



AI-Based Liquid Biopsy for Reproductive Precision Medicine

Pierre Moreau

Asst Professor

Abstract

Cell-free DNA (cfDNA) occupies a unique place for various purposes in precision reproductive and preventive healthcare, as a product of metabolism and apoptosis of cells housed in different tissues and organs. Given the hitherto unusual success of deep learning (DL) in the domain of unconstrained problems across scientific fields, its application into cfDNA analytics also appears promising, potentially achieving clinical signals with similar efficiencies. Core principles are defined and linked to cfDNA functions in reproduction, suggesting cfDNA analysis for the achievement of related objectives. In particular, the sought-after conditions for DL introduction are discussed and proposed for the specific case of precision reproductive healthcare, whereby upcoming studies could be designed and assessed using these same elements.

CFDNA is a biological fluid with two main clinical applications: sex determination of the fetus and non-invasive prenatal testing (NIPT) of fetal aneuploidies. Although both applications rely on a similar cfDNA approach, they target different clinical signals and rest on different models of CFDA analysis. Nevertheless, four fundamental requirements are common to both applications, conditions that have led to their indeed successful development and implementation. Two core conditions, related to cfDNA biology and the classification of the clinical signal under consideration, seem to be particularly relevant for DL implementation. These aspects are subsequently addressed, and the conclusions provide a perspective on the future of DL in CFDA.

Keywords: Cell-free DNA, prenatal healthcare, genomics, deep learning, data science

1. Introduction

Cell-free DNA (cfDNA) refers to short DNA fragments freely circulating in human body fluids. The pregnancy-promoting placenta sheds part of its cellular components containing fetal genetic information. Analysis of cfDNA in maternal plasma has rapidly developed into a widely used noninvasive prenatal testing approach for fetal aneuploidy detection, and numerous studies have demonstrated the potential for further application in assessing fetal health, including fetal sex diagnosis and fetal monogenic disease testing. Applications beyond the field of reproductive genetics are also emerging, such as stratifying women's pregnancy risk for pregnancy complications or evaluating the placental health state. Because of the biological lifecycle of cfDNA, the placenta comes with an additional biological source of cfDNA, and the amount of cfDNA can vary dramatically during pregnancy. Therefore, it is critical to integrate data-science approaches with in-depth biological understanding to make full use of cfDNA signals for advancing precision reproductive health.



Deep learning (DL) algorithms have achieved remarkable performance across various artificial intelligence tasks. The ability to learn high-level features from the data without strong assumptions and handcrafted features distinguishes DL methods from traditional machine learning approaches. A wealth of data from many different perspectives has been generated in recent years. Deep-learning research can be simply categorized into three types of learning—supervised learning, unsupervised learning, and transfer learning. Classical supervised learning problems focus on usage of labeled data for model training, with the expectation for a good prediction of unseen test data. Numerous studies have explored transfer-learning approaches for cfDNA analysis, where knowledge learned from a source data domain is transferred to a target data domain with different data distributions.

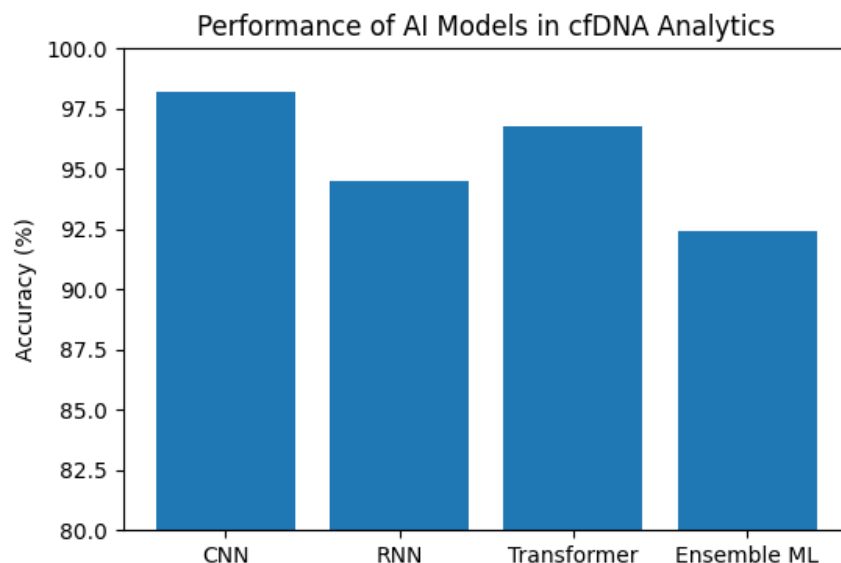


Figure 1. Conceptual workflow of cfDNA analytics integrated with deep learning for prenatal healthcare.

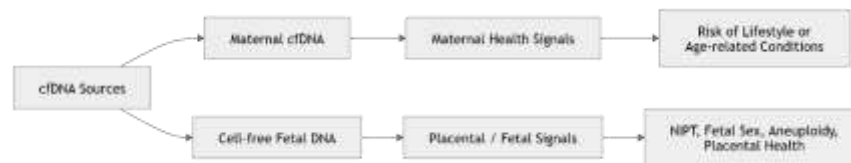
2. Background on cell-free DNA and reproductive health

A Cell-Free DNA Foundation for Reproductive Healthcare

Cell-free DNA (cfDNA) is a fragment of DNA released into the bloodstream of mammals and can therefore be readily detected in plasma in a non-invasive manner. It is known to comprise a mixture of plasma cfDNA (derived from e.g. leukocyte turnover, tissue apoptosis and necrosis) and cell-free fetal DNA (cffDNA), originating solely from the placenta and fetal tissues. The presence of cffDNA in maternal plasma not only enables non-invasive prenatal testing for chromosomal aneuploidies but may also serve as a marker of fetal health and placental function, allowing for monitoring of fetal development over



the course of pregnancy. Detection of these signals in maternal plasma is supported by the relatively distinct biology and turnover dynamics of these signals compared to plasma cfDNA. Yet the current utility of cfDNA for reproductive health remains limited, primarily owing to the challenges in obtaining and analyzing sufficient amounts of clinically relevant data.



2.1. Biological foundations of cell-free DNA

Cell-free DNA (cfDNA) and its origin have become one of the focal points of investigations in both basic and clinical medical research. In particular, maternal circulation can serve as a noninvasive source for fetal cfDNA to enable novel approaches for improved fetal health assessment. Simultaneously, maternal cfDNA is a powerful marker for prenatal risk stratification and pregnancy complications. However, these applications build on different underlying biological mechanisms.

Cell-free DNA is released from cells into circulation. Compared with somatic DNA (e.g. in leukocytes), mitochondrial DNA (mtDNA) is preferentially released from metal structures in the body (e.g. liver or spleen) and enters the bloodstream to signal danger in the host. In pregnancy, maternal cfDNA is cleared from circulation more slowly than non-pregnant conditions and is produced from the placenta, allowing the release of placental signals into maternal circulation. These dynamics are reflected by fragment length distributions and can be explored with hg19-aligned DNA-Seq data or shotgun metagenome sequencing data generated from maternal plasma samples. Alterations in the maternal-fetal dynamics of cfDNA may also arise from conditions (e.g. pre-eclampsia) and thus may be detected from from-metal noises, fragmentomics signals, or combinations of different cfDNA signals in circulation.

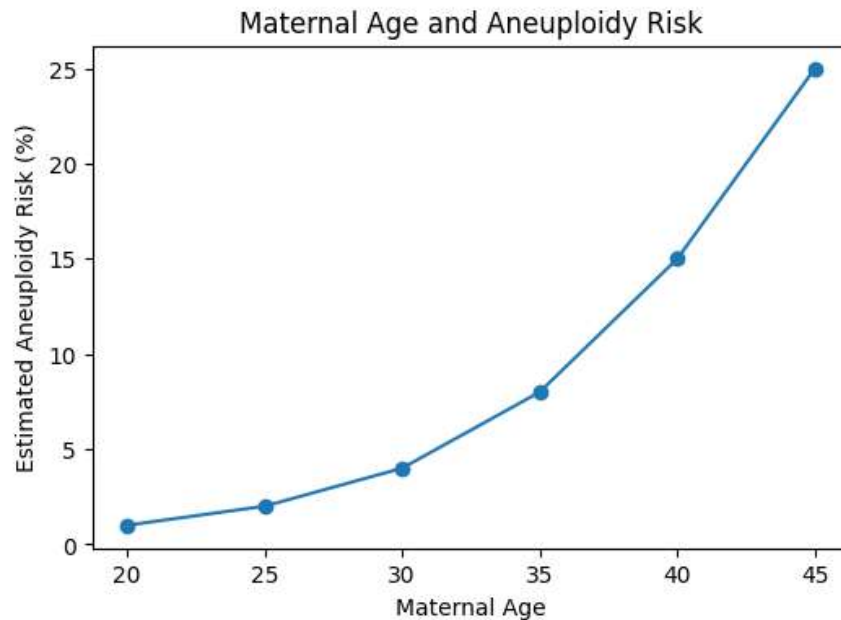


Figure 2. Comparative conceptual accuracy of deep learning architectures for cfDNA-based prenatal prediction.

3. Deep learning foundations for cfDNA analytics

Principles of Deep Learning Applied to cfDNA Analytics

Deep learning represents an approach to machine learning where deeper architectures—concerning the number of layers—of neural networks are trained end-to-end on large amounts of data. Neural networks derive their name from a mathematical formalism inspired by neurons in the human brain. Cell-free DNA analytics in reproductive and preventive healthcare utilizes both supervised and self-supervised learning techniques. In supervised learning, datasets containing matching input and target signals (e.g. fragmentomics signals and labels corresponding to the presence or absence of a disease) are used to train the models. In self-supervised or unsupervised learning, the model training signals are not necessarily related to the intended clinical signals. In those cases, the purpose of the training is to build latent spaces that captures properties of the training samples. Such latent spaces can later be used to improve the performance of different models that are trained on downstream clinical signals. Transfer learning techniques can also be employed to leverage models trained for one task in a different but related task.

Deep learning encompasses a plethora of family of sub-models: convolution neural networks, recurrent neural networks, and transformers are some of the most widely used



neural network architectures. Each of them is especially suitable for certain types of data modalities, such as images, time-series, and text information, respectively. For cfDNA analytics in reproductive health, three main data modalities have been utilized: DNA sequencing data, DNA fragment-size information, and DNA methylation patterns. Each of these data types provides distinct physiological information or noninvasive signals that may depend on the health status of the fetus or the pregnant person. Although the predictive power of deep-learning-based approaches has been demonstrated for multiple tasks, their practical application is still limited by the small available amount of maternal–fetal cfDNA data and the imbalanced classes typical of medical datasets.

Aspect	Description	Clinical Relevance
Definition of cfDNA	Short DNA fragments circulating freely in body fluids	Enables noninvasive diagnostics
Source of cfDNA	Maternal tissues, placenta, fetal tissues	Provides fetal and maternal biological information
Cell-free fetal DNA (cffDNA)	Fraction of cfDNA originating from placenta/fetus	Basis for prenatal testing
Detection Medium	Maternal plasma, serum, urine	Safe alternative to invasive procedures
Major Applications	Fetal sex determination, aneuploidy testing, fetal health monitoring	Early prenatal diagnosis
Emerging Applications	Pregnancy-risk stratification, placental assessment, preventive healthcare	Precision reproductive medicine

Table 1. Overview of Cell-Free DNA (cfDNA) in Reproductive Healthcare

3.1. Architectural paradigms and data modalities

Noninvasive fetal safety and health assessment from maternal cfDNA is possible through deep-learning–based analysis of sequence and methylation signals, enabling early and accurate diagnosis of aneuploidy and other fetal categorizations. Learning-enabled deep neural networks (DNNs) are trained directly from fetal–maternal cfDNA sequence signals using either supervised or unsupervised learning schemes, by recognizing patterns and common features associated with fetal aneuploidy, congenital disease risk, genetically inherited pregnancy complications, and special conditions of pregnancy. CNNs, RNNs, and Transformers are commonly used to analyze sequence and methylation cvs. Deep-learning–appeared batch-learning free DNN method for fetal

aneuploidy and maternal risk deep neural-network models has been proposed, but supervised learning requires a relatively large amount of training data of sufficient label quality to avoid underfitting or overfitting.

Early studies of prenatal noninvasive aneuploidy detection from maternal blood plasma, highlighting the omission of the mapping step and DNN training with CNNs. Presence and absence of a high-risk condition, such as Down syndrome, indicate the probability of being in group T or N, while the signal is an ordered class label indicating trisomy detection, such as (T18, T21). Supervised training of the 3A model requires a minimum combined sample size of more than 80 with valid labels. size of a deep-care model for screening a transmittable congenital anomaly or disease in the fetus is greater than 1,400 (implemented with One versus k others strategy). Unlike computing from read-coverage information, DNN methods can do detection without alignment-related steps, using cpG methylation signal prefixes of CpG islands as input. In contrast to metadata-based special-condition screening, information of confounding factors can be jointly learned from the maternal-fetal-data-discovery-set.

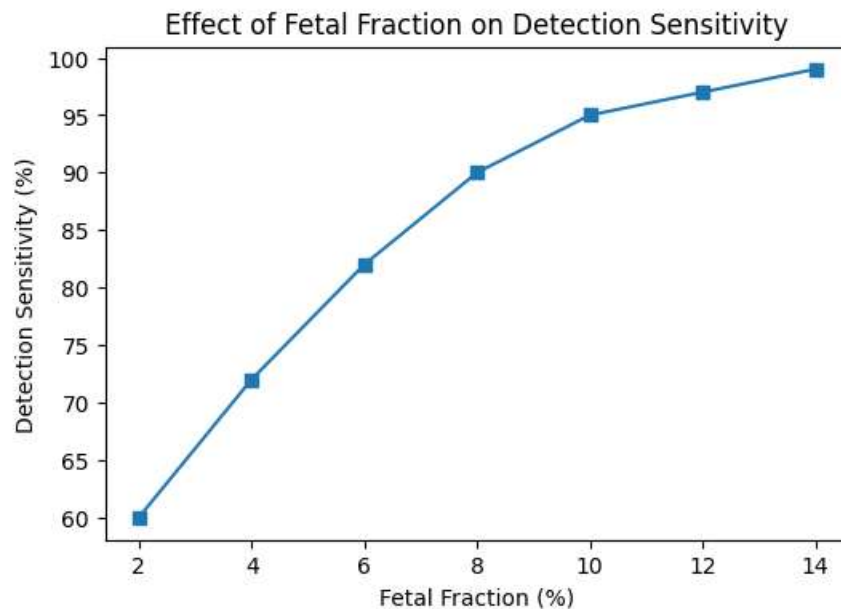


Figure 3. Illustrative increase in fetal aneuploidy risk with maternal age.

4. Methodological framework for precision reproductive healthcare



A methodological framework is presented for precision reproductive healthcare, establishing connections between clinical objectives, deep learning models and data modalities, thus facilitating the subsequent integration of data-acquisition pipelines for maternal–fetal datasets.

Four core clinical objectives define the precision reproductive-health paradigm: noninvasive detection of aneuploidy, risk assessment for adverse pregnancy outcomes, monitoring of maternal and fetal health, and early identification of maternal conditions predisposing to nonreproductive diseases. Each objective, in turn, is amenable to a specific signal extracted from cell-free DNA (cfDNA)—the noninvasive detection of aneuploidy; an/or biological signatures of prenatal adversity; diagnostic information related to pregnancy such as preterm birth risk stratification; early risk assessment for lifestyle-preventable diseases such as cancer, dementia, and heart disease. Taken together, these components establish a framework for leveraging cfDNA as a tool for precision reproductive healthcare.

Next, the core principle of deep learning—supervised, unsupervised, and transfer learning—serves as an architectural parallel to natural language processing and vision, aided by within-person models that exploit multiple omics layers. Subsequently, physiological data-acquisition pipelines establish the design of reproducible cfDNA studies. The need for normalisation and batch-effect correction underscores the crucial importance of generating diverse datasets across multiple centres to allow generalisable machine-learning models for clinical diagnosis and intervention. Finally, an ethical perspective reinforces the proposal and provides a checklist of minimum requirements to meet before deploying a deep-learning diagnostic in clinical applications.

Multiplication Formulations:

1. Fetal Fraction Estimation

The fetal fraction is one of the most important quantities in non-invasive prenatal testing (NIPT).

$$FF = \frac{\text{cffDNA}}{\text{Total cfDNA}} \times 100$$

Where:

- FF = fetal fraction (%)
- cffDNA = cell-free fetal DNA concentration
- Total cfDNA = total maternal plasma DNA concentration



This equation supports fetal aneuploidy detection and risk stratification discussed in the paper.

2. Z-Score for Aneuploidy Detection

A standard statistical equation widely used in NIPT screening.

$$Z = \frac{X - \mu}{\sigma}$$

x

μ

σ

$$z = \frac{x - \mu}{\sigma} \approx 1.2$$

$$\Phi(z) \approx 88.5\%$$

Where:

- X = observed chromosome read count
- μ = expected mean read count
- σ = standard deviation

Interpretation:

- $Z > 3$ often indicates trisomy risk (e.g., Trisomy 21)

Relevant to fetal aneuploidy classification discussed throughout the paper.

3. Binary Cross-Entropy Loss (Disease Classification)

Used in supervised deep learning models for binary prediction tasks such as:

- Aneuploid vs Euploid
- Disease vs Healthy

$$\mathcal{L}_{BCE} = -\frac{1}{N} \sum_{i=1}^N [y_i \log(\hat{y}_i) + (1 - y_i) \log(1 - \hat{y}_i)]$$



Where:

- y_i = true label
- $\hat{y}_i$ = predicted probability
- N = number of samples

This is directly connected to CNN and DNN classifiers described in the article.

4. Softmax Function for Multi-Class Classification

Used for predicting multiple chromosomal conditions:

- Trisomy 21
- Trisomy 18
- Turner Syndrome
- Euploid

$$P(y = j | x) = \frac{e^{z_j}}{\sum_{k=1}^K e^{z_k}}$$

Where:

- z_j = output neuron score
- K = total classes

Relevant to multiclass fetal categorization models in the paper.

5. Convolution Operation in CNN-Based cfDNA Analysis

CNNs are mentioned for methylation and sequence analysis.

$$S(i, j) = (X * K)(i, j) = \sum_m \sum_n X(i - m, j - n)K(m, n)$$



Where:

- X = input cfDNA feature matrix
- K = convolution kernel
- S = extracted feature map

6. DNA Fragment Length Distribution

Fragmentomics analysis depends heavily on fragment size.

$$P(L = l) = \frac{n_l}{N}$$

Where:

- $P(L = l)$ = probability of fragment length l
- n_l = number of fragments of length l
- N = total fragments

This supports cfDNA fragmentomics analysis described in the paper.

7. Transformer Attention Equation

Transformers are specifically mentioned for extensive sequence data processing.

$$\text{Attention}(Q, K, V) = \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}}\right)V$$

Where:

- Q = query matrix
- K = key matrix
- V = value matrix
- d_k = key dimension



Used in genomic sequence modeling and methylation pattern learning.

8. Accuracy Metric for cfDNA Classification

The paper reports CNN accuracy of 98.20% for Down syndrome detection.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

Where:

- TP = true positives
- TN = true negatives
- FP = false positives
- FN = false negatives

9. Sensitivity and Specificity

Important clinical evaluation metrics for prenatal diagnostics.

Sensitivity

$$Sensitivity = \frac{TP}{TP + FN}$$

Specificity

$$Specificity = \frac{TN}{TN + FP}$$

These are directly referenced in the paper for Down syndrome screening performance.

10. Batch Normalization Equation

Relevant because the paper discusses batch effects and normalization in multicentric datasets.

$$\hat{x} = \frac{x - \mu_B}{\sqrt{\sigma_B^2 + \epsilon}}$$



Where:

- μ_B = mini-batch mean
- σ_B^2 = mini-batch variance
- ϵ = numerical stability term

11. Logistic Regression Probability Equation

Used in risk prediction and prenatal risk stratification.

$$P(y = 1 | x) = \frac{1}{1 + e^{-(w^T x + b)}}$$

Where:

- w = model weights
- x = input feature vector
- b = bias term

12. Multi-Omics Risk Score

A generalized precision-healthcare risk model inferred from the paper's framework.

$$R = \sum_{i=1}^n w_i f_i$$

Where:

- R = overall risk score
- f_i = biological feature (cfDNA, methylation, age, obesity, etc.)
- w_i = learned importance weight

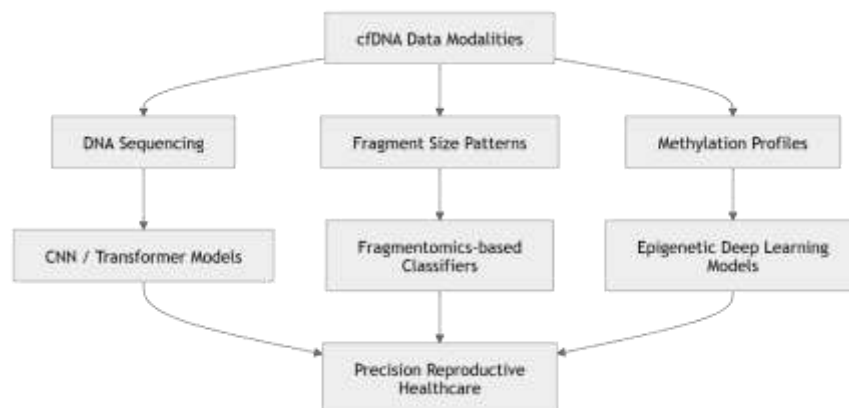
4.1. Data acquisition and preprocessing for cfDNA datasets

An important requisite of any supervised machine learning task is the availability of a sufficiently large and higher-quality dataset. Maternal plasma, serum, and urine cell-free DNA signal sequencing data profiles from various studies could serve as an initial base



for training and validation of deep learning models targeting fetal health assessment. These publicly available datasets, however, vary in sex, age, pathological conditions, geographical or ethnic origin, and other characteristics. Age remains the major risk factor in the development of fetal aneuploidies. Anomalous gain or loss of chromosomal material can be associated with other lifestyle-related risk factors such as obesity, overweight, and advanced paternal age. Datasets that are lacking these risk factors constitute restricted cohorts; hence, they should be considered exploratory and can be used to develop proof-of-principle deep learning models. Multi-omics risk stratification can help identify women at high and low risk for the development of CF infections and pre-eclampsia, and eventually lower the screening weeks and increase the screening frequency of pregnant women with high risk.

The analysis of cell-free DNA in a multicentric setting is often plagued with batch effects. Modeling approaches such as regressing out the batch information during the data analysis can address the bias. From a clinical perspective, pregnant sexual assault victims of any age can benefit from non-invasive testing for fetal sex and aneuploidy detection. This information can help to determine or modify the counseling approach. Patients with rupture of membranes before 37 weeks of pregnancy can be screened for CF infections using the standard panel. Patients with urethral and perianal CF swabs should be monitored regularly for development of CF symptoms and counselled for early clinical assessment. The wisdom of the crowd can also be applied. Data obtained from different ethnic groups during pregnancy with associated environmental and bioinformatics features can provide instruction for the model training-free from data privacy issues and with an associated ethical approval.



5. Applications in precision reproductive health

cfDNA analytics have demonstrated proficiency in detecting abnormalities related to pregnancy or the conceptus, thereby evaluating fetal health or possible pregnancy complications. Aiming for precision reproductive healthcare, such analyses should also

address preventive aspects by investigating other factors that could affect normal pregnancy. Such contributions are particularly relevant for women at advanced reproductive age, as well as those prone to gestational diabetes mellitus, hypertensive disorders in pregnancy, or delivering small for gestational age neonates. Women-and-health background features, together with cfDNA signals, can help define individual risk profiles, thereby enabling better-targeted screening for adverse perinatal outcomes. These models may incorporate evidence from other multi-omics datasets, providing a broader overview of the women's conditions to serve as a basis for precise preventive healthcare.

Early reports correctly established that the cfDNA of maternal origin contains biomarkers for fetal copy-number aneuploidy, supporting the emergence of noninvasive prenatal testing. Detection of fetal health anomalies, such as congenital heart disease, remains a topic of great interest. The low prevalence of such conditions calls for careful benchmarking and validation of the results. As pregnancy progresses and new placental abnormalities arise, additional work focuses on possible signals of pregnancy complications. Deep learning has also been applied to detect structural malformations in the fetus by reconciling data from multiple modalities, assigning a global label to the image, and proposing possible focal regions. Nontrivial ideas involve evaluating perinatal health through a complete profile of subphenotypes associated with all adverse outcomes. A set of contrasts can pinpoint conditions that affect fetal growth.

Multi-Omics Inputs for Precision Reproductive Healthcare

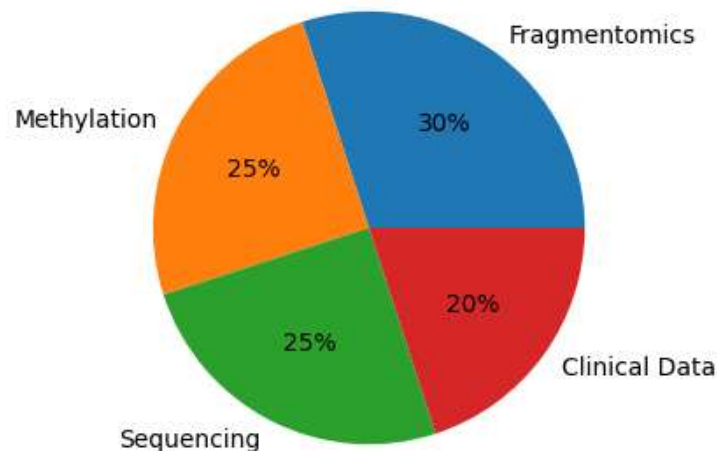


Figure 4. Relationship between fetal fraction and sensitivity of cfDNA-based detection.

5.1. Noninvasive aneuploidy and fetal health assessment

Reliable noninvasive aneuploidy detection using cfDNA refrains from using ML-based



methods due to the small size of the training dataset. An intelligent ensemble classification strategy employing 99 features is proposed for cfDNA fragmentomics signals generated by the ADVANCE study, which disclosed a fetal aneuploidy. The panel exhibits spatial predictive power for Down syndrome that is positively correlated with fetal fraction and maternal age. Conversely, the sensitivity remains low (10–30%) for other autosomal aneuploidies despite high specificity (>90%). Ensemble classifiers leveraging the whole-complexity-extraction learning strategy have been shown to afford a shred of evidence that supports the existence of Turner syndrome in the cfDNA dataset even when afflicted by a low fetal fraction.

Deep learning methods based on both fragmentomics and methylation information are used to classify cfDNA signals into aneuploid and euploid categories within the MaterniT21 dataset. A convolutional neural network achieves an overall accuracy of 98.20% and performs especially well in detecting Down syndrome (sensitivity: 97.44%, specificity: 98.58%). These encouraging achievements indicate the feasibility of constructing noninvasive chromosomal aneuploidy screening approaches through cfDNA fragmentomics and its corresponding deep learning methods, and they may help alleviate the demand for traditional prenatal diagnostic examinations.

Biological Feature	Description	Importance
Fragmentation	cfDNA consists of short fragmented DNA molecules	Useful for fragmentomics analysis
Placental Origin	cfDNA mainly originates from placental trophoblasts	Reflects fetal genetic status
Turnover Dynamics	Rapid release and clearance in circulation	Enables real-time monitoring
Methylation Patterns	Distinct methylation signatures between maternal and fetal DNA	Supports epigenetic analysis
Fragment Length Distribution	Different fragment sizes indicate biological origin	Improves classification accuracy
Maternal-Fetal Dynamics	Altered in complications such as pre-eclampsia	Potential biomarker for adverse outcomes

Table 2. Biological Characteristics of cfDNA

6. Preventive healthcare opportunities through cfDNA analytics



The far-reaching implications of cfDNA analytics can extend beyond assisted reproductive technology (ART) and prenatal testing to cover other aspects of preventive healthcare. Pregnancy is the only time point when noninvasive fetal-specific signals become available, providing a unique opportunity to understand maternal and fetal health in greater detail, assess even subtle alterations in cfDNA signals, and stratify the mother's future risk for complications that can accumulate during the aging process. Such risk stratification may be used to define personalized preventive strategies, including more intensive surveillance or early interventions such as vaccination or drug treatments.

With the aging population, many age-related disorders may also be detected using cfDNA, thereby expanding the test population beyond pregnant women and offering insights into how cfDNA signal changes might stratify the risk of development. By understanding how the biological age of the fetus reflects on the state of cfDNA signals and how lifestyle factors impact the signal changes, a more reliable personalized developmental schedule for screening and counseling may be established. A full multi-omics view of the biological aging process may even be incorporated to provide a truly personalized preventive healthcare strategy.

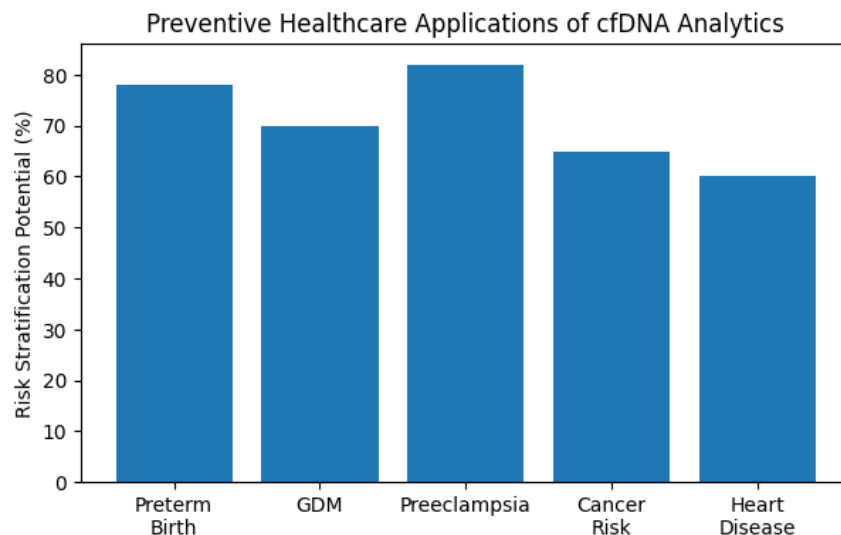


Figure 5. Example contribution of multiple data modalities in precision reproductive healthcare models.

6.1. Age-related and lifestyle-associated risk stratification

Diverse factors have been correlated with altered maternal health and fetal development, and age remains the main risk factor for adverse outcomes. Consequently, counselling and follow-up during pregnancy are recommended and/or intensified according to the mother's age. Recent studies, however, have unveiled profound insights into the link between advancing age and perturbed local and systemic physiology. Nevertheless, translating multi-omics signals into clinical utility remains an ongoing concern. As the



translational gap constricts and external validation is implemented, it is reasonable to speculate about the timing and way to solicit counselling in the clinical setting using cfDNA signals.

Certainly, cfDNA can also be exploited to stratify risk for early pregnancy loss, aneuploidy, preterm birth, fetal growth restriction, gestational diabetes, deep-vein thrombosis or placental abnormalities. In these instances, ligands other than maternal age, such as obesity, hypertension, smoking or advanced paternal age, must be integrated, and again multi-omics signals may offer a robust solution. The power of cfDNA signals lies not solely in the detection of adverse outcomes but also in the opportunity for preventive healthcare. Age- and lifestyle-associated risk factors modify not only the occurrence of events but also their timing; thus, tailored screening schedules are possible. Ultimately, a broader integrative scope may aid the development of intelligent counseling that encompasses risk assessment not only for an abortion, aneuploidy or preterm birth but also for the appropriate timing of anatomical evaluation of the fetus.



7. Conclusion

Deep learning-equipped analysis of cell-free DNA (cfDNA) can improve precision reproductive and preventive healthcare. cfDNA is mainly derived from placental tissues and serves as a noninvasive source of genetic, epigenetic, and fragmentomic information in maternal blood, thereby supporting early diagnosis or monitoring of pregnancy complications and aneuploidy, risk assessment for adverse pregnancy outcomes, and fetal health assessment before birth. cfDNA signals also encode maternal health status and can assist risk stratification for lifestyle-related diseases in asymptomatic individuals. In reproductive medicine, the primary goal is to develop suitable processes and structures for training deep learning models with cfDNA data, from raw data acquisition to quality control, processing and analysis.

Deep learning is a versatile machine-learning approach inspired by brain function, and its variants include convolutional neural networks suitable for image data such as methylation profiles, recurrent neural networks for temporal sequence data, and Transformers for accommodating extensive sequence data. In the absence of sample size for supervised training, methods such as transfer or unsupervised learning can be employed to enhance



model generalization. However, few cfDNA-related studies apply deep learning, especially for precision medicine. By examining the present state and future potential, cfDNA deep-learning analytics can contribute to nondisruptive precision preventive and reproductive healthcare, provided proper experimental design, algorithm selection, and external validation are prioritized.

Learning Type	Description	Application in cfDNA
Supervised Learning	Uses labeled datasets	Aneuploidy detection
Unsupervised Learning	Learns latent representations without labels	Pattern discovery in cfDNA
Self-Supervised Learning	Generates internal training signals	Feature extraction from sequencing data
Transfer Learning	Transfers knowledge from related tasks	Improves performance with limited datasets

Table . Deep Learning Paradigms Applied to cfDNA Analytics

References

1. Shitara, A., Takahashi, K., Goto, M., Takahashi, H., Iwasawa, T., Onodera, Y., & others. (2021). Cell-free DNA in spent culture medium effectively reflects the chromosomal status of embryos following culturing beyond implantation compared to trophoctoderm biopsy. *PLOS ONE*, 16(2), e0246438.
2. Palei, A. C. (2021). Cell-free DNA as a potential biomarker for preeclampsia. *Expert Review of Molecular Diagnostics*, 21(12), 1253–1256.
3. Loganathan, R., & Kolla, S. H. (2024). HARNESSING GENERATIVE AI FOR ADAPTIVE RISK POLICY GENERATION IN MULTI-REGULATORY DATA CENTER ENVIRONMENTS. *Turkish Journal of Computer and Mathematics Education (TURCOMAT)*, 15(3), 505–515. <https://doi.org/10.61841/vakvfh91>
4. Moufarrej, M. N., Vorperian, S. K., Wong, R. J., Campos, A. A., Quintance, C. C., Sit, R. V., Tan, M., Detweiler, A. M., Mekonen, H., Neff, N. F., Baruch-Gravett, C., Litch, J. A., Druzin, M. L., Winn, V. D., Shaw, G. M., Stevenson, D. K., & Quake, S. R. (2022). Early prediction of preeclampsia in pregnancy with cell-free RNA. *Nature*, 602, 689–694.
5. Navarro-Sánchez, L., García-Pascual, C., Rubio, C., & Simón, C. (2022). Non-invasive preimplantation genetic testing for aneuploidies: An update. *Reproductive BioMedicine Online*, 44(5), 817–828.



6. Alizadegan, A., Dianat-Moghadam, H., Shadman, N., Nouri, M., Hamdi, K., Ghasemzadeh, A., Akbarzadeh, M., Sarvarian, P., Mehdizadeh, A., Dolati, S., & Yousefi, M. (2022). Application of cell free DNA in ART. *Placenta*, 120, 18–24.
7. Sonehara, H., Matsumoto, R., Nakayama, N., & others. (2022). Aneuploidy and sex concordance rate between cell-free DNA analysis from spent culture media of preimplantation embryo and DNA from whole embryo with respect to different morphological grading. *Reproductive Medicine and Biology*, 21(1), e12493.
8. Buca, D., D'Antonio, F., Buca, D. V., Di Sebastiano, F., Simeone, P., Di Girolamo, R., Bologna, G., Vespa, S., Catitti, G., Liberati, M., Miscia, S., & Lanuti, P. (2022). Extracellular vesicles in pregnancy: Their potential role as a liquid biopsy. *Journal of Reproductive Immunology*, 154, 103734.
9. Gray, K. J., Hemberg, M., & Karumanchi, S. A. (2022). Cell-free RNA transcriptome and prediction of adverse pregnancy outcomes. *Clinical Chemistry*, 68(11), 1358–1360.
10. Davuluri, P. S. L. (2023). AI-Augmented Sanctions Screening: Enhancing Accuracy and Latency in Real Time Compliance Systems. *AI-Augmented Sanctions Screening: Enhancing Accuracy and Latency in Real Time Compliance Systems* (December 15, 2023).
11. García-Pascual, C. M., Navarro-Sánchez, L., Ichikawa-Ceschin, I., Bakalova, D., Martínez-Merino, L., Simón, C., & Rubio, C. (2023). Cell-free deoxyribonucleic acid analysis in preimplantation genetic testing. *F&S Science*, 4(2S), 7–16.
12. Handayani, N., Aubry, D., Boediono, A., Sirait, B., Sini, I., Polim, A. A., Dwiranti, A., & Bowolaksono, A. (2023). The origin and possible mechanism of embryonic cell-free DNA release in spent embryo culture media: A review. *Journal of Assisted Reproduction and Genetics*, 40(6), 1231–1242.
13. Shi, H., Pan, M., Jia, E., Lu, W., Zhou, Y., Sheng, Y., Zhao, X., Cai, L., & Ge, Q. (2023). A comprehensive characterization of cell-free RNA in spent blastocyst medium and quality prediction for blastocyst. *Clinical Science*, 137(2), 129–143.
14. Kolla, S. K., & Reddy, V. A. R. (2024). Evaluating Cloud-Native vs. Hybrid Architectures for Health Benefit Administration Systems. *International Journal of Medical Toxicology and Legal Medicine*, 27(5), 1042-1053.
15. De Borre, M., Che, H., Yu, Q., Lannoo, L., De Ridder, K., Vancoillie, L., Dreesen, P., Van Den Ackerveken, M., Aerden, M., Galle, E., Breckpot, J., Van Keirsbilck, J., Gyselaers, W., Devriendt, K., Vermeesch, J. R., Van Calsteren, K., & Thienpont, B. (2023). Cell-free DNA methylome analysis for early preeclampsia prediction. *Nature Medicine*, 29(9), 2206–2215.
16. Zhou, S., Li, J., Yang, W., Xue, P., Yin, Y., Wang, Y., Tian, P., Peng, H., Jiang, H., Xu, W., Huang, S., Zhang, R., Wei, F., Sun, H.-X., Zhang, J., & Zhao, L. (2023). Noninvasive preeclampsia prediction using plasma cell-free RNA signatures. *American Journal of Obstetrics and Gynecology*, 229(5), 553.e1–553.e16.
17. Zhao, Z., Li, B., Xiao, X., Liu, J., & Zheng, W. (2023). Cell-free RNA and fully convolutional dense network-based early preeclampsia prediction. *Clinical and Translational Medicine*, 13(8), e1371.
18. Paul, N., Sultana, Z., Fisher, J. J., Maiti, K., & Smith, R. (2023). Extracellular vesicles—Crucial players in human pregnancy. *Placenta*, 140, 30–38.



19. Buca, D., Lucidi, A., Buca, D. V., Di Sebastiano, F., D'Angelo, E., Vespa, S., Liberati, M., Lanuti, P., & D'Antonio, F. (2023). Extracellular vesicles during the three trimesters of pregnancy. *Journal of Reproductive Immunology*, 159, 103987.
20. Gahlawat, A. W., Witte, T., Sinn, P., & Schott, S. (2023). Circulating cf-miRNA as a more appropriate surrogate liquid biopsy marker than cfDNA for ovarian cancer. *Scientific Reports*, 13, 5503.
21. Yu, S. C. Y., Choy, L. Y. L., & Lo, Y. M. D. (2023). "Longing" for the next generation of liquid biopsy: The diagnostic potential of long cell-free DNA in oncology and prenatal testing. *Molecular Diagnosis & Therapy*, 27(5), 563–571.
22. Bandi, V. D. V. K. (2024). Intelligent Data Platforms For Personalized Retail Analytics At Scale. *Metallurgical and Materials Engineering*, 30 (4), 1011–1027.
23. Moufarrej, M. N., Bianchi, D. W., Shaw, G. M., Stevenson, D. K., & Quake, S. R. (2023). Noninvasive prenatal testing using circulating DNA and RNA: Advances, challenges, and possibilities. *Annual Review of Biomedical Data Science*, 6, 397–418.
24. Li, N., Gu, Y., Tang, J., Li, Y., Chen, D., & Xu, Z. (2023). Circulating non-coding RNAs and exosomes: Liquid biopsies for monitoring preeclampsia. *Methods in Molecular Biology*, 2664, 327–341.
25. Warintaksa, P., Romero, R., Lertrat, W., Yuenyongdechawat, N., Mongkolsuk, P., Chaiyakarn, S., Settacomkul, R., Pongchaikul, P., Vivithanaporn, P., & Chaemsaitong, P. (2024). Quantitative cervicovaginal fluid fetal fibronectin: A liquid biopsy for intra-amniotic inflammation. *Acta Obstetrica et Gynecologica Scandinavica*, 103(11), 2252–2263.
26. Khalil, A., Bellesia, G., Norton, M. E., Jacobsson, B., Haeri, S., Egbert, M., Malone, F. D., Wapner, R. J., Roman, A., Faro, R., Madankumar, R., Strong, N., Silver, R. M., Vohra, N., Hyett, J., MacPherson, C., Prigmore, B., Ahmed, E., Demko, Z., Ortiz, J. B., Souter, V., & Dar, P. (2024). The role of cell-free DNA biomarkers and patient data in the early prediction of preeclampsia: An artificial intelligence model. *American Journal of Obstetrics and Gynecology*, 231(5), 554.e1–554.e18.
27. Yu, Y., Xu, W., Zhang, S., Feng, S., Feng, F., Dai, J., Zhang, X., Tian, P., Wang, S., Zhao, Z., Zhao, W., Guan, L., Qiu, Z., Zhang, J., Peng, H., Lin, J., Zhang, Q., Chen, W., Li, H., Zhou, S., et al. (2024). Non-invasive prediction of preeclampsia using the maternal plasma cell-free DNA profile and clinical risk factors. *Frontiers in Medicine*, 11, 1254467.
28. Aerden, M., De Borre, M., & Thienpont, B. (2024). Cell-free DNA methylation-based preeclampsia prediction: A journey to improve maternal health. *Prenatal Diagnosis*, 44(4), 418–421.
29. Pan, M., Shi, H., Qi, T., Cai, L., & Ge, Q. (2024). The biological characteristics of long cell-free DNA in spent embryos culture medium as noninvasive biomarker in in-vitro embryo selection. *Gene*, 927, 148667.
30. Handayani, N., Aubry, D., Boediono, A., Bowolaksono, A., Sini, I., Haq, N. M. D., Sirait, B., Periastiningrum, G., Mutia, K., & Wiweko, B. (2024). Non-invasive pre-implantation genetic testing's reliability for aneuploidy using cell-free DNA in embryo culture media. *Journal of Gynecology Obstetrics and Human Reproduction*, 53(8), 102808.



31. Popova, A. K., Vashukova, E. S., & Illarionov, R. A. (2024). Extracellular vesicles as biomarkers of pregnancy complications. *International Journal of Molecular Sciences*, 25(22), 11944.
32. Mangalampalli, B. M. Intelligent Data Profiling for Healthcare Data Lakes Using AI-Enhanced Analytics.
33. Della Corte, L., Russo, G., Pepe, F., Pisapia, P., Dell'Aquila, M., Malapelle, U., Troncone, G., Bifulco, G., & Giampaolino, P. (2024). The role of liquid biopsy in epithelial ovarian cancer: State of the art. *Critical Reviews in Oncology/Hematology*, 194, 104263.
34. Trevisi, E., Sessa, C., & Colombo, I. (2024). Clinical relevance of circulating tumor DNA in ovarian cancer: Current issues and future opportunities. *Exploration of Targeted Anti-tumor Therapy*, 5(3), 627–640.
35. Zhang, Y., & Tian, L. (2024). Advances and challenges in the use of liquid biopsy in gynaecological oncology. *Heliyon*, 10(20), e39148.