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Advancing Reproductive and Organ Health Management through cell-free DNA Testing and Machine Learning

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Abstract

Science or medicine is a never-ending quest for cure and healing. The science of Reproductive Health issues and addressing them for help is an innate human vocation. The word "advancing" in the title infers that there has been some work done in Reproductive Health, which indeed is true. The paper outlines the expansion in scope of Reproductive Health issues from the erstwhile obstetrical complications of pregnancy associated with high morbidity and mortality in young women of reproductive age to the present concerns of infertility and prevention of sequelae of pregnancy complications related to high morbidity and mortality in mothers and neonates. Efforts have also been made in organically coordinating Reproductive Health with general health to optimally achieve and maintain overall health through all stages of life.

The tool is the innovative use of cell-free DNA testing solutions that quantifies maternal, fetal, and placental cfDNA to deliver compelling clinical insights into Reproductive and Organ Health Management. Computational insights developed by ML can augment the value of cfDNA testing solutions through advanced patient selection, data interpretation, and building predictive models for clinical outcomes based on cfDNA signatures and in conjunction with other omics. The end goals are to (1) Develop a simple, accurate, and cost-effective cfDNA based test to screen all women before conception, at the first-trimester pregnancy scan and at the risk assessment visit in the postpartum period irrespective of obstetrical history. (2) Improve predictive accuracy of known pregnancy complications.

Keywords: *Reproductive Health, Infertility, Pregnancy Complications, Maternal Morbidity, Neonatal Mortality, Cell-Free DNA, Cf DNA Testing, Organ Health, Clinical Insights, Machine Learning, Predictive Models, Omics Integration, Patient Selection, Data Interpretation, Preconception Screening, First-Trimester Scan, Postpartum Assessment, Cost-Effective Testing, Obstetrical History, Health Management.*

I. INTRODUCTION

A long-standing challenge for clinical medicine has been to match patients with the specific organ and reproductive system health needs they have at the right scale and time. This is an extraordinarily complex problem, one that is hard to understand just by looking at a patient and asking questions. If it were easy, we would not have the high incidence of gastrointestinal symptoms like GI-SIBO, endometriosis, or Crohn's disease that are often misdiagnosed or take a long time to diagnose. We seem to be further away than we think from understanding the crosstalk of systems designed for digestion, reproduction, and immunity. This applies not just to the organs involved but to the microbiomes associated with them and their collective noise.

In this case, noise represents specific signatures associated with maternal or fetal health, inflammation, trophoblast invasion defects, and the gap period in ebbs and flows and organizational fault lines that can lead to obstetric complications and elective surgery. Tremendous effort has been made to establish the biological markers associated with various disorders. To further investigate this problem with imagination, we used advances in machine learning and novel ultrasound imaging technology to explore how better quantitative data can

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help from the available pool. We also used cfdNA to explore other methods combined with pregnancy biological markers for better maternal health monitoring. These multiple vignettes combine quantitative and qualitative observations to create a backdrop from which machine learning and AI can create their own models using large internal and external datasets.

They explore, also as illustrative case studies, three observable signals from the developing fetus: fetal growth restrictions by measuring abdominal circumference, fetal ratios via Doppler signals for multiple pregnancies, and fetal anomalies signaled by non-specific increase in teratoma-causing variants in hybrid cfdNA molecules. By our introductory vignette, it is evident that sometimes the moves themselves talk to each other and some other times to a choir from which something novel and unexpected emerges, all this within the prenatally homeostatic womb.

A. Purpose and Scope of the Study

Most of the information needed for organ and reproductive health management is recorded and stored in routine clinical laboratories. A variety of physiological conditions can be monitored and provide signals for decision making on the occurrence of disease. A multitude of molecular methods have been developed to help researchers and clinicians understand disease biology. However, a substantial gap continues to exist between our knowledge of molecular and physiological processes regulating health and disease, the development of new laboratory methods that detect health status signals earlier, and clinic integration of the methods to positively affect health outcomes. The purpose of this study is to introduce a test that fills this gap, promoting both organ and reproductive health in women. The test utilizes machine learning to integrate plasma cell-free DNA concentration, size-profile, and multi-Omic sequence data—including host, microbiome, and heteroplasmy sequence-level information—into predictive models of disease occurrence and progression.

Women typically begin their journey through pregnancy as young as 20 years of age, with accompanying increases in chance of disease onset as the years progress. Women with any of the 6 conditions, mainly reproductive or organ, and the women who experience pregnancy complications, are at risk for serious sequelae, acquisition of financial and emotional debt, or death of women and/or offspring. If not at risk, gene-disease associations for women exist, with pathways and risk genes common to multiple genes, including organ, autoimmune, and reproductive conditions. The time needed to perform current laboratory tests is especially critical to organ health management.

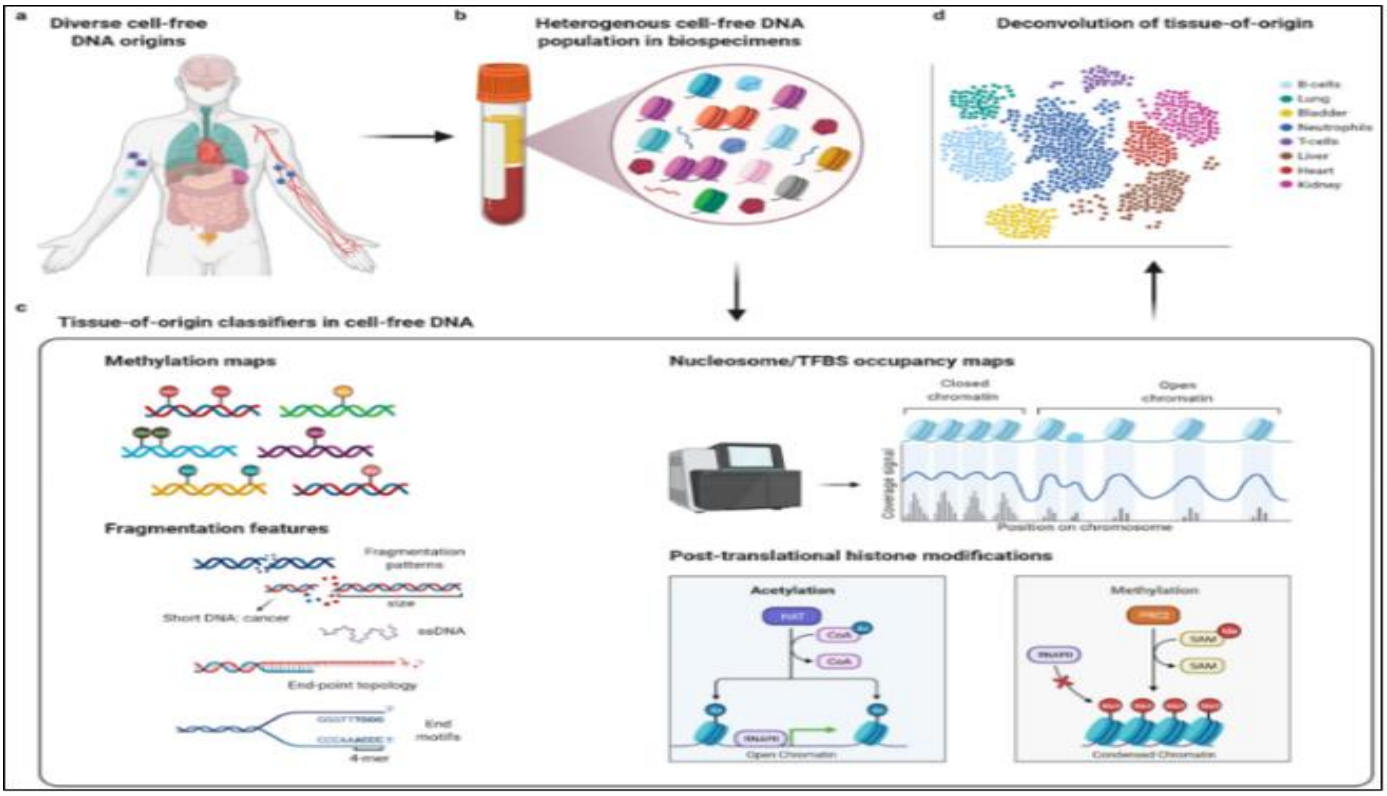

Fig 1 Origin of Cell-Free DNA Molecules through Tissue-Specific Epigenetic

II. OVERVIEW OF CELL-FREE DNA TESTING

Cell-free DNA testing, or liquid biopsy, is a non-invasive, highly sensitive, and specific modality for health condition monitoring through analysis of the cell-free component of blood, urine, and other bodily fluids. The cfDNA is a distinct molecular feature, fragmented in a size range that reflects the pathological process, derived from various tissues, which regulates the spatio-temporal activity of DNA- and RNA-based processes in the

organism. cfDNA testing revealed genomic signal aberrations in unaffected individuals who turn out to later develop the disease, thus pioneering a new field of research on the potential of cfDNA to detect hidden disease entities and indicate imminent or early acute pathological processes. Work in this direction has matured to applications in the early detection of still asymptomatic malignancies, Alzheimer's disease, Covid-19 pneumonia, and fetal genetic disorders, with the ultimate goal of detecting these diseases long before the onset of clinical symptoms to improve management.

The underlying regulation links cfDNA and RNA measurements. cfDNA is constitutively released by normal and malignant cells and reflects their status via their methylation patterns, transcriptional activity and mutational load, and subsequent RNA processing and degradation. Aberrations of one or more of these molecular features may serve as common biomarkers in multiple disease areas, including those covered by PCR, genotyping, and next-generation sequencing applications, such as the diagnosis and prognosis of cancers and other diseases, organ transplantation, gestational progress, aging, and pregnancy complications. We present hereafter a representative overview of working and potential applications.

- *Equation 1 cf DNA Fragmentation Score (CFS):*

$$CFS = \frac{1}{n}\sum_{i=1}^{n} |l_i - \mu|$$

Where:

- l_i: Length of cfDNA fragment i
- μ: Mean fragment length
- n: Total number of fragments analyzed

A. What is Cell-Free DNA?

Cell-free DNA testing provides a non-invasive option to assess the presence of genetic changes associated with a variety of disease processes. The technology was first introduced into clinical practice by the development of non-invasive prenatal testing for fetal sex determination based on the detection of Y chromosome DNA, which was later shown to be associated with specific fetal aneuploidies. From this successful introduction into clinical care, interest in both NIPT and other indications of maternal/fetal cfDNA testing exploded within various clinical laboratories. More recently, an expansion of cfDNA's application into the area of solid organ pathology has increased cfDNA's utility further.

All somatic cells undergo constant processes of death and renewal, resulting in release of cellular debris into the surrounding extracellular space. Because the cellular membrane is also the site for the majority of cell signaling processes important for cell survival and function, loss of cellular membrane integrity leads to cell death and release of portions of the cellular contents into the extracellular space. Normally, clearance of extracellular debris is accomplished by tissue macrophages and other phagocytes. However, when the rate of cell death exceeds the ability of phagocytes to clear the debris, the cellular contents (including cfDNA) can accumulate in the plasma and the tissue microenvironment. Thus, the presence of increased levels of cfDNA in the bloodstream or any tissue microenvironment is a reflection of pathological processes that are associated with increased cell death, including infections, elevations in the number of dying malignant cells, organ transplant immunological rejection, infarction of various organs, and progression of organ dysfunction due to various non-infectious conditions.

The term cfDNA refers to any DNA present in the extracellular environment and has largely been used interchangeably with circulating free DNA. Comparably, the term circulating tumor DNA has been used to refer to those instances of tumor-derived cfDNA that are associated with various malignancies.

B. Applications in Reproductive Health

Aberrant levels of cell-free DNA during gestation can be found in the circulation of women with various obstetric complications, including preeclampsia, fetal growth restriction, spontaneous abortion, and placental abruption. While the presence of placental-derived cfDNA has been used in commercial prenatal tests to screen for aneuploidies, the landscapes and contributions of genomic, epigenomic, and methylomic alterations in circulating cfDNA during pregnancy remain underexplored. Recent studies have revealed that alterations in placental-derived cfDNA can be induced by adverse pregnancies and can be detected at the first trimester. By combining transcriptomic, epigenomic, and genomic DNA alterations in placental cfDNA, researchers were able to establish a unique signature for pregnancies affected by preeclampsia. In addition, placenta-derived cfDNA levels have been correlated with gestational age, suggesting that altered placental function that happens during specific gestational ages can be used in developing prediction tests for specific pregnancy complications such as aberrant placentation. Other placenta-derived cfDNA modifications, such as methylation, can become predictive of growth restriction especially when combined with maternal factors.

Such tests are particularly important as prenatal detection of complications such as fetal growth restriction is crucial to determining the right timing for delivery, which help in reducing adverse outcomes. Early diagnosis through intervention-aware tests can decrease maternal and newborn morbidity and mortality. Current commercial tests are mainly limited by the low positive predictive values and high false-positive rates. Integration of paternal sperm can also affect the composition of cfDNA found in maternal circulation. Methods developed to separate cfDNA from nucleated blood cells can reduce the contamination of maternal cfDNA in plasma further improving the performance of these tests.

C. Applications in Organ Health

Cell-free DNA (cfDNA) is being touted as one of the most significant biomarkers of organ health and disease. The advent of massively parallel sequencing revolutionized our ability to characterize cfDNA, especially in solid organ transplant medicine. cfDNA makes up a low-fraction of total cell-free blood DNA, which is the product of apoptosis, necrosis, and lysis of cells in circulation. The significant portion of DNA existing in these asymmetric concentrations compared to other body fluids led to study of cfDNA as a biomarker for a variety of disease processes, such as genetic conditions and malignancy for organ health assessments.

In SOT patients, measurement of cfDNA amounts, fragmentation size, and patterns relative to donor DNA were reported as having diagnostic and prognostic ability for active rejection, gastroesophageal reflux disease, cardiovascular complications, acute graft injury and dysfunction. Quantifying the total amount of cfDNA and assessing the composition of that pool can help identify acute rejection episodes when histological correlation is poor. These technologies have also shown value for assessing risk in those born with congenital heart disease and asthmatics early in life who have undergone lung transplantation for stage III bronchopulmonary dysplasia. Newer applications are currently being evaluated, including dynamics of pre-and post-transplant microbiome. Combined with machine learning strategies, organ transplant outcomes are optimized when personalizing treatment decisions and algorithms.

III. MACHINE LEARNING IN HEALTHCARE

The use of machine learning (ML) in healthcare has revolutionized how we find solutions to the problems the industry faces. Its ability to provide accurate predictions and automate manual tasks using advanced computational techniques has opened new avenues. By applying techniques that allow computers to learn from data, ML can build models for a wide array of clinical applications, which can benefit patients and save resources when utilized in clinics.

The need for the continued development of ML approaches is fueled by the continuous advancement of digital technology in healthcare. This has created a multitude of data, including health records that integrate laboratory results, computerized imaging, genetic data, Internet of Things (IoT), and biosensor data. These large amounts of intricate data can present a difficult challenge. However, using ML can help provide a solution to the increasing complexity of healthcare data and operational problems. Modeling the risk of Type 2 Diabetes Mellitus (T2DM) through various patient risk factors or estimating the amount of time until a cardiovascular event occurs using hospital readmission records are some examples. Recent research has particularly focused on the use of ML to solve previously hard-to-solve medical problems. However, estimates suggest that over 400 ML algorithms have been applied to healthcare-related problems, including computer-aided diagnosis in radiology and dermatology. At this time, the main challenges for the implementation of ML in clinical practices are: training time, algorithms management, cost, available skills, and integration with radiological task workflows.

In this chapter, a brief overview of ML concepts and algorithms is provided, along with a summary of selected healthcare application areas, fundamental challenges, and selected illustrative examples. The hope is that this will guide research bioengineers that are new to ML into deeper and more specialized literature in the respective fields of application. The ML concepts and algorithms highlighted in this chapter include supervised learning with classification and regression algorithms, semi-supervised learning, deep learning, reinforcement learning, unsupervised learning, clustering algorithms, and dimensionality reduction algorithms.

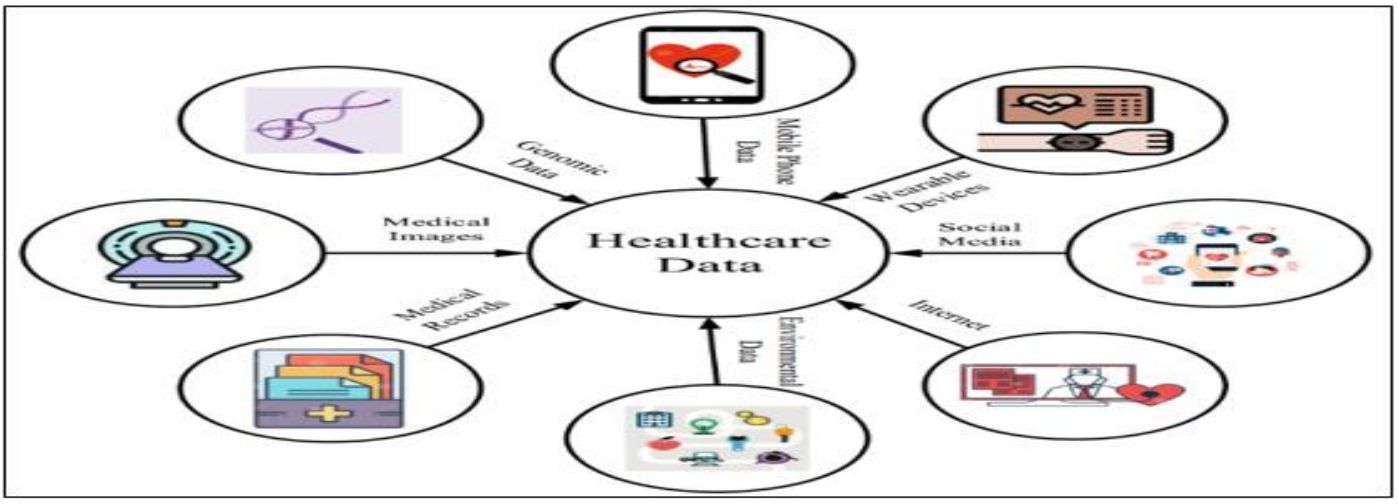

Fig 2 Machine Learning (ML) in Medicine

D. Introduction to Machine Learning

Machine learning is a field of artificial intelligence that uses statistical and probabilistic techniques to allow computer systems to learn on their own without human intervention. It is a subfield of computer science that has gained increasing popularity due to the increases in

computational power and the availability of large datasets. ML works by exploiting the mathematical theory of algorithms and is designed to learn from data and build m

Odels such that the predictive power improves over time, either through repetition or by using knowledge acquired from previously encountered situations. The knowledge can be stored in the form of parameters, heuristics, or designs that allow the system to perform better on the tasks.

The history of ML goes back to the 1950s when early pioneers designed general learning approaches and algorithms that would allow machines to acquire knowledge through experience, representing that knowledge symbolically, and applying that knowledge to solve complex problems. One of the first ML tasks was to teach computers to play chess. Other ML tasks involved language and vision. As in most areas of artificial intelligence, problems such as computing power and the availability of large training databases have limited the plenitude of ML techniques that were developed and potential applications. Until recently, most of ML resembled a complex form of curve-fitting. However, breakthroughs in mathematical theory, increased computer power, and the availability of much larger training sets have compelled researchers to investigate deeper new ML techniques and have fueled the growing interest in ML.

E. Machine Learning Algorithms Used in Healthcare

To address the diverse clinical issues in the healthcare domain, numerous machine learning (ML) models in numerous flavors and types are deployed. Intuitively, such diversity stems from different problem definitions that ML is employed to solve. These problems can be regression or prediction tasks; they can be modeling tasks where ML is produced to capture the dependency structure of clinical data; or they can be plotting tasks, including identifying patients with specific classifications. Due to the varying categories of clinical problems tackled by ML, there are also multiple ML solutions bred and funneled to answer the need in the healthcare domain: from predictive ML algorithms that offer a fast path to identifying associations with clinical outcome variables from data, to rule-based latent variable models used to simplify patient stratification and understanding of the patient decision process, to deep learning (DL) whose potential role as an entry point to healthcare big data is increasingly acknowledged.

Predictive models estimate the numerical value of an output variable from samples and a small number of outputs through analysis or simulation. These outputs can also take on discrete values. In this latter case, the techniques are standard classifiers for decision-making regarding the value of a categorical output variable, such as disease detection or ill-prognosis assessments based on data. Predictive models are currently the sole ML family assisting clinicians in specialized and non-specialized large-scale patient environments. Their goal is based on known patterns in clinical records, contrary to clinical decision rules, which permit specific automated screening of clinical status to expedite decision-making regarding a patient's treatment.

F. Challenges in Implementing Machine Learning

Despite its promises, machine learning still faces hurdles concerning the implementation of predictive models in healthcare. Unique challenges stem from the design of studies, the methodological choices and validation as well as the setting of thresholds, but also from practicalities related to regulatory requirements and that surround the clinical environment. The medical domain bears unique sample size constraints, especially for rare diseases, leading to small discrete datasets. Small datasets challenge supervised learning strategies that often produce overfitted models. But, efforts to address these challenges are emerging, including using ensemble learning with labeled sources of similar domains. Generally available datasets have tested rare diseases overfitting techniques like transfer learning using an AlexNet trained on images of healthy individuals.

This led some to state that lack of data is no longer an issue, which is debatable. The issue is to select the good data to ensure accurate predictions and that allow lab-testing will confirm the machine learning model's predictions. The sensitivity versus specificity balance has several measurements with specific practical implications that are further complicated by dynamic predictive models, or individualized predicted probabilities which are update-able thanks to wearable sensors. Engaging the appropriate tertiary care stakeholders is critical to ensure model's appropriate calibration and to ensure model design is based on relevant clinical considerations, before validating or performing subsequent refinements.

Machine learning tools are susceptible to biases in training datasets that lead to improper real-world models, or derived products in the clinical context. Not only are there consequences of lack of robustness and replicability, but also ethical and liability implications in the medical domain. Botting AI's generative capabilities create other model-specific potential biases. Most manufacturers still do not provide adequate clarity on how the AI tools were developed. Validation of the machine's algorithm's decision engine will be critical for surgical oncology, where prediction of neoadjuvant chemotherapy efficacy on MMR-P tumors is not yet clinically possible in the absence of reliable histological or molecular signatures. Code autonomy and lack of digital tracking will also complicate responsibility in case of error.

IV. INTEGRATION OF CELL-FREE DNA TESTING AND MACHINE LEARNING

Machine learning provides a new paradigm to stratify different chip-chip patient subpopulations identified from the cfDNA testing so that better and safe solutions can be applied for adverse outcomes prevention and populations with an adverse outcome risk can be identified for closer monitoring and work-up. In order to achieve this, however,

a clear integration of the cfDNA assay and machine learning paradigms and processing pipeline must be generated. Various algorithms may be implemented to differentially stratify cfDNA testing patient subpopulations toward different stratification objectives ranging from diverse feature objectives for sample size optimization to risk prediction for high-risk patients. Therefore, the cfDNA machine learning integration paradigm description is presented below as a general flowchart without specific implementation examples.

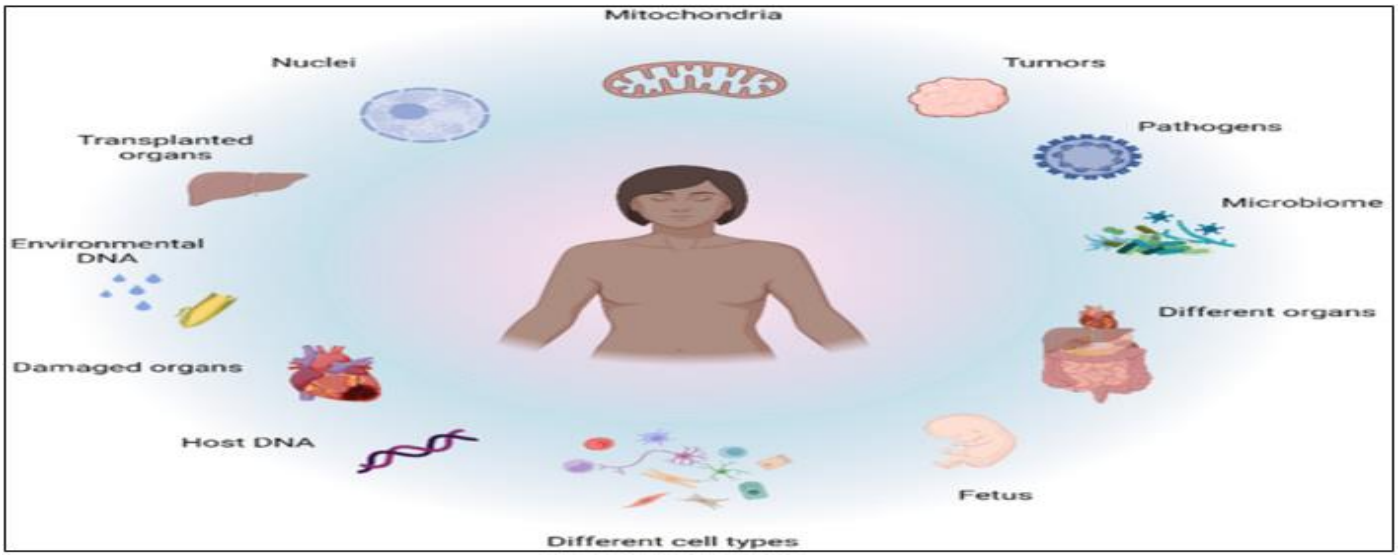

Fig 3 Importance of Cell-Free DNA Biology

A. Data Collection and Preprocessing

Initially, data that are relevant to cfDNA testing for reproductive and organ health management must be gathered into a single database or data warehouse. Such data can include cfDNA testing data, medical history, and risk factors, demographics, as well as any other relevant data that could potentially impact the outcomes of interest. Data preprocessing will then include data filtering and curation as required for usage in machine learning training and validation.

B. Feature Selection and Extraction

Data collected and processed must be evaluated for each objective or subcommittee to determine and optimize the features that will provide the best respective outcomes in sample size and prediction ability. Feature selection and extraction methods to achieve this goal can include algorithm-based backward and forward selection, recursive feature elimination, tree-based selection, logistic regression, and probability effect size to determine the effect size of various features in statistical metric outcomes relevant to each model optimization goal. The feature sets will affect the machine learning objectives that are optimized; these include model accuracy prediction, and sample size, as well as prediction and calibration for each unique cfDNA subcommittee integration goal.

C. Data Collection and Preprocessing

Cell-free DNA testing is a non-invasive prenatal testing tool that analyzes cfDNA in the plasma of pregnant women to determine a fetus's risk for a variety of genetic disorders, including Down syndrome, which is also known as Trisomy 21. In recent years, the use of cfDNA testing has expanded beyond prenatal health and is being increasingly used to detect prenatal T21 status as well as more serious maternal pathologies associated with T21 such as preeclampsia, stillbirth, and miscarriage, as well as post-delivery organ transplant rejection. For either application, an array-based platform utilizing a non-biased approach for genome-wide methylation analysis is used. This type of platform uses an endonuclease-based typing tool to analyze sequence capture raw data to identify reads with T21, maternal, and other chromosomal level endonucleolytic signatures and use those for bioinformatics analysis. The end result of the bioinformatics analysis is a report with genome-wide and chromosome-specific methylation representations for each condition.

The array-based platform utilizes 20,048 CpG covered probes in the genome that are associated with 12,274 Refseq genes. Chromosome 21-specific hypomethylated probes are used to evaluate T21, while sex chromosomes are utilized for fetal sex determination. The probes on chromosomes 2-5, 7, 10, 12, 14, 16-18 are used for fetal sample assignments, while the remaining probes are methylation tested for the mother and the fetus. Methylation data for post-delivery organ transplant rejection are obtained using a CpG methylation microarray analysis of cfDNA recovered from plasma samples. Methylation data for prenatal T21 is obtained from a methylation database. Methylation data and clinical characteristics for other conditions are collected from clinical publications.

D. Feature Selection and Extraction

Feature selection, in conjunction with feature extraction, plays a vital role in supervised machine learning. The study of a supervised algorithm's ability to efficiently manage a high dimensional space, where most of the variables are irrelevant or redundant, can significantly improve a model's learning performance and

quality. Some of the possible advantages of using feature selection include better model accuracy, faster model training, increased model interpretability, and greater model generalizability. Due to the limited number of available samples, it is crucial to reduce the number of input variables, as the ML model may overfit the sample training set without feature selection. Moreover, having features that are correlated with each other will contribute noise to the model and, as a direct result, decrease the model's accuracy.

The first phase of feature selection is to identify a subset of features from the whole feature set that contributes the greatest amount of information for discrimination among the sample classes. Next, a function evaluation and search method must be employed to select the subset, while removing irrelevant features or very small contributions. This can be done in various ways, employing a wrapper, filter, or embedded methods. Wrapper methods use the model's prediction performance as a feedback measure for evaluating the sub comparisons, balancing selection and learning. While wrapper methods normally produce the most accurate feature subset, they also impose a considerable computation time and expense. Therefore, filter methods, which use the model's criterion function directly to evaluate the significance of each feature according to the class label only, are generally preferred. In addition to the possible use of randomized sub sampling of the training data, other normal statistical techniques, such as scrutiny, regression coefficients, and mutual information, can also be employed for dimensionality reduction.

- *Equation 2 GC Bias Normalization*

$$G' = \frac{G}{1 + \gamma \cdot (GC - \bar{GC})}$$

- G': Normalized read count
- G: Original count
- GC: GC content
- γ: Correction factor

E. Model Training and Validation

While ML model-building optimally involves several iterations of training, validation, and adjusting hyperparameters that can result in overfitting models and variations in performance, this study primarily focused on initial training of the model. The goal was to circumvent various issues with regard to achieving broadly robust discrimination and prediction outcome accuracy and performance in as short and efficient a timeframe as possible. That said, the development pipeline consisted of CNN training using K-fold cross-validation, model selection (based on the model achieving the lowest validation loss), and evaluation on an independent test set. These are described in succinct detail below. Hence, to evaluate the generalizability of the deep learning models over unseen data, three-class and two-class model training were performed with the following K-fold splits: (1) 5-class, 2-class, balanced two-class case; (2) triplicate balanced two-class, D1, D2 cases vs. others splits for the D1 + D2 vs. other model; and (3) triplicate balanced two-class D1 vs. D2-inset cases split.

V. CASE STUDIES

One of the unique aspects of our platform approach to innovation delves into both new diagnostic capabilities and their unique contributions to decision-making. In this section, we present two case studies: the first highlights the innovative prenatal diagnostic capability of non-invasive cell-free DNA testing for fetal genomic abnormalities and its rapid adoption in obstetrics. The second highlights the unique contributions of organ donor-derived cell-free DNA testing to clinical decision-making and outcomes. The dramatic and rapid adoption of non-invasive prenatal testing to screen for fetal genomic conditions from maternal plasma cell-free DNA has exemplified the power of a diagnostic that uniquely changes practice and clinical decision-making. In 2010, a rare connection between maternal pregnancy-associated plasma protein A and cell-free fetal DNA was reported. This protein was found to only enter maternal circulation from the fetal placenta and was present in pregnant women in infinitesimally low concentrations relative to the cell-free fetal DNA level. The target cell-free fetal DNA concentration and the three-decade-long enormous technological advances in DNA sequencing and the sheer spike in sequencing capacity finally paved the way for the introduction of non-invasive prenatal testing in late 2011. The rapid adoption of this testing over the past decade has made significant waves in obstetrics, doubling the incidence of early stage screening for Down Syndrome-related fetal sequelae. Most importantly, this testing has demonstrated a significantly lower false positive rate compared to chorionic villus sampling and amniocentesis.

They were among the first to focus on the potential non-invasive reproductive and maternal health applications of cell-free DNA testing. In 1977, a proof of concept paper on the quantitative determination of tissue-specific fetal DNA in the maternal circulation during pregnancy and labor was published. Almost fifty years later, important expansions of these concepts into maternal allogeneic cell-free DNA to assess maternal immune tolerance of the fetus and its role in pregnancy-associated conditions at the placental interface such as miscarriages and preeclampsia were made.

A. Reproductive Health Case Study

Cell-free DNA testing is a fundamentally non-invasive technology that was proven to have universal clinical diagnostic applicability. Given the unique cfDNA signature in pregnancy, there has been a wealth of study evaluating its clinical potential. For pregnancy, cfDNA biomarkers have been investigated for both mother and baby health. Fetal cfDNA was shown to reflect the gamma globulin concentration and non-invasive chromosome testing to identify fetal copy number variation. Maternal

cfDNA have been shown to indicate an at-risk pregnancy; elevated levels have been found around the time of preterm birth in association with maternal inflammation, including chorioamnionic infection. Here we discuss the cases of gestational diabetes type 1 and premature premature rupture of membranes to highlight how integrating more machine learning biomarkers with cfDNA in biological networks can reveal even more cfDNA signatures for other complications of pregnancy given insightful clinical backgrounds. Following healthy childhood development and transition ahead into reproductive age, further cfDNA-linked work with artificial intelligence/machine learning has been completed on uterine fibroids amongst groups without and with recurrent pregnancy loss, where both focused on focusing regulatory networks with combined transcriptomics. A quality control filter identified transcript regulatory networks up, as well as down-regulated in fibroids of women with recurrent pregnancy loss, whilst signatures correlated and were confirmed against other groups.

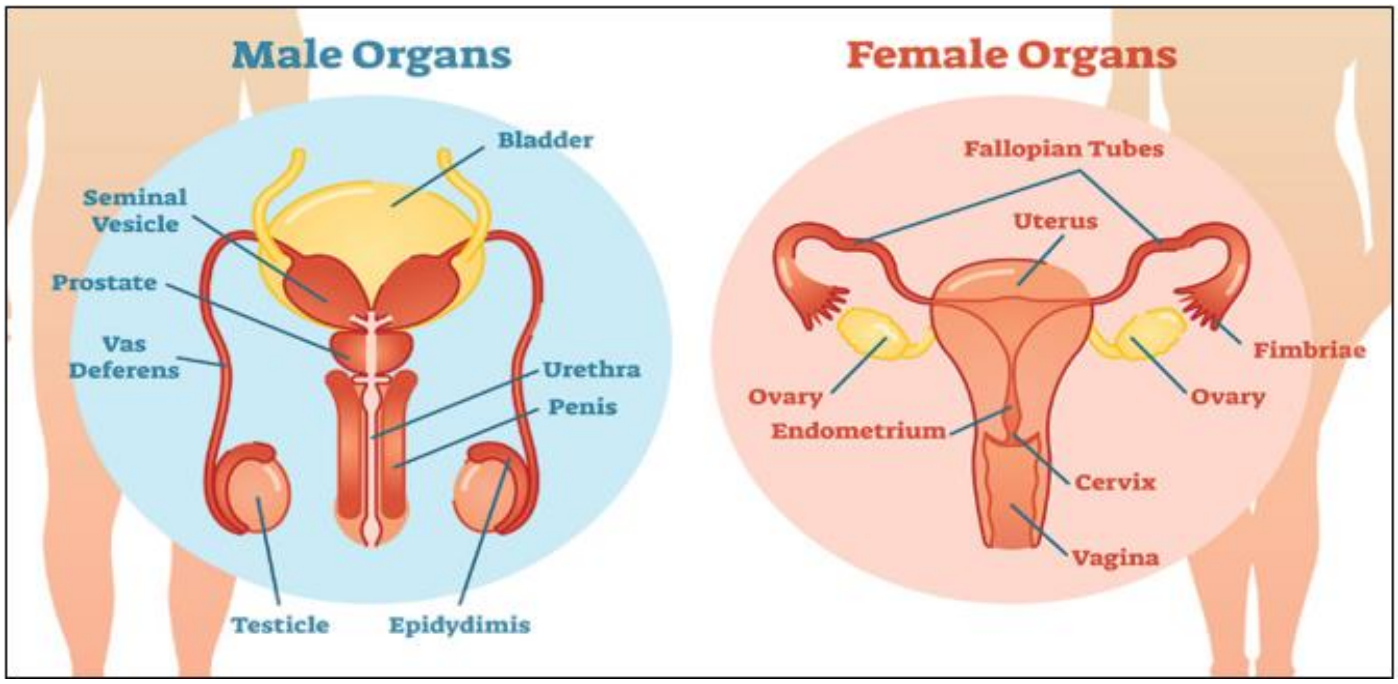

Fig 4 Reproductive Health

B. Organ Health Case Study

We have developed a machine learning model that utilizes organ-specific methylation-based signatures and blood-derived variables to predict the likelihood of developing or having an organ health condition. The inputs used by the model were derived from a longitudinal, multi-omics dataset, which included blood-derived variables, toxicogenomic exposure signatures, metabolomic, and proteomic data, collected from healthy individuals over a 6-year period and longitudinally followed for the development of organ health conditions. The health conditions analyzed in the model included liver health conditions, cardiometabolic health conditions, and kidney health conditions.

The predicted likelihood of an organ health condition was validated retrospectively against participant medical history. The model was also externally validated with an independent cohort with a separate known timeline of health outcomes. Both internal and external validation showed that the model achieved high sensitivity and specificity for predicting the likelihood of developing or having an organ health condition. This chapter details the ML model development, along with predictions, and validation details for our psychographic models for NASH, KD, and CVD, based on diagnostic testing data, along with an interactive dashboard providing decision support for diagnostics and therapeutics.

VI. ETHICAL CONSIDERATIONS

A transitional shift toward utilizing cfDNA for the assessment of organ health has been proposed that extends organ transplant donor and recipient monitoring to outpatient population-level screening of multiple organ conditions as a preventative initiative. Herein, the area of transplant monitoring, specific to organ rejection, serves as the proof-of-concept for this application of cfDNA and machine learning. However, innovation in the health technology sector is often hampered by the required detailed ethical groundwork that must be addressed. In particular, using cfDNA and machine learning to assess for both single and multiplexing organ-specific disease detection cases falls short of ethical approval due to not properly addressing three fundamental cornerstones of ethical considerations: informed consent, data privacy, and data security. These issues also apply to the area of transplant monitoring in a less academically inspiring way. Consequently, we delve into these ethical challenges specific to our multi-organ noninvasive molecular testing for the detection and stratification of pregnancy health outcomes using cfDNA as haplotypes. By doing so, we aim to provide guiding principles for others interested in

the feasible application of cfDNA in the organ health sector. For any future application of cfDNA-based screening to ensure the informed consent of patients involved, the ethical discourse needs to be carried out from the bottom up, detailing the fine points of the new technology, and the specific transgression of what patients are risking should they choose to supply DNA for the creation of machine learning models.

A. Informed Consent

Gainful use of cell-free DNA testing for reproductive and organ health purposes at the patient level is a new application for non-invasive prenatal testing methods. Importantly, while non-invasive prenatal testing is routinely considered a risk-reducing tool for only a subset of patients carrying a pregnancy, here we review the implementation of these methods in a risk-enriching manner, first in the general population, and then across the lifespan and intending for people both consuming and not consuming pregnancies. In this capacity, cell-free DNA is utilized as a routine screening measure, akin to blood type or routine blood work, implemented at the clinical generalist level. In this regard, we do not presently address testing at the clinical specialist level.

The landscape of informed consent for medical applications of non-invasive prenatal testing has grown alongside the clinical development of these important and population-reducing tests. The first techniques were specialized tests designed to span only a limited number of clinically significant microdeletions in the plasma of pregnant females. The subsequent clinical expansion was marked by an early transition to broader-based panels of increased diagnostic function, which in turn provoked unique and unsolved challenges in the realm of informed consent. In this setting, prenatal maternal plasma cell-free DNA sequencing was compared head-to-head with either amniocentesis or chorionic villus sampling for multiple fetal and maternal clinical endpoints, both in safety terms and for definitive microdeletion diagnosis. In these studies, sequencing was assembled using technology in the diagnostic exome capture format, designed to decode the complete clinical and constellation of allelic state variants, including copy number variants, SNPs, and small microvariants, detectable with high-sequencing and high-depth.

B. Data Privacy and Security

Several data privacy and security concerns arise when considering the use of plasma cfDNA sequencing for reproductive health applications. A potential concern when performing any form of sequencing is that it may be possible to identify individuals from public genetic databases. It is important to emphasize that the identification risk is preferably reduced by allowing the individual to choose whether their samples are to be used for research studies, preventative measures, and clinical practice using cfDNA. If individuals opt-out, no such data from those specific individuals would have to be stored. Additionally, there is a lower risk of identification if all cfDNA related data is encrypted and stored, only to be analyzed subsequently by designated groups performing machine learning analyses, since these analyses do not typically allow reverse-feeding of data inputs.

Relying on input encryption can be further complemented by relying on differential privacy, an approach that seeks to provide a means of a quantifiable mathematical guarantee that ensures a machine-learning framework does not significantly differ in probability distribution with or without any single individual's data. With differential privacy, individuals do not have to be identified to essentially anonymity at some cutoff. Data privacy in this manner is of paramount importance when analyzing personal and sensitive cfDNA sequencing data, especially in a clinical setting, given the known family relationships that cfDNA can reveal.

C. Implications for Patient Autonomy

Any solution that couples new biomedical technology and ML poses particular challenges to maintaining the role of the patient as autonomous decision-maker. In our proposed thesis, patients would either opt in to cfDNA testing and subsequent digital diagnosis/treatment recommendations or be funneled into these channels indirectly with little choice or awareness. The rapid turnover of new cfDNA diagnostic tests that are capacity-expanded with digital ML tools leads to particular issues of informed consent and the blurring of the lines between medical opinion and automated recommendations for autonomous patients. Our proposals for normalizing cfDNA tests for diagnoses of diverse conditions and arranging noninvasive predictions of health status are intended to encourage the use of the cfDNA tests by as wide a number of patients as possible. Use of digital recommendations for further testing and treatments may also function as motivators of patient self-care and wellness. There is already some evidence for this phenomenon in the area of coaching toward self-improvement in domains like weight loss. The power of collective intelligence/trust in shifting personal behaviors should become even more powerful when those innovations are possible because of truly personalized, rapid-response algorithms.

As a result, we anticipate that cfDNA use may be the first step in larger scale digital intervention in health decision-making processes across all providers and patients in the referral networks. In summary, we contend that the introduction of such powerful biomedical/ML tools would encourage patients to include novel technologies in their health literacy, which is a long-designated barrier to patient participation in the detection and management of health issues and the decision-making processes for using certain diagnostic techniques or therapeutic approaches.

VII. REGULATORY LANDSCAPE

While our focus on using machine learning with cell-free DNA for advancing reproductive and organ health management is promising and novel, machine learning for

clinical decision support is no exception to the saying, "with great power comes great responsibility." Our work builds on both common clinical standards and recent innovations in personalized healthcare. In parallel, there is a growing awareness of policy and regulation needs as technology for reproductive and organ health testing advances. Regulatory processes are important for both the consideration of what constitutes medical necessity for testing and the broader societal considerations built into describing the difference between research quite literally to improve medical care for vulnerable populations compared to academic research accomplishments that do not connect back to these specific societal progressions supporting affected families. The direct sentences expressing what is at stake here are these:

"The AI techniques used in the healthcare industry are primarily focused on the backend process, enabling ease of work for doctors. Until AI emerges as a virtual doctor performing the slightest procedure of healthcare service, the industry cannot be fully harnessed.

"Accelerating AI in the healthcare industry is undoubtedly a priority issue but the strict testing and validation processes need to be made pragmatic and efficient for lifecycles of AI services."

Before we specifically discuss efforts around genetically-informed health and access, we provide further context regarding current policies around cfDNA testing and AI for healthcare. Our focus is primarily on the US situation but without adequately navigating patient data privacy and security, any method is unable to provide impactful decision support. The healthcare industry is primarily regulated by relevant authorities—both of which while enabling innovation are also tasked with protecting patient trust and safety for medical technologies.

A. Current Regulations on Cell-Free DNA Testing

Advances in technology have outstripped regulation, as the first commercial cell-free DNA assay, for fetal chromosomal abnormalities, was allowed to enter the clinical marketplace, after only pre-market review, without formal pre-market approval, in 2011; these tests now have been approved by the relevant authorities. Since that time, a variety of other cell-free DNA technologies have entered the clinical marketplace, some claiming to assist in the diagnosis of conditions primarily associated with other organs, such as cancers, while others claim to provide information just as prenatal tests can. In both cases, the government has ceded oversight for laboratory developed tests, those performed by laboratories with the proper clinical accreditations, to the relevant regulatory bodies, which perform inspections of such labs on a regular basis. As a result, a wealth of these tests that have received neither premarket review nor formal premarket approval have been made available, with just a urology-specific and two preconception tests subjected to oversight. However, recent efforts, suggesting tightening of regulation, have led to agency-sponsored workshops, which have surveyed the sensitivity, specificity, and clinical benefits of using such tests. This non-personalized use of pseudogenomic databases needs to be carefully considered, as presently available cell-free DNA tests may not be fit for clinical diagnostic purposes.

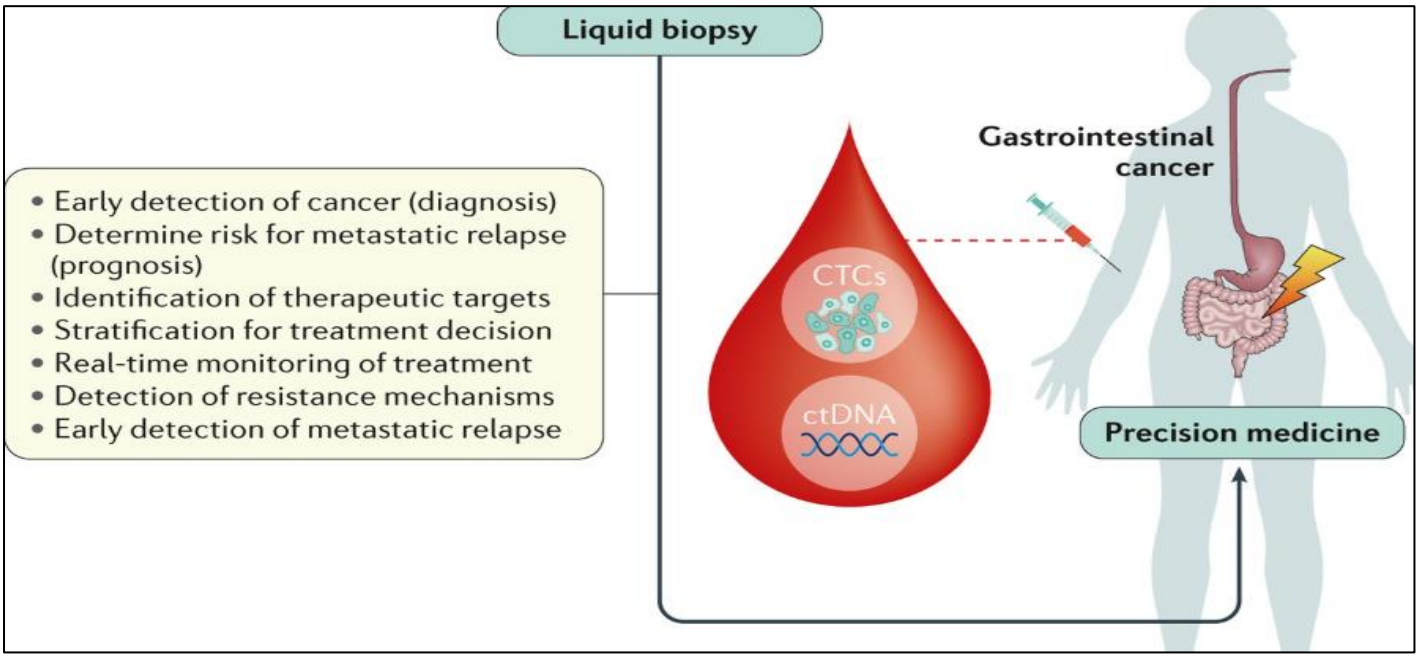

Fig 5 Cells and Cell-Free DNA in Gastrointestinal Cancer

B. Machine Learning Regulations in Healthcare

In healthcare, the regulation of software in the form of ML/AI is a relatively new and evolving discussion. AI-based software programs have been used as medical devices for many years, but the distinction between classic software codes and ML-based software has usually not been explicitly described. Traditional software devices are categorized into three classifications (Class I, II, III) based on the level of exposure of the patient to potential risks, but these paradigms may not apply equally to novel ML-

and traditional software-based medical devices. Regulatory agencies however have started requiring specific considerations when reviewing and approving ML-based software algorithms. In particular, there are outlined specific information that needs to be submitted in premarket submissions. These recommendations include the provision of benchmark performance metrics, a detailed discussion regarding the algorithm development process, a description of the dataset content, labeling, and additional considerations to ensure that models can be properly validated, which is crucial for their adoption in clinical practice. In addition, there has started requiring assurances regarding continuous model updates through learning during the approved hospital deployment phase. Despite these considerations, the regulatory oversight of ML-based algorithms lags behind the regulatory framework of many traditional risk class II medical devices. Particularly, many ML-based algorithms are developed without presubmission review. Additionally, the previously described caveats have raised the cost of premarket submission for the developers of simple ML-based algorithms. This predicament emphasizes the need for a more nuanced regulatory framework that is specific to the unique challenges and strengths of medical device software.

C. Future Directions for Policy

While challenges to date have largely emerged from administrative guidance, we expect to see more formal policymaking developing around these issues. In response, clinical authors of much of the literature thus far need to engage in the policy discussion, and regulators should consider adding clear statements to their proposed or final rules for which uses of these technologies are acceptable in what contexts. Done correctly, evidence-based regulatory processes can help foster parallel innovation outside the protected system. In an iterative way, the Technology Adoption Lifecycle can be employed to help order questions about which regulations need to change and when. Can early examples of use be quickly called out? Failing that, if innovation actually can be shown to pass through the Divination Phase, what then? What tests would allow empirical verification that the innovation is real? What follow-up mechanisms would allow two-sided learning about improper snapshots, outcome correlation, and potential substitutes? What regulatory guardrails might hold back the problems about which industry fears we will learn during that phase, and permit market pull to allow truly new models to move into Late Adoption? Would that lead to unexpected side effects from the original regulatory precaution against naive procedural models when the truly innovative model is not naive? Finally, perhaps most importantly, what mechanisms could decrease some stakeholders' perceived need to game the system, and properly buffer against comparable regulatory failures in the Divination Phase?

VIII. FUTURE DIRECTIONS

In recent years cell-free DNA testing has garnered interest as a minimally-invasive, early diagnostic approach for cancer and other degenerative diseases. Advancements in next-generation sequencing and computational tools have made characterizing cfDNA accessible, cheap and fast. However, while there are many tests available clinically for diagnostic and prognostic purposes, validated and regulated cfDNA tests are still limited in the rest of medicine outside pregnancy, due to the underlying technical challenges of cfDNA analysis in other tissues and its molecular characteristics, as well as the potential for ethical dilemmas surrounding the use of cfDNA in testing.

In this chapter we have taken an interdisciplinary approach and explored the state of reproductive and organ health management with cfDNA testing and artificial intelligence integration. We have summarized and outlined current developments and challenges in this area, as well as future directions we anticipate the field will take. In employing a combination of cfDNA technologies, computational tools and biological validation, the future of cfDNA testing holds vast potential for and has far-reaching implications for personalized medicine and preventative healthcare. From refining organ-matched responder predictions to end-of-life care to realizing a non-invasive prenatal test that can predict all fetal, placental and maternal complications and ensure optimal health and safety for all, we believe that the future for cfDNA testing and AI integration is bright and there is much work ahead for experts across disciplines to collaborate in bridging the gap between academic development and clinical implementation.

A. Advancements in Technology

As technology continues to advance rapidly, new possibilities for maternal-fetal medicine and organ transplant care emerge. In reproductive health, pharmacogenomics can lead to better outcomes for in vitro fertilization patients by selecting appropriate medications. Equally, artificial intelligence can harness vast amounts of clinical data and genomic information, allowing for efficient anomaly detection in imaging interpretation, risk prediction, and anomaly classification. In transplant management, there is a great need for non-invasive monitoring tools that specifically address the danger of delayed graft function. Here, innovative non-invasive embryonic stem cell signatures from urine are able to inform clinicians on the risk and severity of graft injury. Another exciting non-invasive biomarker is cell-free DNA, which can provide information about graft injury and the involvement of pathogens in a clinically accessible format.

In addition to detecting danger signals, the integration of machine learning systems to improve and individualize current risk prediction models will allow for optimization of management for each transplant patient. There is also great promise in predictive algorithms using

low-cost small wearable devices integrated with machine learning to inform about patients' wellbeing as well as detection and identification of adverse pregnancy outcomes. Both fields of maternal-fetal medicine and organ transplant management require an interdisciplinary approach where specialists in both pregnancy care and organ functionally collaborate in order to implement and validate such new technologies.

B. Potential for Personalized Medicine

Testing for diseases such as cancers of various types is rapidly moving towards earlier stages in some cases. We have learned painful lessons that testing for conditions that are not known to recur, such as Alzheimer's disease, can backfire. For that reason, it is perhaps fortunate that we are only so recently able to look at cell-free DNA for the more than 50 percent of cancer patients for whom no earlier disease-defining events, such as signs or symptoms, lead to diagnosis at localized stages. Cancer is the ultimate condition for personalized medicine, being heterogenous even beyond what could reasonably be expected from genetic mutations abnormal for any particular patient, with tumor microenvironment influences set multiple decades earlier being commonplace. Clearly, any test that can correctly provide a higher signal-to-noise ratio in detecting any disease should definitely move towards being a screening test, particularly when minimally of not invasive and worldwide implementation are options. Tests should ultimately aid in better and more precise decisions about whether or not treatment is given. For cancer patients, that has been the mantra in all other aspects of treatment decision-making, such as tumor type, burden, stage, grade, function of the immune system, health of the patient, residual physical capacity, and other factors that can prognosticate for survival and effect of therapy on that. We must do the same for other diseases believed to be represented by cell-free DNA in a similar way, especially because most currently available options, including those already done on very low fraction fetal DNA encased within the cell-free DNA of the mother, are not risk-free.

C. Collaboration between Disciplines

The expansion and acceptance of new medical technologies often involves multiple academic disciplines—engineering, statistics, computer science, and of course medicine—and for decades, the areas of reproductive and organ health have been investigators' and patients' gainers with these developments. The forenamed technologies are now tools in the physician's armamentarium to help evaluate and manage a variety of disease conditions. Current applications within the noninvasive prenatal testing arena have substantially improved pregnancy outcomes, most notably through major reductions in invasive testing of the fetal karyotype. Cell-free DNA testing applications within the organ health management sector at this early stage have much room for optimization. Applications early in pregnancy, pre-pregnancy, and in reproductive-age non-pregnant patients are waiting for their successes.

NIPT is currently the most publicly recognized cfDNA application, bringing to light the advantages provided to prenatal patients. The use of storage and analysis technology from NIPT will allow the process and ease of implementation of further applications towards reproductive and organ health management. Intelligent testing also has the potential to minimize environmental costs. Computer technologies employed in other bioinformatic areas will allow the creation of liver or recurrent miscarriage predisposition detection platforms that can be implemented in most centers and offices. Convenient point of care tests for women and their gynecologists exist presently; however, the addition of the advanced statistical, machine learning, and big data technology that has revolutionized other areas, can create the ability for addressing, in one test, multiple genetic and epigenetic factors that are responsible for organ health.

➢ *Equation 3 ML-Based Diagnostic Output*

$$D = \sigma(WX + b)$$

- D: Diagnostic prediction
- X: Feature matrix
- W, b: Weights, bias
- σ: Activation function

IX. CONCLUSION

There is an increasing recognition of the systemic processes that are involved in maintaining the health of various organ systems of the body. In so doing, interest in a move away from the more discreet approach of silencing specific organs at risk of or suffering from disease to a regulatory model of broader systemic risk and resilience integrated, moreover, across multiple organs and biological systems is enhanced. Centripetal management of human health towards the prevention of end-stage organ disease is likely to be one of the important questions of interest in the post-COVID world of global health. Various inter-organ systems of communication have been recognized. One particularly interesting area of research is that of the cross-communication between reproductive biology, and pregnancy in particular, and organ health. A failure of communication, predicted on disease in one of these systems, signaling adversely to the zonal niche of the other, leads to adverse health outcomes. The sense of relief felt at the realization that reversible Male-Factor Infertility is not an uncommon cause of Reproductive Loss, which makes a diagnosis of wasting, life-threatening, paraneoplastic syndromes related to a Bolus-Secretion of Ovarian Steroids to be very deliberately considered in the Differential Diagnosis of Happens when Gone Wrong operates in the opposite direction.

Both Cell-Free DNA Testing and Machine Learning can provide that integrated approach to organ and reproductive system health management over a Woman's Life Cycle. They can also illuminate our understanding of

the pathophysiology of events as diverse as Reproductive Loss, Premature Ovarian Failure, Porphyria Cutanea Tarda, and why women are less likely than men to have serious and life-threatening consequences of Hodgkin's Lymphoma and other forms of vascular injury and tissue damage. Identifying women Menopause Premature, Early, and Late, by also discrete longitudinal but dynamical changes in CfDNA Levels, would allow new studies to consider some of those biochemical, energetic, and communicative root causes of the adverse health outcomes across multiple organ systems.

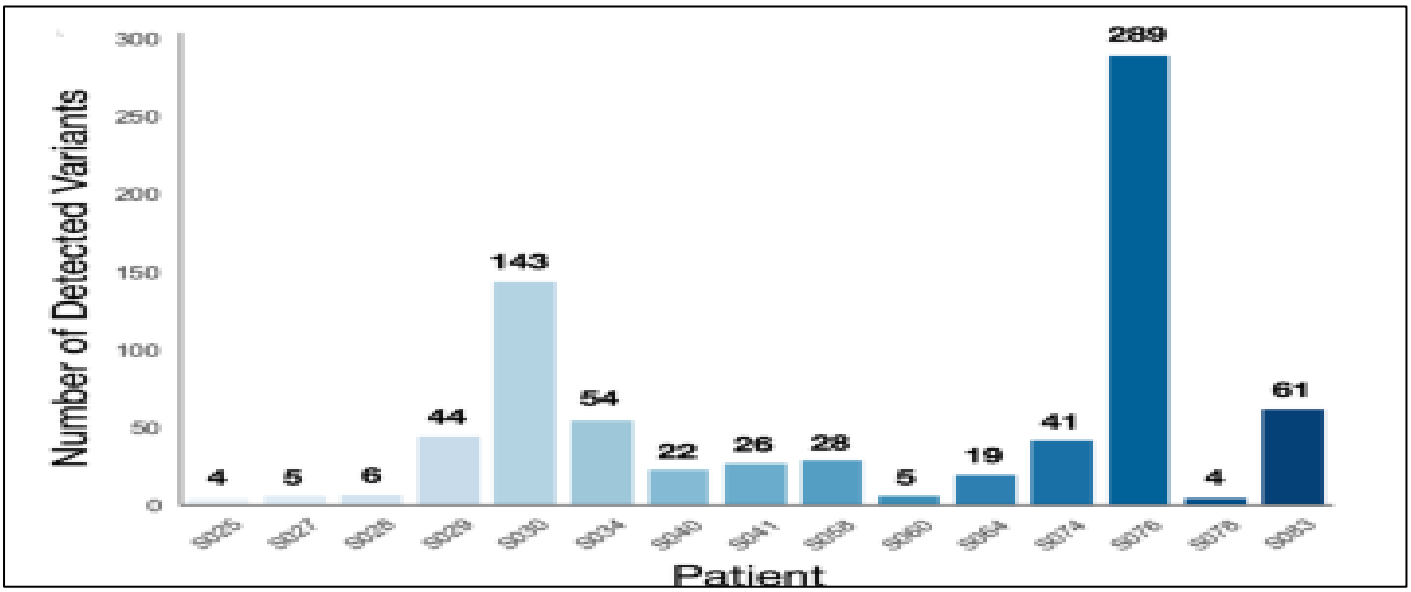

Fig 6 Cell-free DNA Sequencing Panels

A. Final Thoughts and Implications for Future Research

We have outlined a vision to enhance the synergistic convergence of reproductive and organ health management through advances in engineering, bioinformatics, and algorithmic intelligence. Notably, cell-free DNA testing with artificial intelligence powered digital PCR technology has the potential to revolutionize broad-scale screening and precision diagnosis of organs and pregnancies through non-invasive assessment of both exo- and endo-genetic landscapes with high spatial-temporal resolution. The proposed generic cfDNA testing framework is supported by a wealth of precedent evidence from a variety of human experiences, elucidating that cfDNA can be utilized to stage and monitor downstaging of organ disease via diagnostic and prognostic measurement of cfDNA markers for DNA damage and/or the corresponding tumor-associated DNA methylation signatures in plasma/serum extracted cfDNA. The precedent literature independently confirms the predicted cfDNA testing biosignatures of germline and fetal-associated genetic and epigenetic signals for reproductive monitoring and disease screening.

Potential applications of this technology in reproductive and organ health disease screening, stage monitoring, and non-invasive progeny and transplant rejection monitoring are discussed. Despite the current skepticism about the merit of non-invasive prenatal testing for transplant recipient pregnancy management and studies generating little information, we further hypothesize that cfDNA testing, focusing on detection of temporal-flux amplified recipient cfDNA fragment markers and AI-masked fetal DNA interrogation, has the potential to achieve unprecedented insights into decision-making on treatment of rejection episodes in kidney, liver, and heart transplant recipients and refined stratification of reproductive conservative management versus surgical intervention on ectopic pregnancy and recurrent miscarriages. We are inspired by recently established multi-organ interactive networks indicating physical relationships of health and disease among different human organs like kidney-liver-heart and liver-uterus axes.

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