Background

Cancer is a genetic disease. Most cancers are sporadic, meaning they develop during a person's lifetime. A few cancers are inherited, meaning they are present at birth. The hallmark of every human cancer is a condition called 'aneuploidy,' which refers to an abnormal chromosome number compared to normal cells. While normal cells have 46 chromosomes, cancer cells may have fewer or more than 46. This unique characteristic can serve as a marker for cancer.

Human cancers fall into two main types: the majority are solid tumors, while about 15-20% are blood cancers, such as leukemia and lymphoma. Traditionally, cancer detection relies on 'gold standard' imaging methods like MRI, CT, and PET scans. These methods are invasive and very expensive. More importantly, by the time cancer is detectable through these methods, it is often at an advanced stage, as it takes approximately 3 billion cells to form a small nodule that a PET scan can detect.

Due to these limitations, several attempts have been made over the past decade to use liquid biopsies, rather than tissue biopsies, to confirm cancer diagnoses by analyzing circulating tumor cells or cell-free DNA. These methods are labor-intensive and prone to technical issues, and most liquid biopsy assays focus on specific gene mutations for prognostic purposes rather than general cancer screening. Recently, a few companies have claimed the ability to detect multiple cancer types using liquid biopsy. Table 1 provides a comparison of the available techniques.

Unmet Need: There is an urgent need for the medical community—and humanity at large—to detect cancers at much earlier stages so that effective treatment can begin sooner. Over the past decade, InteGen LLC has developed several innovative technologies, the most recent of which utilizes oncosomes found in plasma through liquid biopsy, using peripheral blood as the source material. While the medical community has primarily used exosomes—small extracellular vesicles—for cancer therapies, oncosomes, as the largest type of exosome, have all the necessary characteristics to serve as reliable markers for cancer detection.

Beyond the size difference, exosomes and oncosomes have distinct compositions. Exosomes contain very little DNA, while oncosomes carry a full set of genomic DNA, similar to any other cell in the body. A key distinction is that exosomes are produced by all cells, including cancer cells, whereas oncosomes are produced exclusively by cancer cells. InteGen has developed proprietary, efficient methods to isolate oncosomes from plasma. Additionally, extensive genetic profiling has demonstrated that the genetic composition of oncosomes mirrors that of the original tumor cells (see Fig 1). Further, each oncosome has been shown to be aneuploid—a hallmark of tumor cells—

through InteGen's rapid DNA hybridization technology, which completes in just 15 minutes. These unique characteristics make oncosomes highly effective surrogate markers for cancer detection.

Proof-of-Concept Study: In a proof-of-concept study, InteGen recruited 100 samples, including approximately 50 from cancer patients and 50 from healthy controls. The results demonstrated high specificity and sensitivity. Notably, 100% accuracy was achieved in monitoring cancer treatment using oncosome counts from a 3 cc blood sample (see Table 2). The normal range is 0-30 oncosomes, with any count above 30 indicating a potential cancer signal.

Traction: Dr. Babu has traveled extensively, presenting the results of the proof-of-concept study and the technology to key stakeholders, including potential distributors, clinical reference laboratories, and medical oncologists. The breakthrough assay has generated tremendous excitement and positive acceptance. In some countries, there is even a waiting list for distribution partnerships, and due diligence is underway to select the most suitable partner(s).

Triple-Blind Study:A multi-center, international triple-blind study is currently in progress, with participants including King's College London and the Karolinska Institute in Sweden. The study will analyze a total of 500 samples, approximately 350 from patients and 150 from controls. Completion is expected by late 2024 or early 2025, with the aim of validating observations from he proof-of-concept and initial blind studies.

Data integrity: This study is IRB-approved, with an independent study coordinator overseeing data collection. Participating doctors will not have access to test results, and the InteGen laboratory will not have access to clinical information. At the end of the study, the study coordinator will compile all data, including unique sample codes, clinical information, and laboratory results, and then share the analyzed results with individual study centers and the Principal Investigator, Dr. Babu. Each center will receive information only on its own patients, while Dr. Babu and Dr. Saima, a professor at King's College London, will receive the complete study results simultaneously. Dr. Saima has agreed to curate the data, allowing any interested parties to verify the data's integrity and audit the compilation and analysis process.

Marketing Plan: In clinical practice, only a small number of tests used in patient care are FDA-approved. Most laboratory tests that clinicians rely on are not FDA-approved but are considered Laboratory Developed Tests (LDTs). LDTs are regulated by CLIA rather than the FDA and are intended for patient care rather than research.
To introduce any new test developed by manufacturers, such as the OncoSure assay by InteGen, individual laboratories must conduct a mini-validation, typically involving 25 samples, to confirm the manufacturer's clinical study results. Once validated, the laboratory can offer the test as an LDT. Although FDA clearance is advantageous, it is not an absolute requirement. However, FDA approval

provides certain benefits, and InteGen intends to pursue this option while also seeking laboratory partners with the infrastructure needed for mini-validation to offer the assay as an LDT. Notably, several laboratories worldwide have already expressed strong interest in this process.

FDA approval is a lengthy, time-consuming process. However, the FDA offers a provision for 'Breakthrough Technology Designation' for disruptive innovations, which aligns well with InteGen's invention. InteGen will pursue this designation, as it can typically be obtained within 60 days and offers significant marketing advantages once granted. Similarly, InteGen will seek CE marking for European and other markets where CE is preferred over FDA approval. CE marking is generally quicker to obtain than FDA approval.

Competitors: Grail is the most significant competitor, with its assay available on the market for over a year, though it has not yet received FDA approval. A new competitor from India has also recently announced an assay. Table 1 outlines the attributes of these two competitors' assays, comparing the strengths and weaknesses of all three companies' offerings.

Finances: InteGen Cdx has forecasted its finances for the next five years, with details provided in the accompanying Excel spreadsheet. Compared to the traditional 10X ROI expected for most venture-funded projects, the ROI for this opportunity is exceptionally high, based on a very conservative approach.

AMENDMENT

The blind study was modified due to delays in coordinating with the IRBs at King's College London and the Karolinska Institute in Sweden. Data from these institutions will be included in a larger confirmatory study planned for completion in late 2024 or early 2025.

Because the blind study enhances the credibility of our findings, the following changes were implemented. Initially, oncosome enumeration relied solely on DAPI staining. However, it was observed that relying exclusively on morphology with DAPI staining could lead to false positives and negatives, as scoring depends on size, shape, and staining intensity. Other cellular material and artifacts could sometimes mimic oncosomes, potentially impacting results. This prompted an immediate adjustment to the scoring method, introducing InteGen's proprietary DNA probe hybridization on oncosomes. Only positively hybridized structures were scored as oncosomes, while non-hybridized structures were excluded from enumeration for that case and from the entire study.

Dr. Babu personally blinded all proof-of-concept study materials and applied hybridization to the previously DAPI-stained slides. Three independent technicians scored each case, and, due to the

high consistency among their results, an average score was used as the final oncosome count.

Additionally, around 40 cases that were studied blindly from the outset at three medical centers were included in this study. A few cases lacked clinical confirmation of the data and were therefore excluded from the final count for this amended study. Any repeat studies from the proof-of-concept were also excluded from the final subject count. The results of the blind study are presented in Table 3, with corresponding specificity, sensitivity, and accuracy. The 100% concordance between genetic remission, as scored by laboratory results, and clinical remission, noted in the proof-of-concept study, was confirmed in this blind study.

In conclusion, with the submission of this report, we, InteGen LLC, declare the completion of the clinical study.

Appendix Attachments:

Please refer to the attached Excel spreadsheet for 5-year financial projections.

Table 1

	TEST NAME		
ATTRIBUTES	Galleri	HrC	Oncosure
Accuracy	Low	Very High	Very High
Testing mode	Non-reflex, 1 test	Reflex, 2 tests	Reflex, 2 tests
Turnaround	3-4 weeks	1st 5 days, 2nd EST > 10 days	1st 2 hours, 2nd 3 hours
Methodology	NGS	1st RT-PCR, 2nd NGS	1st FISH, 2nd RCA/FISH
Ease of Use	Complex	Complex	Easy
Price	$998	EOC ~ $1000	EOC ~ $895
Centralized testing	Yes	Yes/No	No
Underlying principle	Differing Methylation patterns	Embryonic/cancer stem cell markers	Oncosome profiling
Blood sample	10 cc	10 cc	3 cc
Point of Care testing	No	No	Possible
Mobile testing	No	No	Possible

Table 2

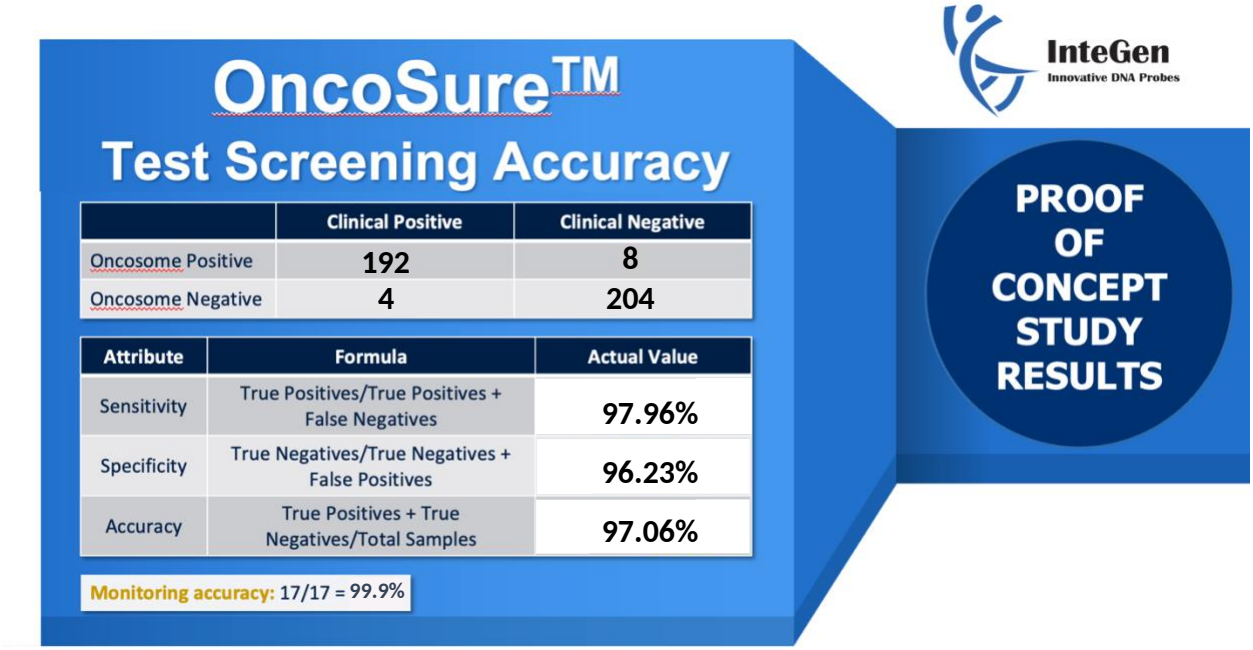


Table 3 Proof-of-concept/Blind study results

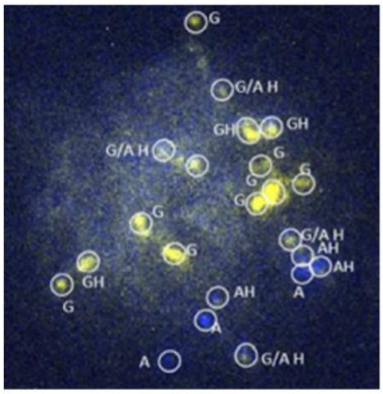
	Clinical positive	Clinical negative	TOTAL
Oncosome positive	192	8	200
Oncosome negative	4	204	208
TOTAL	196	212	408

False +ve result: 4
False -ve result: 2

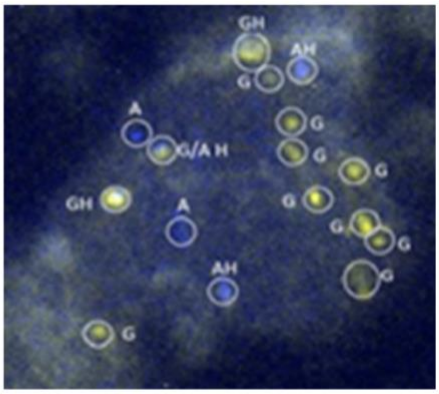
Sensitivity = 97.96%
Specificity = 96.23%
Accuracy = 97.06%

Figure 1

Similar Chromosome Profiling



Parental Tumor cell



Oncosome

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