~~WHAT IS~~ CLAIM~~ED I~~S:

1. A method of analyzing cell free DNA (cfDNA) in an isolated biological sample, comprising:

~~obtaining a biological sample comprising cfDNA;~~

extracting cfDNA from the isolated biological sample to provide purified cfDNA, wherein the purified cfDNA comprises a plurality of cfDNA fragments, each fragment corresponding to a specific tissue or cell type;

quantifying the cfDNA fragments to generate a genome-wide cfDNA copy number profile, wherein the genome-wide cfDNA copy number profile comprises a plurality of copy number signals, each copy number signal corresponding to a cfDNA fragment; ~~and~~

subtracting a baseline reference profile from the genome-wide cfDNA profile, wherein the baseline reference profile is generated using non-negative matrix factorization to decompose cfDNA signals of control samples; and

comparing the genome-wide cfDNA copy number profile to a set of known cfDNA signatures comprising reference cfDNA profiles to determine cell damage, tissue damage, or organ damage.

2. The method of Claim 1, wherein the biological sample comprises blood, plasma, serum, urine, cerebrospinal fluid, saliva, lymphatic fluid, aqueous humor, vitreous humor, cochlear fluid, tears, milk, sputum, vaginal discharge, or any combination thereof.

3. The method of Claim 1, wherein quantifying comprises sequencing the cfDNA using sequencing-based DNA molecule counting.

4. The method of Claim 1, further comprising enriching cfDNA fragments of interest.

5. The method of Claim 1, wherein quantifying comprises performing hybridization-based DNA quantification.

6. The method of Claim 1, wherein extracting comprises size-based enrichment to exclude gDNA and enrich for cfDNA fragments.

7. The method of Claim ~~1~~4, wherein enriching comprises amplification of the cfDNA.

8. The method of Claim 7, wherein amplification comprises PCR amplification or genome-wide amplification.

9. The method of Claim 1, wherein each copy number signal is indicative of a relative contribution of cfDNA from a specific tissue or cell type.

10. The method of Claim 1, wherein the tissue type is kidney, muscle, heart, vascular, liver, brain, eye, lung, adipose, gland, bone, bone marrow, cartilage, intestine, stomach, skin, or bladder.

11. The method of Claim 1, wherein the cell type is blood cells, neuron cells, kidney cells, epithelial, extracellular matrix cells, beta cells, or immune cells.

12. The method of Claim 1, wherein the genome-wide cfDNA profile is used to quantify amounts of cfDNA from multiple organs for providing an assessment of organ or multi-organ health.

13. The method of Claim 1, wherein the sample is obtained and analyzed periodically from a subject to monitor health over time.

14. The method of Claim 13, further comprising monitoring organ transplant over time.

15. The method of Claim 1, wherein the genome-wide cfDNA profile is indicative of drug toxicity or efficacy in an organ.

~~16. The method of Claim 127, wherein the biological sample is a maternal sample, and wherein the genome-wide cfDNA profile is indicative of fetus health, and wherein a change in organ health condition is a change in organ health condition of the fetus.~~

~~17.~~16. The method of Claim 1, wherein multiple organs are quantified simultaneously by projecting the genome-wide cfDNA profile onto a set of reference cfDNA profiles corresponding to various tissue and cell types.

~~18. The method of Claim 1, further comprising subtracting a baseline reference profile from the genome-wide cfDNA profile.~~

~~19.~~17. A method of monitoring disease progress in a subject, comprising:

~~obtaining a biological sample from the subject, wherein the biological sample comprises cell free DNA (cfDNA);~~

quantifying ~~the~~ cfDNA in ~~the~~an isolated biological sample from the subject to obtain a genome-wide cfDNA profile comprising a plurality of copy number signals, each copy number signal corresponding to a cfDNA fragment of a specific cell type or tissue type; ~~and~~

subtracting a baseline reference profile from the genome-wide cfDNA profile, wherein the baseline reference profile is generated using non-negative matrix factorization to decompose cfDNA signals of control samples; and

comparing the plurality of cfDNA copy number signals to a set of known copy number signals of healthy subjects,

wherein a difference of copy number signal in the sample compared to the known copy number signals correlates to a disease progress in the subject.

~~20.~~18. The method of Claim ~~19~~17, wherein total cfDNA is enriched from the sample, prior to quantifying the cfDNA.

~~21.~~19. The method of Claim ~~19~~17, further comprising comparing the plurality of copy number signals to a profile of known copy number signals of diseased patient samples.

~~22.~~20. The method of Claim ~~19~~17, wherein the biological sample comprises blood, plasma, serum, urine, cerebrospinal fluid, saliva, lymphatic fluid, aqueous humor, vitreous humor, cochlear fluid, tears, milk, sputum, vaginal discharge, or any combination thereof.

~~23.~~21. The method of Claim ~~19~~17, wherein quantifying comprises sequencing the cfDNA using sequencing-based DNA molecule counting.

~~24.~~22. The method of Claim ~~19~~17, wherein quantifying comprises performing hybridization-based DNA quantification.

~~25.~~23. The method of Claim ~~19~~17, wherein the disease is selected from heart failure, lung damage, diabetes, Crohn's disease, or kidney disease.

~~26.~~24. The method of Claim ~~25~~23, wherein enriching comprises amplifying the cfDNA through targeted amplification or genome-wide amplification.

~~27.~~25. A method of monitoring tissue and organ health in a subject, comprising:

~~obtaining a biological sample from the subject, wherein the biological sample comprises cell free DNA (cfDNA);~~

quantifying ~~the~~ cfDNA in ~~the~~an isolated biological sample from the subject to obtain a genome-wide cfDNA profile comprising a plurality of copy number signals, each copy number signal corresponding to a cfDNA fragment of a specific cell type or tissue type; ~~and~~

subtracting a baseline reference profile from the genome-wide cfDNA profile, wherein the baseline reference profile is generated using non-negative matrix factorization to decompose cfDNA signals of control samples; and

comparing the plurality of cfDNA copy number signals to a set of known copy number signals of healthy subjects,

wherein a difference of copy number signal in the sample compared to the known copy number signals correlates to a change in organ health condition in the subject.

~~28.~~26. The method of Claim ~~27~~25, wherein total cfDNA is enriched from the sample, prior to quantifying the cfDNA.

~~29.~~27. The method of Claim ~~27~~25, further comprising comparing the plurality of copy number signals to a profile of known copy number signals of samples from a patient having poor tissue or organ health.

~~30.~~28. The method of Claim ~~27~~25, wherein the biological sample comprises blood, plasma, serum, urine, cerebrospinal fluid, saliva, lymphatic fluid, aqueous humor, vitreous humor, cochlear fluid, tears, milk, sputum, vaginal discharge, or any combination thereof.

~~31.~~29. The method of Claim ~~27~~25, wherein quantifying comprises sequencing the cfDNA using sequencing-based DNA molecule counting.

~~32.~~30. The method of Claim ~~27~~25, wherein quantifying comprises performing hybridization-based DNA quantification.

~~33.~~31. The method of Claim ~~27~~25, wherein enriching comprises amplifying the cfDNA through targeted amplification or genome-wide amplification.