EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
Cell-Free DNA BCT

DECISION SUMMARY

A. DEN Number:

DEN200001

B. Purpose for Submission:

New device

C. Measurand:

Not applicable

D. Type of Test:

Not applicable

E. Applicant:

Streck, Inc.

F. Proprietary and Established Names:

Cell-Free DNA BCT

G. Regulatory Information:

Regulation	Name	Product Code	Panel
21 CFR 862.1676	Blood collection device for cell-free nucleic acids	QMA	Chemistry (75)

H. Indications for Use:

1. Indication(s) for use:

Cell-Free DNA BCT is a direct-draw venous whole blood collection device intended for the collection, stabilization, and transport of venous whole blood samples for use in conjunction with cell-free DNA next-generation sequencing liquid biopsy assays that have been cleared or approved for use with samples collected in the Cell-Free DNA BCT device.

2. Special conditions for use statement(s):

- Performance characteristics for this device have only been established on the Guardant360 CDx assay (P200010), which was performed at one Guardant Health laboratory.
- Prescription use only.
- Do not store outside of established conditions.

- Do not transfer samples drawn into tubes containing other anti-coagulants and/or preservatives into Cell-Free DNA BCT.
- Do not use past expiration date printed on label.
- Do not use for clinical chemistry assays or assays other than liquid biopsy next-generation sequencing.
- Do not use for collection of materials to be injected into patients.
- Cell-Free DNA BCT is not intended for the stabilization of RNA nor is it intended for viral or microbial nucleic acids.

3. Special instrument requirements:

   Not applicable.

I. Device Description:

Cell-Free DNA BCT is a sterile, single use, direct-draw blood collection tube comprised of 3 components (i.e. glass tube with rubber stopper, anticoagulant, and cell preservatives). The blood collection tube is a 10mL evacuated tube manufactured with USP Type III glass containing cerium oxide (to prevent color change associated with gamma irradiation sterilization). Each tube includes 200 µL ± 10% of liquid reagent. The reagent composition includes an anticoagulant K3EDTAand a preservative.

The device is intended to be placed inside a tube holder or an adaptor that contains a needle designed to pierce the tube closure and allow blood to flow into the tube. Once the vein has been penetrated (using a standard blood collection needle or a blood collection set), the tube is pushed into the holder, and the blood enters the tube. Once a tube has drawn the appropriate amount of blood (10 mL), it is disengaged from the holder and inverted 10 times to mix the reagents with the blood. The specimen is then transported to the lab for plasma isolation and extraction of cfDNA.

J. Standard/Guidance Document Referenced (if applicable):

CLSI EP25-A (Replaces EP25-P) Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.

ISO 11137-1: Sterilization of health care products-Radiation: Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

K. Test Principle:

Not applicable.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. Precision/Reproducibility:

   Repeatability
   Within-lot (between tube) variability was evaluated using native specimens collected from 33 patients with advanced stage solid tumors run on the Guardant Health Guardant360 CDx assay (P200010). Venous whole blood was drawn into 4 Cell-Free DNA BCTs from a single lot per subject. A single lot of Guardant360 CDx sample preparation kit was used by the blood collection vendor to isolate plasma within 7 days after blood collection. Plasma was then shipped to Guardant Health (GH) on dry ice and stored at -80°C until further processing. Sequencing was performed using 6 NextSeq 550 Sequencers (Illumina). Of the 132 samples processed, 131 samples passed all GH Quality Control metrics and were included in the final analysis. The sample that was excluded was found to have evidence of contamination during sample processing. Variability between replicates for each patient was evaluated based on variant call agreement for somatic variants. A concordant positive call reflects detection of an identical sequencing alteration between replicates, and a discordant call reflects the presence of an alteration in one replicate and the

absence of that same alteration in another replicate. Average positive agreement (APA) and average negative agreement (ANA) were calculated as follows:

$$APA = \frac{\#\ concordant\ positives}{\#\ concordant\ positives + \frac{\#\ discordant\ calls}{2}}$$

$$ANA = \frac{\#\ concordant\ negatives}{\#\ concordant\ negatives + \frac{\#\ discordant\ calls}{2}}$$

Average positive agreement (APA) was calculated overall and for those variants detected at mutation allele frequency (MAF) $\geq$ 1x the limit of detection (LoD), whereas average negative agreement (ANA) was reported panel-wide across all reportable positions and variants. This statistic includes all called variant sites, not just the eligible variants sites based on LoD in the source samples, so includes positions with expected stochastic detection due to low mutant molecule count. The results are summarized below:

Concordant positive calls (overall | ≥ 1x LoD)	Discordant calls (overall | ≥ 1x LoD)	Overall APA	APA (≥ 1x LoD)	Panel-Wide ANA
40 | 32	11 | 5	(b) (4)		

Reproducibility

Lot to lot variability was evaluated using native specimens collected from 30 patients with advanced stage solid tumors run on the Guardant Health Guardant360 CDx assay (P200010). Venous whole blood was drawn into Cell-Free DNA BCTs representing 3 different lots. All Cell-Free DNA BCTs were processed into plasma within 7 days after whole blood collection, and the plasma was frozen at -80°C ± 10°C until analysis using the Guardant360 CDx Test. Variability between Cell-Free DNA BCT lot was evaluated based on variant call agreement for somatic variants. APA and ANA were calculated as described previously. The results are summarized below.

Lot Comparison	Overall APA	APA (≥ 1x LoD)	Panel-Wide ANA
1 vs 2	(b) (4)		
1 vs 3			
2 vs 3			

b. *Linearity/assay reportable range:*

Not applicable.

c. *Traceability, Stability, Expected values:*

Shelf-life

To validate device performance across the claimed shelf life when the device is stored prior to blood collection under the recommended storage conditions (2-30°C), venous whole blood was collected from 30 healthy subjects. Three lots of Cell-Free DNA BCTs were tested under the following conditions: without storage (T0), 8.5 months after manufacture (T8.5), 12.5 months after manufacture (T12.5), 18.5 months after manufacture (T18.5), and 24.5 months after manufacture (T24.5). Prior to blood collection, Cell-Free DNA BCTs were stored at 2, 22, or 30°C. For T0, venous whole blood was collected into 2 Cell-Free DNA BCTs for each of the 3 lots. After collection, T0 Cell-Free DNA BCTs were held at 22°C for a maximum of 4 hours. For the remaining timepoints (8.5, 12.5, 18.5, 24.5 months), 7 Cell-Free DNA BCTs were collected at each aged timepoint from each subject representing the following conditions: 1 conventional K_2EDTA Vacutainerstored at 22°C for a maximum of 4 hours (which was considered the baseline condition), 2 Cell-Free DNA BCTs stored at 2°C, 2 Cell-Free DNA BCTs stored at 22°C, and 2 Cell-Free DNA BCTs stored at 30°C. Each set of Cell-Free DNA BCTs collected from the same patient, sharing the same pre-collection storage temperature, were divided into two conditions: immediate processing (D0) and storage for 8 days (D8). Plasma was then isolated from the whole blood samples and cfDNA was extracted using the same kit as used in the Guardant Health Guardant360 CDx assay (P200010). cfDNA concentration was assessed using droplet digital PCR (ddPCR) and fluorometry, and size and overall cfDNA sample integrity was assessed by electrophoresis. At T0, cfDNA concentration, size, and integrity was compared between Cell-Free DNA BCTs that were not stored and tubes that were stored at 22°C for 8 days after blood collection. The results support that cfDNA concentration, size, and integrity were maintained for 8 days when stored at 22°C after collection. At each timepoint (8.5, 12.5, 18.5, 24.5 months), samples drawn into Cell-Free DNA BCTs were compared to blood samples drawn into K_2EDTA tubes that were processed into plasma on the same day as blood collection. The results support that devices stored at 2-30°C for 18.5 months prior to blood collection are able to maintain cfDNA concentration and integrity when blood specimens are stored for up to 8 days after blood collection.

Additional Studies

Additional studies were conducted to assess robustness to centrifugation, draw volume, stopper closure assembly stability, stopper pullout force, stopper resealing, and anticoagulant effectiveness. Study protocols, acceptance criteria, and results for these studies were provided and found to be acceptable.

d. *Detection limit:*

Not applicable.

e. *Analytical specificity:*

Preservative

To validate that the preservative formulation does not interfere with the Guardant Health Guardant360 CDx assay (P200010), three venous whole blood specimens were collected into candidate devices from each of 12 subjects with advanced stage solid tumors. Cell-Free DNA BCTs were manufactured to reflect the normal preservative formulation ("reference"), 2x Preservative A, or 2x Preservative B. After collection, whole blood samples were processed into plasma and then shipped to Guardant Health for cfDNA extraction and sequencing. cfDNA analysis was conducted using the Guardant 360CDx assay. Performance was evaluated based on sample-level molecule recovery, exon-level molecule recovery, and variant call concordance relative to the reference Cell-Free DNA BCT. Each variant called in the reference sample was evaluated in the experimental condition samples by positive percent agreement (PPA). The total number of concordant and discordant calls for all reference positive calls in a given experimental condition was counted across patients and used to calculate PPA. For each reference – treatment sample pair, each eligible site that is negative in the reference sample will be assessed for presence of a somatic call in the treatment sample via Negative Percent Agreement. The total number of concordant and discordant calls for all reference negative calls in a given experimental condition will be counted across patients and used to calculate NPA using the following equation, expressed as a percentage. PPA and NPA were calculated as follows:

$$PPA\ (Experimental + \mid Reference +) = \frac{\#\ concordant\ positive\ calls}{\#\ reference\ positive\ calls}$$

$$NPA\ (Experimental - \mid Reference -) = \frac{\#\ concordant\ negative\ calls}{\#\ reference\ negative\ calls}$$

PPA was calculated overall and for those variants detected at mutation allele frequency (MAF) $\geq$ 1x the limit of detection (LoD), whereas average negative agreement (ANA) was reported panel-wide across all reportable positions and variants. The results confirmed that increasing either component of the preservative does not interfere with the ability of the Cell-Free DNA BCT to preserve cfDNA suitable for assay performance.

Endpoint	Metric	2x Preservative A	2x Preservative B
Sample-level Molecule Recovery Difference (fold change)	Median of NSC fold (condition/reference)	(b) (4)	
Relative exon-level coverage	Lower bound of 95% CI		
Variant call concordance	PPA		
	PPA (≥1x LoD)		
	NPA		

Incomplete Mixing

The instructions for use indicate that the tube should be inverted 10 times after collection. To evaluate the impact of variations in mixing after blood collection, specimens were collected from 12 subjects with advanced stage solid tumors. Venous whole blood was collected into three Cell-Free DNA BCTs per subject. Cell-Free DNA BCTs collected from each patient were inverted 10 times, 5 times, or 15 times. After collection, whole blood samples were processed into plasma and then shipped to Guardant Health for cfDNA extraction and sequencing. cfDNA analysis was conducted using the Guardant 360CDx assay. Performance was assessed based on (b) (4) (b) (4) relative to 10 inversions. As described above under the Preservative interference study, PPA and NPA were used to assess variant call concordance. The results indicated that inadequate or overmixing may result in diminished performance.

Endpoint	Metric	5 Inversions	15 Inversions
Sample-level Molecule Recovery Difference (fold change)	Median of NSC fold (condition/reference)	(b) (4)	
Relative exon-level coverage	Lower bound of 95% CI		
Variant call concordance	PPA		
	PPA (≥1x LoD)		
	NPA		

Short Draw

To evaluate potential interference caused by underfilling Cell-Free DNA BCTs, specimens were collected from 15 subjects with advanced stage solid tumors. Venous whole blood was collected into three Cell-Free DNA BCTs per subject. Cell-Free DNA BCTs were manufactured to reflect the normal reagent (e.g. preservative and anticoagulant) formulation ("reference"), 2x volume of Reagent, or (b) (4) Reagent. These conditions were intended to reflect 10 mL whole blood collected, 5 mL whole blood collected, and (b) (4) whole blood collected. After collection, whole blood samples were processed into plasma and then shipped to (b) (4) for cfDNA extraction and sequencing. cfDNA analysis was conducted using the Guardant 360CDx assay. Performance of the Guardant360 CDx assay was assessed based on (b) (4) (b) (4). As described above under the Preservative interference study, PPA and NPA were used to assess variant call concordance. The results indicated that underfilling of the Cell-Free DNA BCTs with less than 5 mL of blood may lead to poor product performance. A precaution has been included in the labeling warning users to fill the tube completely.

Endpoint	Metric	2x Reagent (5mL whole blood)	(b) (4) Reagent (b) (4) whole blood)
Sample-level Molecule Recovery Difference (fold change)	Median of NSC fold (condition/reference)	(b) (4)	
Relative exon-level coverage	Lower bound of 95% CI		
Variant call concordance	PPA		
	PPA (≥1x LoD)		
	NPA		

		(b) (4)

Tube Stopper
Extractable and leachable studies were performed to identify substances within the tube stopper that may interact with patient specimens and interfere with the ability of the tube to preserve cfDNA. The results support that extractables from the tube stopper are not anticipated to interfere with device performance.

f. Assay Cut-off:
Not applicable.

g. Specimen Stability

cfDNA Stability
To validate that specimens collected into the device maintain their integrity throughout the claimed shelf life, the sponsor collected specimens from patients with advanced stage solid tumors into aged Cell-Free DNA BCTs that were between 1 month and 17 months post-manufacture. Cell-Free DNA BCTs were stored at room temperature between manufacture and blood collection. For each patient, venous whole blood was collected into four Cell-Free DNA BCTs: two Cell-Free DNA BCTs from the youngest lot (approximately 1 month post-manufacture) which served as the reference conditions (R1 and R2) and one Cell-Free DNA BCT from each of the older lots (8 months and 17 months post-manufacture) which served as test. All Cell-Free DNA BCTs were processed to plasma within 7 days after whole blood collection, and the plasma was frozen at -80°C ± 10°C. cfDNA analysis was conducted using the Guardant 360CDx assay. The sponsor assessed the stability of the Cell-Free DNA BCTs in terms of variant call concordance (PPA and NPA) between the reference condition (1 month) and the test conditions (8 and 17 months). The results support that cfDNA isolated from the device is of sufficient quantity, quality, and integrity for the intended downstream application throughout the claimed shelf life of the device.

Positive Percent Agreement (PPA) Variant Call Concordance

Condition	**ΔPPA1 (PPA_{r1t}-PPA_{r1r2})**	**95% Confidence Interval of ΔPPA1**	**ΔPPA2 (PPA_{r2t}-PPA_{r2r1})**	**95% Confidence Interval of ΔPPA2**
(b) (4)				

Negative Percent Agreement (NPA) Variant Call Concordance

Condition	ΔNPA1 (NPA_{r1t}-NPA_{r1r2})	95% Confidence Interval of ΔNPA1	ΔNPA2 (NPA_{r2t}-NPA_{r2r1})	95% Confidence Interval of ΔNPA2
(b) (4)				

Post-Collection Storage of Venous Whole Blood prior to plasma separation

To characterize preservation of cfDNA in the candidate device compared to K_2EDTA tubes prior to plasma separation when venous whole blood samples are stored for up to 7 days post-blood collection, venous whole blood was collected from 30 healthy subjects. The candidate device and K_2EDTA tubes were tested under the following conditions: plasma isolation immediately after collection (Day 0, held a (b) (4) for (b) (4) hours), stored at (b) (4) for 7 days, stored at (b) (4) for 7 days, or stored at (b) (4) for 7 days. A total of eight tubes are collected from each donor (4 K_2EDTA tubes and 4 Cell-Free DNA BCTs) and each tube was held at one of the conditions described previously. Plasma was then isolated from the whole blood samples and cfDNA was extracted using the same kit as used in the Guardant Health Guardant360 CDx assay (P200010). cfDNA concentration was assessed using (b) (4), and size and overall cfDNA sample integrity was assessed by (b) (4). For each condition evaluated, the Day 0 (b) (4) tube was used as the baseline. The results demonstrated that the candidate device is able to preserve cfDNA specimen concentration and integrity better than K_2EDTA tubes when Cell-Free DNA BCTs are stored post-blood collection for up to 8 days at (b) (4).

To validate that storage of Cell-Free DNA BCTs at 2-30°C prior to whole blood collection or storage of whole blood specimens in the Cell-Free DNA BCT for up to 7 days after blood collection does not impact Guardant Health Guardant360 CDx assay (P200010) performance, the sponsor collected whole blood specimens from patients with advanced stage solid tumors. Cell-Free DNA BCTs used in this study represented: as soon as feasible after manufacture (T0), 3.2 months (T3.2), 7.2 months (T7.2), 12.2 months (T12.2), 18.2 months (T18.2), and 24.2 months (T24.2) after manufacturing. T0 Cell-Free DNA BCTs were not stored prior to blood collection. T3.2, T7.2, and T12.2 Cell-Free DNA BCTs were stored at the extremes of the recommended empty storage temperature range (b) (4) and (b) (4) prior to blood collection. At each timepoint, venous whole blood was collected from 30 subjects and then plasma was either isolated one day after blood collection (D1) or after 7 days of storage (D7). Plasma was stored at (b) (4) until cfDNA extraction and analysis using the Guardant Health Guardant360 CDx assay (P200010). Variability between conditions (Cell-Free DNA BCT storage at (b) (4) or (b) (4) prior to collection; plasma isolation one day after blood collection or plasma isolation after 7 days of storage) was evaluated based on variant call agreement for somatic variants. APA and ANA was calculated as described previously.The APA and ANA values between D1 and D7 within each combination of time point, storage temperature, and Cell-Free DNA BCT lot are shown below. The results demonstrate that storage of whole blood specimens in the Cell-Free DNA BCT for up to 7 days after blood collection does not impact Guardant Health Guardant360 CDx assay (P200010) performance.

APA and ANA Variant Call Concordance between D1 and D7 within each time point, storage temperature, and lot.

Condition	APA	APA (above LoD)	ANA	ANA (above LoD)
(b) (4)				

(b) (4)

The APA and NPA values between 2°C and 30°C within each combination of time point, storage temperature, and Cell-Free DNA BCT lot are shown below. The results demonstrate that storage of Cell-Free DNA BCTs at 2-30°C prior to whole blood collection does not impact Guardant Health Guardant360 CDx assay (P200010) performance.

APA and NPA Variant Call Concordance between 2°C and 30°C within each time point and lot.

Condition	APA	APA (above LoD)	ANA	ANA (above LoD)
(b) (4)				

h. Shipping Stability

The sponsor conducted a series of tests to demonstrate that the device is robust to extreme temperature (b) (4) and physical stress conditions (e.g. vibration, drops, compression) that may be encountered during shipping before or after sample collection. Study protocols, acceptance criteria, and results for these studies were found to be accepable.

2. Comparison studies:

a. Method comparison with predicate device:

Cell-Free DNA BCT vs. K_2EDTA BCT Concordance

The purpose of this study was to establish concordance between test results obtained with cfDNA isolated from the Cell-Free DNA BCT and test results obtained with cfDNA isolated from K_2EDTA BCTs since K_2EDTA BCTs were used to collect samples in the clinical studies supporting the safety and effectiveness of the Guardant360 CDx (P200010).

Blood from non-small cell lung cancer Stage III or IV patients, prescreened externally for CDx positive and negative markers EGFR L858R, EGFR T790M, EGFR exon 19 deletions), were collected by utilizing two K_2EDTA BCTs and two Cell-Free DNA BCTs. The second K_2EDTA BCT was not processed for this study. A total of 59 patients were enrolled, some with and others without CDx variants, and whole blood samples were tested from three tubes, two Cell-Free DNA BCTs and one K_2EDTA tube.

The performance of K_2EDTA BCTs relative to Cell-Free DNA BCTs was evaluated through a call agreement analysis which tests the difference of the (b) (4)
(b) (4)

Of the one-hundred and seventy seven ((b) (4) aliquots ((b) (4) samples across 3 Cell-Free DNA BCT designations), 176 (b) (4) passed in-process and post-sequencing Quality Control (QC) metrics at Guardant Health. Of the 176 passing post-sequencing metrics (b) failed sample QC, leaving (b) (4) of (b) (4) (b) (4) samples passing QC metrics. Three of the (b) (4) patients with S1, S2, and K1 runs were excluded from call concordance analyses because of QC failures of at least (b) (4) of (b) (4) replicates.

In total, (b) (4) patients met study criteria for inclusion, including (b) (4) distinct CDx variants observed in at least one tube. Call concordance across tubes, aggregating across all CDx variants, is shown below.

CDx Call concordance

	S1+		S1-	
	S2+	S2-	S2+	S2-
K1+	(b) (4)			
K1-				

The PPA and NPA values across the entire set of CDx variants (aggregated), and for each CDx variants is summarized below. K_2EDTA tubes and Cell-Free DNA BCTs demonstrated expected levels of positive agreement, PPA(b) (4) for CDx variants. Discordant detection was observed below LoD, with agreement above LoD being (b) (4) K_2EDTA and Cell-Free DNA BCTs demonstrated expected levels of negative agreement, NPA(b) (4) for CDx variants. The delta PPA and delta NPA values, shown below, were within acceptable limits. The data confirmed concordance between test results obtained with cfDNA isolated from Cell-Free DNA BCT and test results obtained with cfDNA isolated from K_2EDTA BCTs.

PPA and NPA Values for all CDx variants

	All EGFR CDx Variants		EGFR T790M		EGFR L858R		EGFR Exon 19 Deletion	
Tube Pairing	**PPA**	**NPA**	**PPA**	**NPA**	**PPA**	**NPA**	**PPA**	**NPA**
K_2EDTA | Cell-Free DNA BCT #1	(b) (4)							
K_2EDTA | Cell-Free DNA BCT #2								
Cell-Free DNA BCT #2 | Cell-Free DNA BCT #1								
Cell-Free DNA BCT #1 | Cell-Free DNA BCT #2								

Delta PPA and NPA values for all CDx variants

Condition	Value
ΔPPA1 (K_2EDTA | Cell-Free DNA BCT #1 - Cell-Free DNA BCT #2 | Cell-Free DNA BCT #1)	(b) (4)
ΔPPA2 (K_2EDTA | Cell-Free DNA BCT #2 - Cell-Free DNA BCT #1 | Cell-Free DNA BCT #2)	
ΔNPA1 (K_2EDTA | Cell-Free DNA BCT #1 - Cell-Free DNA BCT #2 | Cell-Free DNA BCT #1)	
ΔNPA2 (K_2EDTA | Cell-Free DNA BCT #2 – Cell-Free DNA BCT #1 | Cell-Free DNA BCT #2)	

b. Matrix Comparison:

Not applicable.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable.

b. Clinical specificity:

Not applicable.

c. Other clinical supportive data (when a. and b are not applicable):

Refer to P200010.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Not applicable.

M. Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

N. Identified Risks to Health and Mitigation Measures:

Identified Risk	Mitigation Measures
Blood pathogen exposure/Injury	Certain design verification and validation

Identified Risk	Mitigation Measures
Failure to collect and transport sample	Certain design verification and validation
Insufficient sample quantity and quality	Certain design verification and validation

O. Benefit/Risk Analysis:

Summary of the Assessment of Benefit
For the Proposed Indications for Use

The Cell-Free DNA BCT may be used to collect and stabilize whole blood for further processing and testing of cell-free DNA (cfDNA). The tube may preserve cfDNA and minimize cellular contamination for up to 7 days following collection and storage at 18-25 degrees Celsius. Standard blood collection in an EDTA containing tube is typically stored for no longer than 2 hours prior to centrifugation. After the sample undergoes centrifugation, the plasma is stored in cold temperatures, then it is shipped to a laboratory which can perform the assay. The benefit of the device can be realized in situations where blood cannot be processed to plasma immediately, and when limiting the amount of genomic DNA contamination is critical to assay performance.

Summary of the Assessment of Risk
For the Proposed Indications for Use

According to the National Cancer Institute's Biorepositories and Biospecimen Research Branch cf-DNA specific Guidelines, "cfDNA concentrations and cellular DNA contamination are greatly influenced by the type of blood collection tube used as well as the processing steps employed, which include the duration and conditions of a pre-centrifugation delay and parameters relating to centrifugation or filtration." Additionally, they state, "the mutant allele frequency in cfDNA samples is also sensitive to blood collection tube type, storage duration and conditions, and a combination of storage conditions and extraction methods." The risks associated with the candidate blood collection tube (BCT) device can include preanalytical and analytical issues, including delay in patient results due to insufficient cfDNA yield, insufficient anticoagulation, insufficient draw volume, and other analytical risks. Injury to laboratory personnel can occur due to broken BCTs during transport/centrifugation or leaking/breakage/splashing during handling of BCTs. Additionally, false results can occur due to insufficient yield and quality deficiencies, such as cellular DNA contamination, insufficient inversions/mixing, cfDNA instability, interference, lot-to-lot variability, etc.

The extent of the clinical risks from false results using a Cell-Free DNA BCT are dependent on the target tumor cell mutation and the purpose for testing (e.g. companion diagnostic testing for targeted cancer treatment, repeat sampling to monitor recurrence after surgery, understanding molecular profile of tumor(s) before and after treatment). For example, if used for the purposes of blood collection to identify a tumor mutation prior to initiation of targeted drug therapy, a falsely positive result can lead to potential unnecessary exposure to toxicity from the drug. A falsely negative result due to poor analytical performance of the Cell-Free DNA BCT can contribute to a missed opportunity to treat a patient with targeted cancer treatment. These clinical risks cannot be controlled by the candidate BCT device since the clinical risks of false results are dependent on the target tested and assay used.

Summary of the Assessment of Benefit-Risk
For the Proposed Indications for Use

Despite the benefits of the device described above, the analytical performance of the Cell-Free DNA BCT involves risks that must be mitigated to ensure safe and effective performance of the device. General controls are insufficient to mitigate the risks of the device. However, the probable clinical benefits would outweigh the probable risks for the device when considering the mitigation of the risks provided for in the special controls. Device design verification and validation, including verification and validation of design features and specifications as specified in the special controls, helps ensure that users of the device are not exposed to undue risks of blood-borne pathogen exposure or injury during use of the device, including blood collection, transportation, and

centrifugation processes. Additionally, further design verification and validation, including the clinical and analytical studies specified in the special controls, helps ensure that the device reproducibly and reliably collects, transports, stabilizes, and isolates cell-free nucleic acids, resulting in cell-free DNA samples that are of sufficient quantity and quality to be suitable for use with a next-generation sequencing liquid biopsy test system. Once the combination of the required general controls and the special controls established for this device are taken into consideration, the probable benefits would outweigh the probable risks.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Summary of the Benefit/Risk Conclusion

For the Proposed Indications for Use

Given the combination of the required general controls and the special controls established for this device, the probable benefits would outweigh the probable risks.

P. Conclusion:

The De Novo request is granted and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:
Product Code:
Device Type: Blood collection device for cell-free nucleic acids
Class: II (special controls)
Regulation: 21 CFR 862.1676