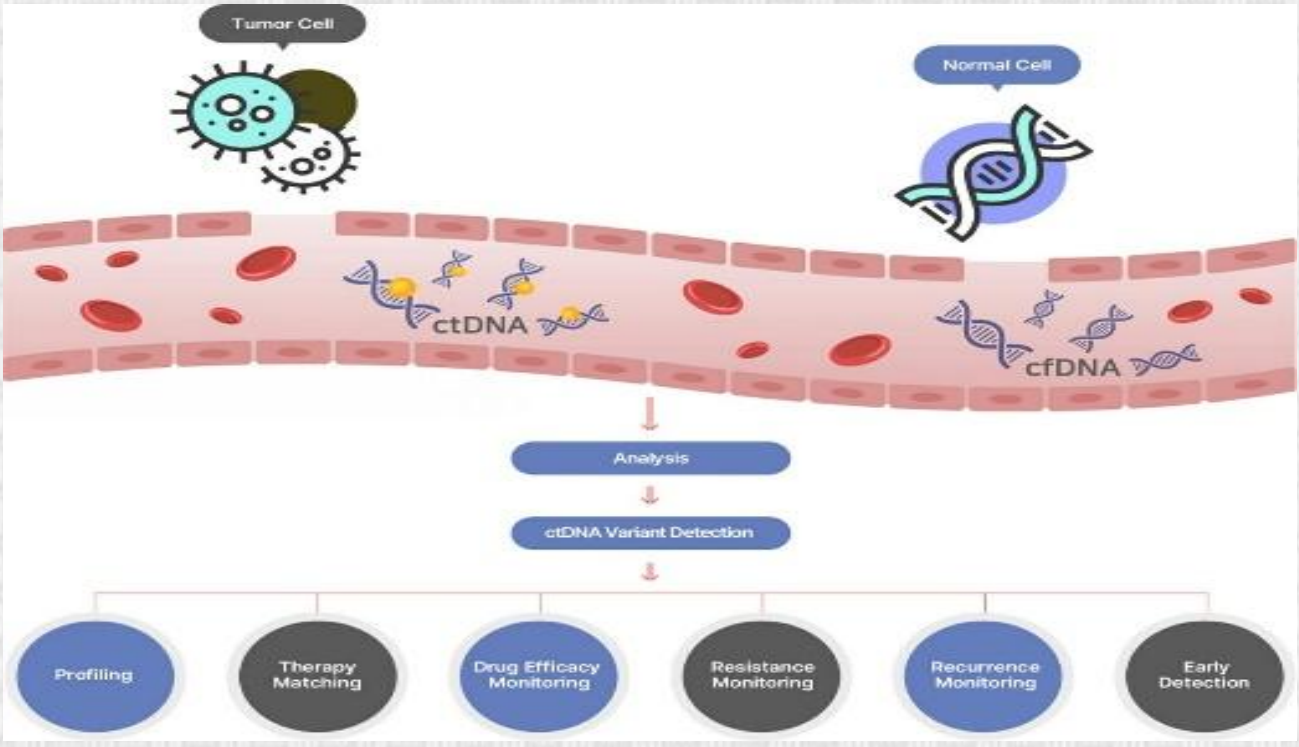
(C) Circulating DNA

** Liquid biopsies can also analyze circulating tumor DNA (ctDNA), which is released by tumor cells, alive or dead.*

** Normal cells also release DNA fragments, known as circulating free DNA (cfDNA) or cell-free DNA, which can include both normal and tumor-derived DNA.*

** The proportion of tumor derived DNA in the blood is often very low (as little as 1 in 10,000) and varies by tumor type, making detection easier for certain cancers similar to circulating tumor cells, ctDNA may contribute to metastases under lab conditions.*

** While the body usually clears circulating DNA, advanced cancer can overwhelm this process due to chronic inflammation and cell death, leading to higher ctDNA levels that are associated with disease progression.*



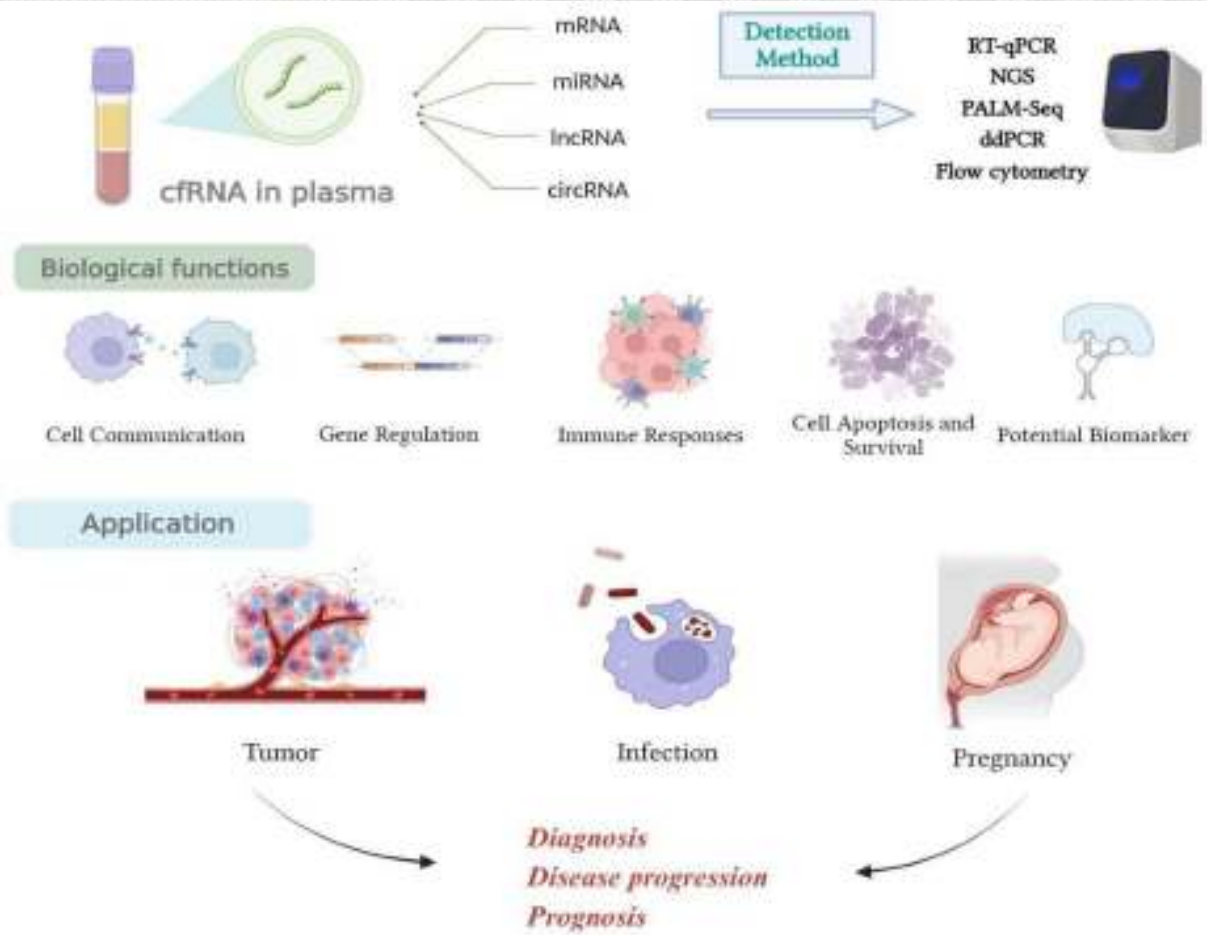
(D) Circulating RNA

** Circulating RNA, found in the blood, is a key component analyzed in liquid biopsies.*

** Types of RNA in blood include those involved in gene expression and regulation, such as messenger RNA (mRNA) and microRNA (miRNA).*

** While mRNA shows potential as a cancer biomarker, it degrades quickly in blood, complicating its study.*

** Conversely, miRNA is relatively stable and frequently abnormal in cancer, making it a promising candidate for liquid biopsy-based cancer diagnostics.*



(E)Exosomes

** Exosomes are small vesicles released by nearly all cells into biological fluids like blood.*

** These vesicles contain DNA, RNA, and proteins from their originating cells, protected by a membrane that preserves them for analysis.*

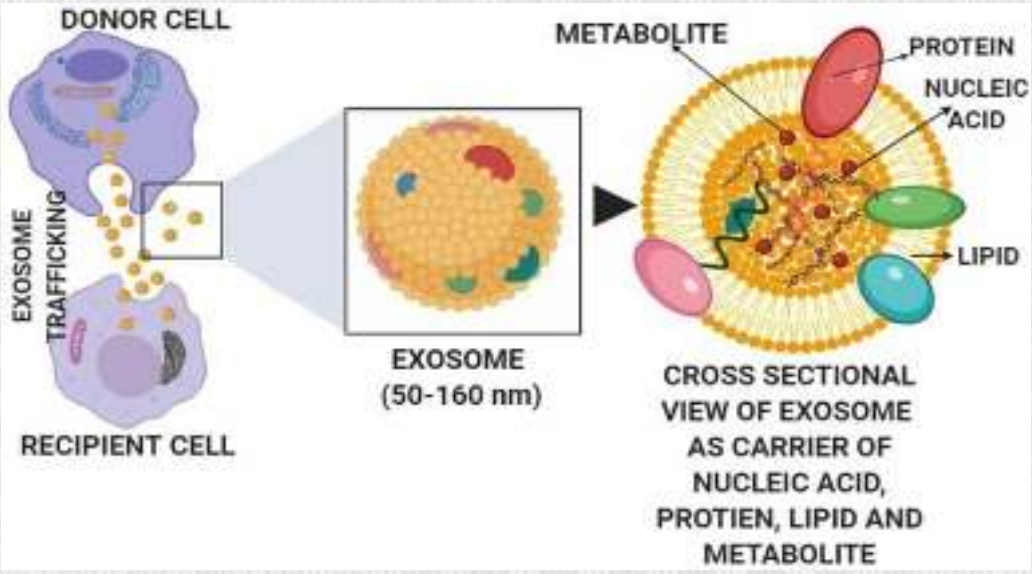
** This is particularly useful for studying unstable molecules like RNA, which provide insights into protein production and gene regulation.*

** Tumor-derived exosomes carry genomic information about tumor mutations and actively influence their surroundings.*

** They can promote tumor growth, metastasis, immune suppression, and the development of blood vessels needed by tumors.*

** Tumor cells release over 10,000 exosomes daily, adding to the billions produced by normal cells.*

** However, researchers have yet to develop a reliable method to distinguish tumor exosomes from those of healthy cells, though this is an active area of study.*



TUMOUR HETEROGENEITY

Do different cells in my tumor show different mutations?

PREDICTING TREATMENT RESPONSE

Is there a medication that targets my cancer?

MOLECULAR EVOLUTION

Has my tumor developed different mutations? How do mutations evolve in cancer?

PROGNOSIS

What is the expected course of my cancer

Steps Involved to Identify the Tumor Cells using Liquid Biopsy Samples

MONITORING TREATMENT RESPONSE

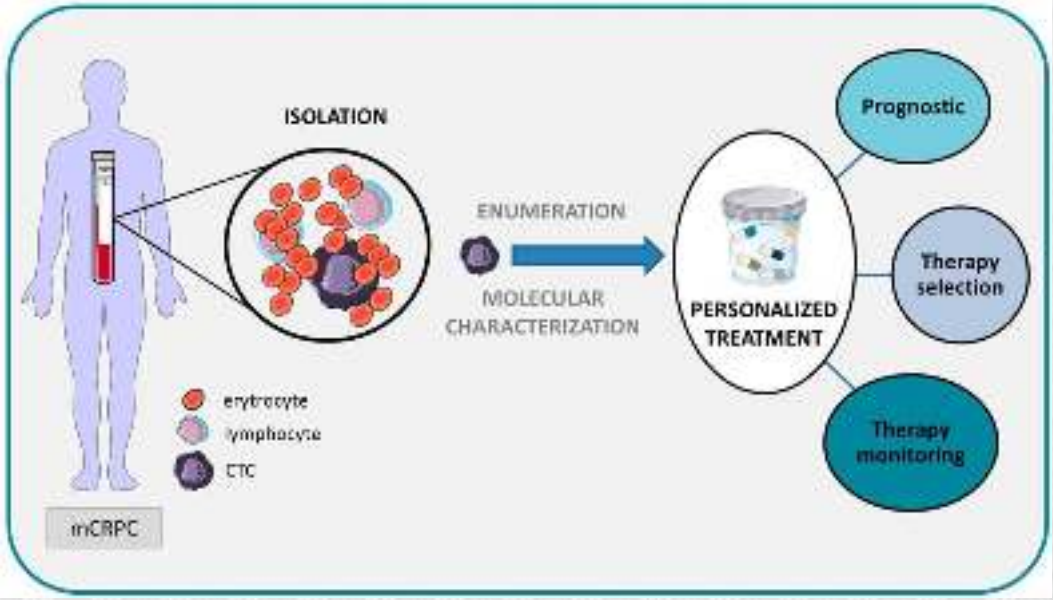
How is my cancer responding to treatment?

SCREENING

Do I have cancer?

MONITORING RECURRENCE

Has my cancer come back?

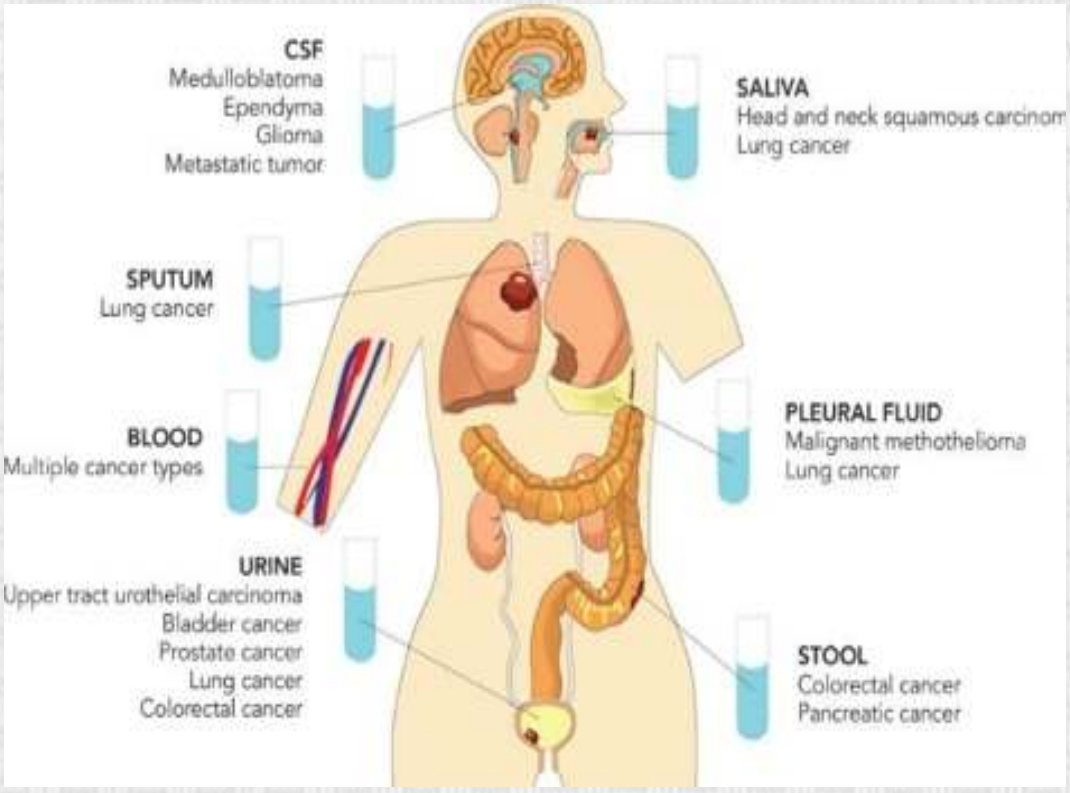


How are Liquid Biopsy Test Performed?

The general steps involved in Liquid Biopsy Sample Collection

1. Sample Selection

Blood is the most common sample type used in liquid biopsies. It is collected through a standard venipuncture (blood draw) procedure. Other fluids like urine, stool, saliva, pleural fluid, CSF, sputum may be used depending on the target condition.



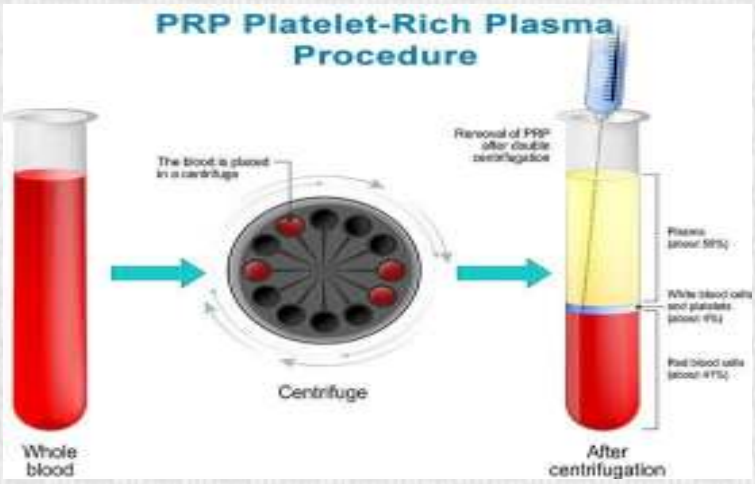
2. Sample Collection

* Liquid biopsy is a non-invasive method used to collect samples from body fluids (like blood, urine, or saliva) to detect biomarkers associated with diseases, particularly cancer.

* The main advantage of liquid biopsies over traditional tissue biopsies is that they are less invasive, quicker, and easier to perform.

3. Sample Preparation

After collection, the blood sample is typically processed to isolate specific components of interest, like circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), exosomes, or RNA. Plasma or serum is typically separated from whole blood using a centrifuge.



4. Analysis

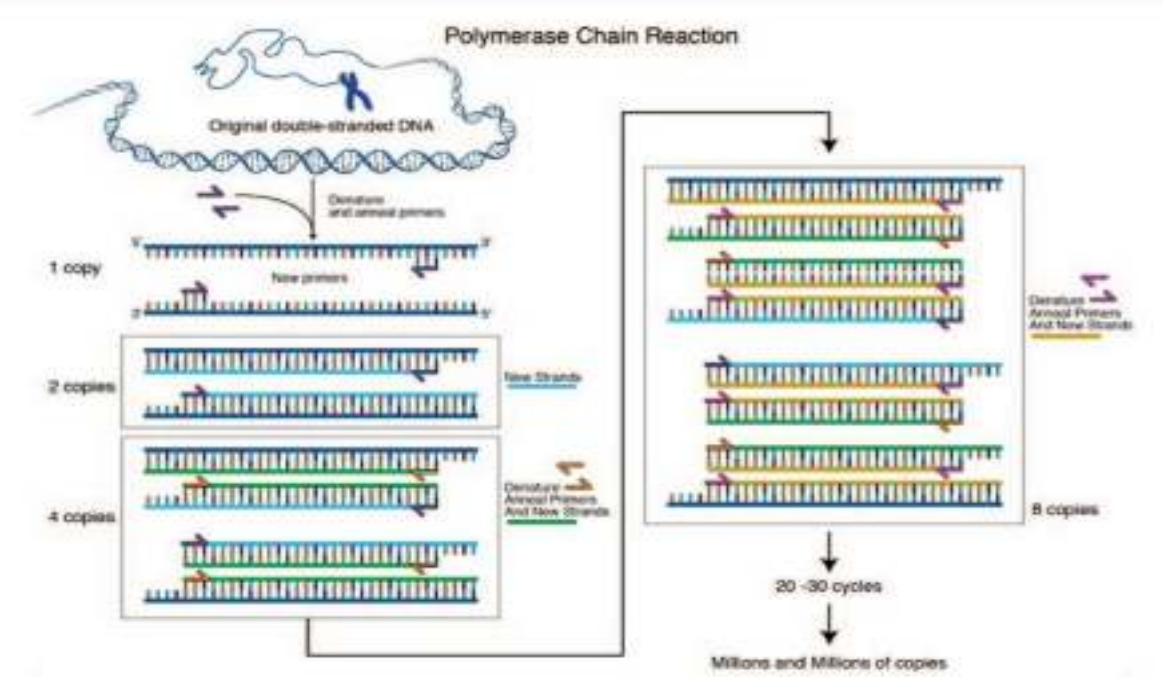
Methods Used for Liquid Biopsy

A) Genomic Characterizing:

1. Polymerase chain reaction:

* PCR is a method that makes small amounts of DNA easier to detect and analyze, similar to "xeroxing DNA.

* The process involves heating double-stranded DNA to separate it, lowering the temperature for primers to bind, and using DNA polymerase to copy the strands. This cycle repeats, doubling the DNA each time, creating a billion copies in a few hours.

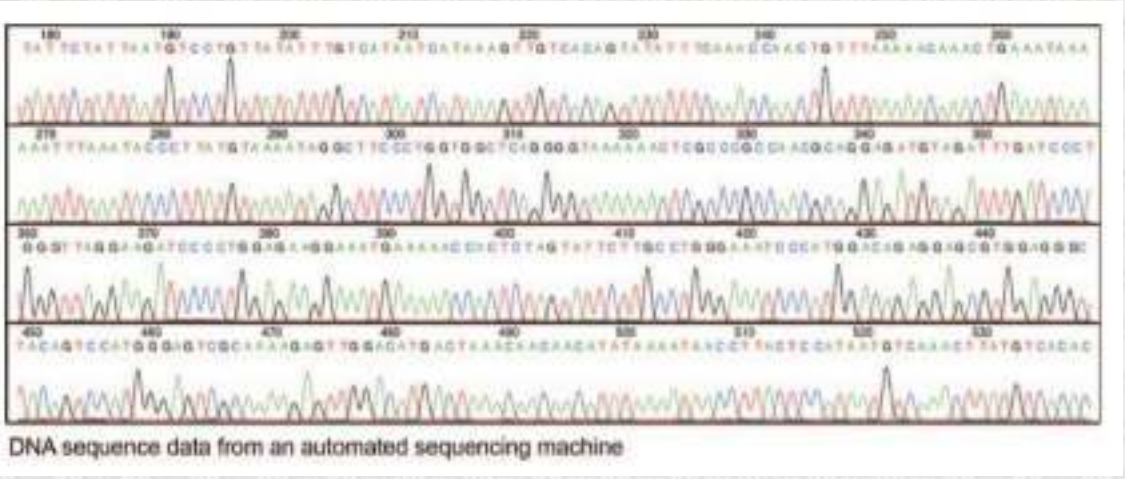


2. DNA Sequencing:

** DNA sequencing determines the nucleotide bases in DNA, which make up its structure and enable it to replicate.*

** In the Sanger method, DNA is split into two strands, and one is copied using chemicals that halt the copying at different points.This creates smaller DNA fragments.*

** The researchers identify the nucleotide at the end of each fragment and assemble them to reveal the original sequence.*



DNA sequence data from an automated sequencing machine

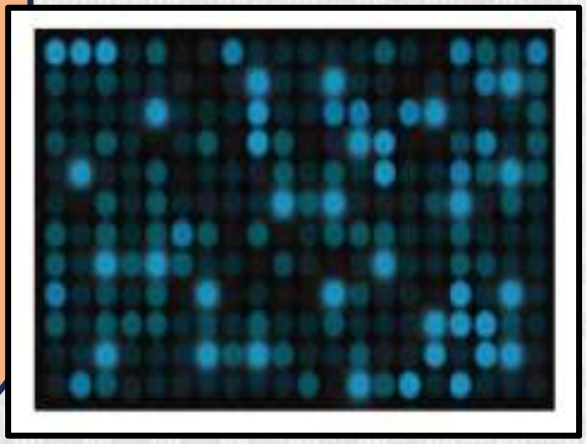
3. DNA Microarrays:

** Microarrays detect thousands of genes simultaneously using small DNA sections arranged in a grid on a glass surface.*

** The microarray appears as tiny dots in rows and columns, with each dot containing a specific DNA sequence that pairs with a corresponding sequence from a tissue sample.*

** After preparing the DNA sample, the double-stranded DNA is separated, cut into fragments, and dyed.*

** When placed on the microarray, bound DNA lights up, allowing identification of sequences using computer information. The detection may involve one to four colors.*

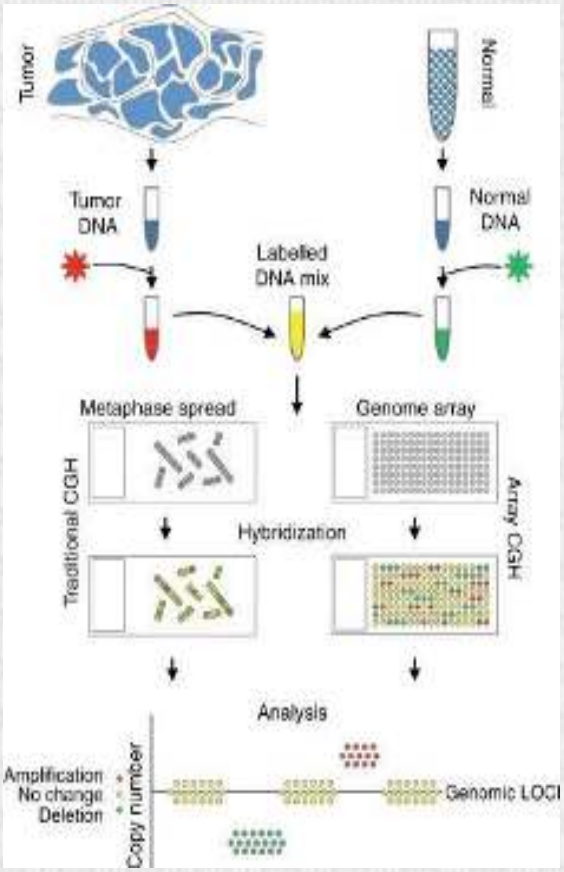


4. Comparative Genomic Hybridization:

** DNA microarrays can be combined with a procedure known as comparative genomic hybridization to detect copy number variations and regions of DNA that are gained or lost.*

** In this test, DNA samples from someone with cancer and someone without cancer are placed in a microarray and labeled with different colored fluorescent dyes.*

** The samples are allowed to bind to DNA sequences of interest and then the amount of fluorescence is compared using a specialized scanner.*



B) Methods Used to Detect

** Methods Used to Detect RNA Several of the methods just described for the detection of DNA have been adapted to detect RNA and can be used to assess circulating RNA and microRNA.*

** Reverse Transcription-PCR Reverse transcription-PCR is similar to PCR except that it detects RNA instead of DNA. Reverse transcription-PCR uses the same steps as PCR. MicroRNAs MicroRNAs are not a method but rather a type of RNA that was discovered in 1993.*

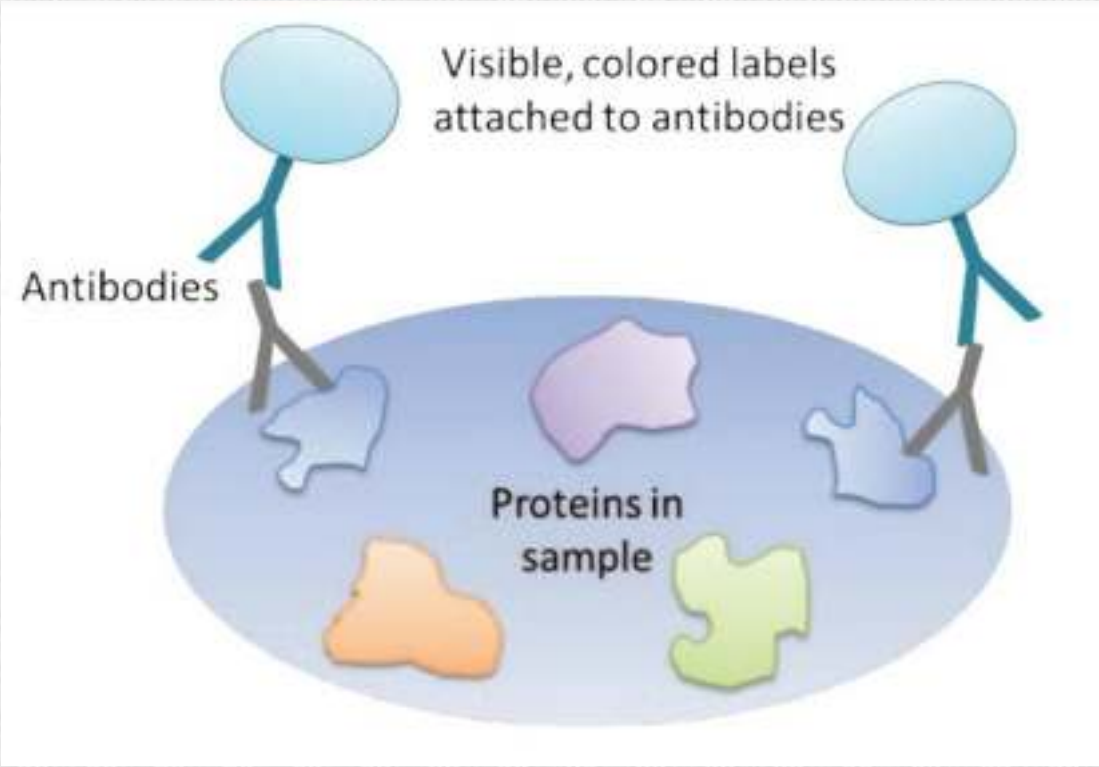
** MicroRNA or miRNAs are small, single-stranded RNA molecules approximately 19 to 25 nucleotide bases in length that bind to specific parts of larger RNA molecules, preventing them from making proteins.*

** In this way, microRNAs inhibit gene expression. Some of the tests for microRNA use quantitative real-time, reverse-transcription PCR.*

C) Methods Used to Detect Proteins:

Immunohistochemistry:

Immunohistochemistry is a method used to detect proteins in biological liquids or membranes. It uses antibodies, which are labeled with a fluorescent marker, to bind to a specific protein. If the protein is present, the antibodies bind and a visible label is seen, while unbound antibodies wash off. This technique can be qualitative or quantitative.



Diagnostic Test Accuracy:

1. Analytical Validity:

** A Measure of how well the test measures what it purports to measure.*

2. Sensitivity:

** The ability of the test to correctly identify those patients with the biomarker or condition.*

3. Specificity:

** The ability of the test to correctly identify those patients without the condition.*

** Stated another way, a test is specific if it gives a positive result only when the condition is present for instance, a specific test for a cancer mutation would give a negative result for everyone who does not have the mutation and only give a positive result if someone does have the mutation.*

Advantage and Disadvantage

Advantages of Liquid Biopsy

Non-invasive: *Liquid biopsies use blood or other bodily fluids, reducing the need for invasive procedures like tissue biopsies.*

Early Detection: *Liquid biopsy can detect cancer biomarker at early stage, potentially improving treatment outcomes.*

Real-time Monitoring: *Liquid biopsies allow continuous monitoring of a patient's condition and treatment response, providing timely adjustments in therapy.*

Disadvantages of Liquid Biopsy

Limited Sensitivity: *In some cases, liquid biopsies may not detect all diseases or may miss early-stage cancers or rare mutations.*

False Positives/Negatives: *The test can sometimes give false results, leading to unnecessary treatments or missed diagnosis.*

Cost: *While they may reduce long-term costs, liquid biopsy tests can still be expensive, particularly in the early stages of their development.*

Future Direction:

** The future of liquid biopsy is shaping the next era of healthcare.*

** With the ability to detect diseases like cancer early, it offers a non-invasive, accurate alternative to traditional biopsies.*

** Advancements will make liquid biopsies even more precise, enabling earlier detection and better treatment outcomes.*

** Personalized medicine will thrive, allowing for tailored therapies based on genetic insights.*

** Liquid biopsy could also revolutionize disease monitoring, offering real-time tracking of progress and treatment effectiveness.*

** As the technology evolves, it will become a key tool in routine health screenings.*

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6.Ashworth TR. A case of cancer in which cells similar to those in the tumours were seen in the blood after death. The Medical Journal of Australia. 1869; 14: 146–147.

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