November 18, 2019

NantHealth, Inc.
Aleece Nolasco
Vice President, Regulatory Affairs
9920 Jefferson Blvd
Culver City, CA 90232

Re: K190661
Trade/Device Name: Omics Core
Regulation Number: 21 CFR 866.6080
Regulation Name: Next generation sequencing based tumor profiling test
Regulatory Class: Class II
Product Code: PZM
Dated: September 26, 2019
Received: September 27, 2019

Dear Aleece Nolasco:

This letter corrects our substantially equivalent letter of November 9, 2019.

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Donna M. Roscoe -S

Donna Roscoe, Ph.D.
Chief, Molecular Genetics Branch
Division of Molecular Genetics and Pathology
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K190661

Device Name

Omics Core

Indications for Use *(Describe)*

The Omics Core assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and tumor mutational burden (TMB) for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. Omics Core is a single-site assay performed at NantHealth, Inc.

Type of Use *(Select one or both, as applicable)*

☑ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

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510(K) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

1. SUBMITTER

NantHealth, Inc.
9920 Jefferson Blvd.
Culver City, CA 90232

Contact Person:
Aleece Nolasco
Vice President, Regulatory Affairs
Phone: 310-405-7549
Email: Aleece.Nolasco@NantHealth.com

Date prepared: October 21, 2019

2. DEVICE

Name of Device	Omics Core
Common Name	Next Generation Sequencing Tumor Profiling Test
Classification Name	Next Generation Sequencing Based Tumor Profiling Test (21CFR 866.6080)
Regulatory Class	II
Product Code	PZM

3. PREDICATE DEVICE

MSK-IMPACT (Integrated Mutation Profiling Of Actionable Cancer Targets): A Hybridization-Capture Based Next Generation Sequencing Assay, DEN170058

This predicate device has not been subject to a design-related recall.

No reference devices were used in this submission.

4. DEVICE DESCRIPTION

4.1. Test Principle

The NantHealth Omics Core assay is a custom targeted whole exome sequencing platform, utilizing solution-phase exon capture and sequencing, to report somatic alterations (point mutations, small insertions and deletions) in 468 genes and sequencing of 19,396 protein-coding genes (whole exome) to determine overall tumor mutation burden in tumor specimens.

Genomic DNA is extracted from both a tumor and a patient-matched normal control sample. Sequence libraries are prepared through a series of enzymatic steps including shearing of double-stranded DNA, end repair, A-base addition, ligation of barcoded sequence adaptors, and low cycle PCR amplification. Single barcoded sequence libraries are captured using the biotinylated probes. Captured DNA fragments are then pooled and sequenced on an Illumina NovaSeq 6000 as paired-end reads. Sequence reads are then aligned to the reference human genome. Somatic alterations are identified in the tumor DNA by direct comparison to the matched normal DNA.

4.2. Equipment, Supplies and Reagents

Table 1 summarizes some of the main equipment, supplies, reagents, and software used by the Omics Core assay.

All reagents, materials and equipment needed to perform the assay are qualified by NantHealth.

Table 1: Equipment Supplies, Reagents, and Software

Library Prep	Kapa Hyper Prep Kit
Hybridization	IDT xGen® Exome Research Panel v1.0
Sequencer Chemistry	2-Channel SBS Chemistry
Sequencer	Illumina NovaSeq 6000
Bioinformatics	Omics Core software

4.3. Omics Core Workflow

The following figures provide an illustrated overview of the flow of the Omics Core testing process from sample receipt, through testing, to the report. Detailed descriptions of each aspect of the assay are provided in subsequent sections.

The laboratory workflow for Omics Core is illustrated in Figure 1.

The bioinformatics workflow for Omics Core is illustrated in Figure 2.

Figure 1: Laboratory Workflow

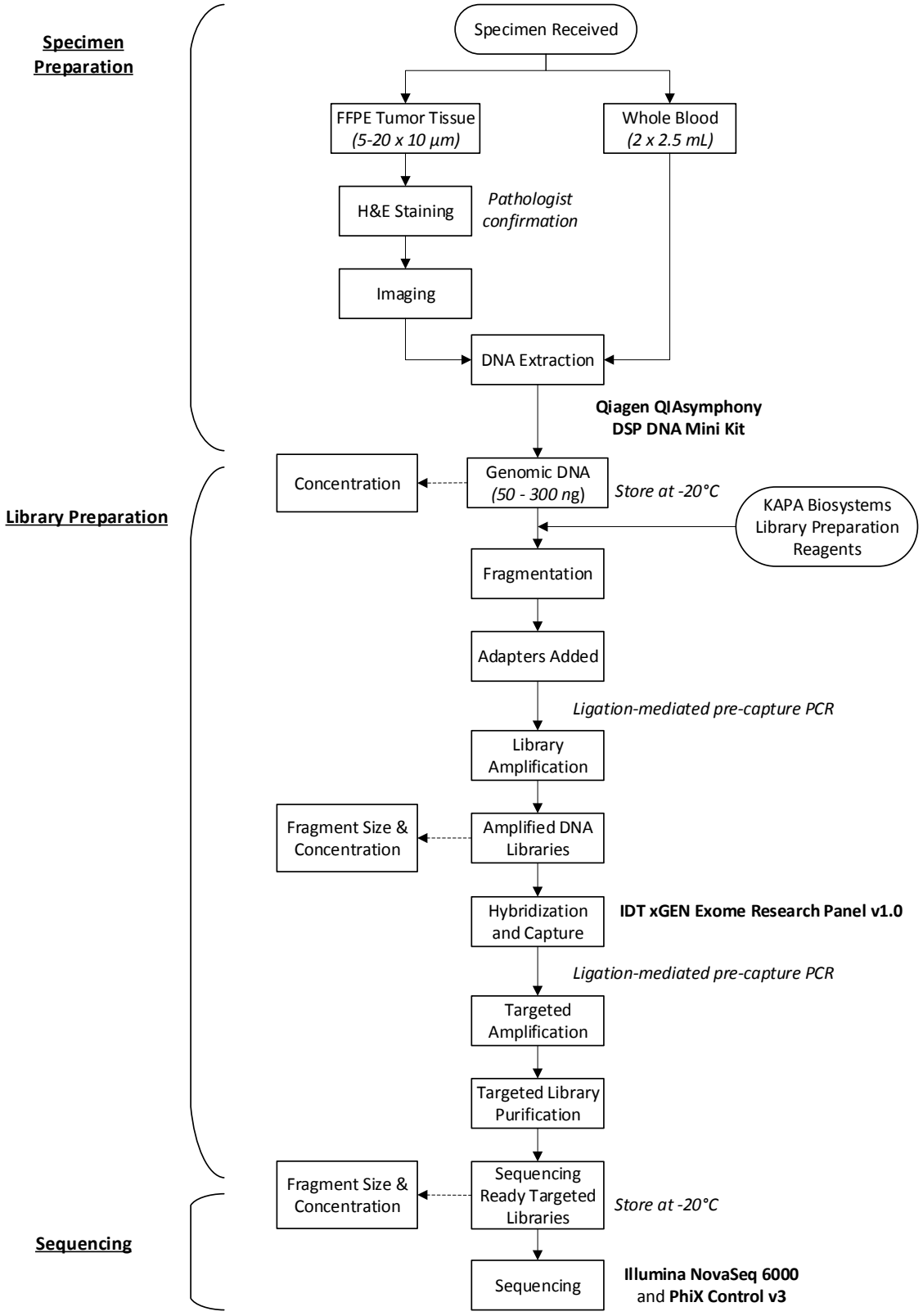
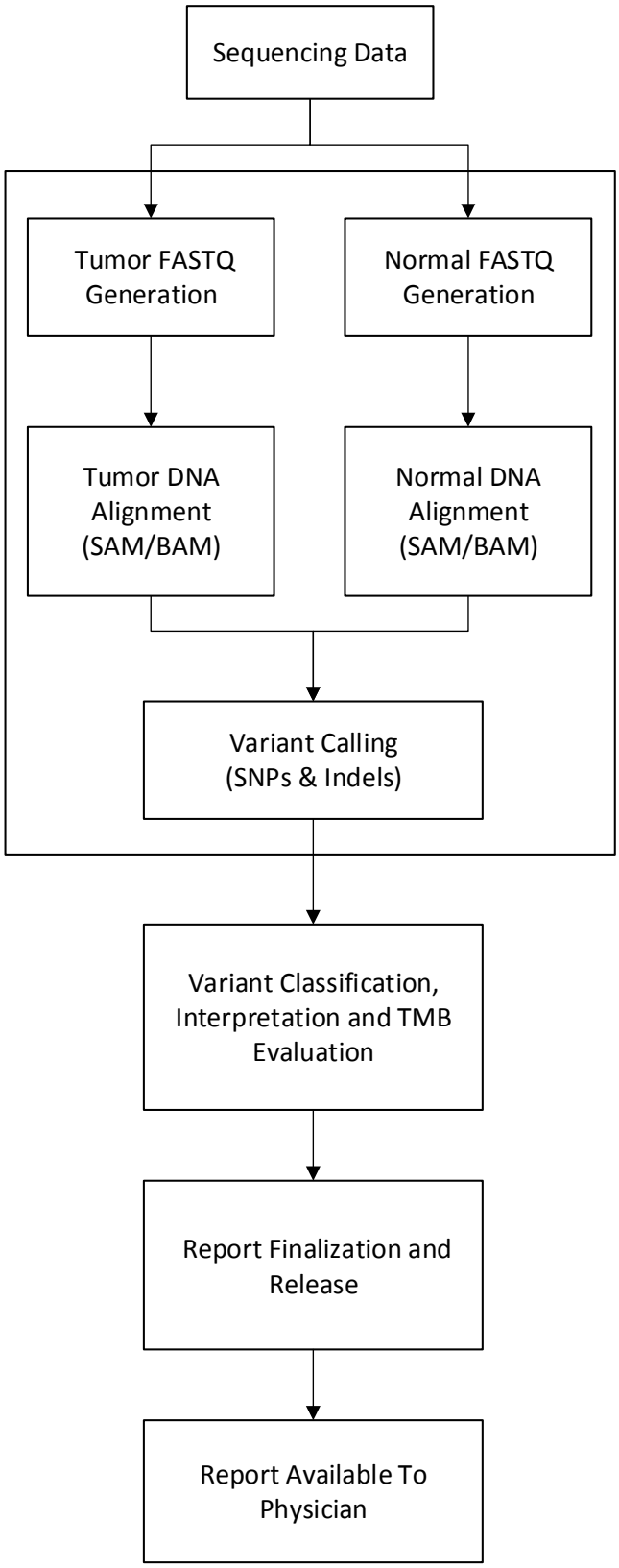


Figure 2: Bioinformatics Workflow



4.4. Indications For Use

The Omics Core assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and tumor mutational burden (TMB) for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. Omics Core is a single-site assay performed at NantHealth, Inc.

The Indications For Use statement for Omics Core is not identical to the predicate device. Omics Core is intended to provide information on tumor mutational burden (TMB) and not intended to provide information on microsatellite instability. Omics Core reports TMB as additional information on the tumor tissue. TMB is reported via two metrics: (1) total number of somatic non-synonymous exonic variants within the 19,396 genes (whole exome) surveyed and (2) a calculation of mutation rate by counting all somatic, synonymous and non-synonymous variants detected in gene coding regions and dividing by the approximate size of the exome (33.7 Mb). TMB is reported as mutations per megabase (mut/Mb) unit. Mutations included in the calculation of TMB must be present at 5% allele frequency or greater after direct comparison between tumor and matched normal DNA. TMB is reported as rate (not as High/Low) and as a mutation within the category of "Cancer Mutations with Potential Clinical Significance" to be signed off by the Medical Director. This difference does not constitute a new Indications For Use nor raises different issues of safety and effectiveness.

5. COMPARISON OF TECHNOLOGICAL CHARACTERISTICS WITH THE PREDICATE DEVICE

The primary technological characteristics and indications for use of the Omics Core assay are substantially equivalent to MSK-IMPACT. A substantial equivalence table comparing overall similarities and differences between Omics Core and MSK-IMPACT is provided in Table 2.

Table 2: Comparison of Omics Core with Predicate Device

Characteristics	**Predicate Device:** MSK-IMPACT (DEN170058)	**Subject Device:** Omics Core
Similarities		
Indications For Use	The MSK-IMPACT assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.	The Omics Core assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and tumor mutational burden (TMB) for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. Omics Core is a single-site assay performed at NantHealth, Inc.
Technology	Hybrid Capture	Same
Specimen Types	Formalin-fixed, paraffin-embedded (FFPE) tumor tissue matched with normal specimens from patients with solid malignant neoplasms	Same
Target Population	Patients with solid malignant neoplasms	Same
Genes on Panel for Reporting SNVs and Indels	468	Same
Test Environment	Single-site assay (performed at Memorial Sloan Kettering Cancer Center)	Same. Single-site assay (performed at NantHealth, Inc.)
Controls	• Matched normal • Positive control • Negative control • No template control (NTC)	Omics Core uses the same types of controls.

Characteristic	**Predicate Device:** MSK-IMPACT (DEN170058)	**Subject Device:** Omics Core
Differences		
Black List	73 exons	203 exons
Variant types	Intended to provide information on somatic mutations (point mutations and small insertions and deletions), and microsatellite instability	Same except Omics Core provides information on tumor mutational burden (TMB) and not microsatellite instability (MSI).
Instrument	Illumina HiSeq® 2500 Sequencing System	Illumina NovaSeq™ 6000 Sequencing System
Determination of Pipeline Thresholds	• Based on >200X target coverage, • 100X for ≥ 98% target exons, • hotspot mutation calling threshold (mutation coverage (DP) ≥ 20, mutant reads (AD) ≥ 8, mutation frequency (VF) ≥ 2%, and non-hotspot mutation threshold (DP ≥ 20, AD ≥ 10, VF ≥ 5%).	• Based on ≥ 500X target coverage, • ≥ 100X for 95% of target exons, and a mutation calling threshold of allele frequency (AF) ≥ 2% with Conf > 15 and heuristic filters, • The minimum read depth for variants in the Omics Core assay are allele depth (AD) ≥ 2 and overall depth (DP) ≥ 4.
Assay cut-off	MSK-IMPACT does not report mutations below 2% for known hotspot mutations and 5% for non-hotspot mutations.	Omics Core does not report mutations below 2% for all mutations.
Clinical Evidence Curation Oncopanel results are reported under one of these two categories: • "Cancer Mutations with Evidence of Clinical Significance" or • "Cancer Mutations with Potential Clinical Significance."	Classification criteria were developed by MSK using the in-house OncoKB database. OncoKB undergoes periodic updates through the review of new information by a panel of experts	Classification criteria were developed by NantHealth, Inc. NantHealth periodically updates Omics Core through the review of new information available.

6. PERFORMANCE DATA

Table 3 summarizes the performance data that are provided in support of the substantial equivalence determination. Performance specifications were established following special controls outlined for next generation sequencing based tumor profiling test (21 CFR 866.6080).

Table 3: Omics Core Performance Specifications

Characteristic	Performance Specifications
Specimens	The specimens accepted for testing are formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks and two vials of whole blood for the normal comparator. If a tumor block is not available, slides containing tumor sections are acceptable. The FFPE blocks and slides are prepared per industry standards by the requesting medical facility. Tumor sample requirements are 5-20 unstained sections, 10 microns thick. Tumor sections must have more than 10% of tumor cells; however, sections containing >20% viable tumor are preferred for testing.
Pre-Analytical	DNA samples are normalized to yield 50-300ng input in 60µl prior to shearing.

Characteristic	Performance Specifications
Precision	Precision was assessed using 12 FFPE clinical tumor samples and 1 commercial cell line. A total of 530 variants were identified in the samples that included 483 SNVs, 32 deletions, and 15 insertions. Precision – Panel-Wide Reproducibility: The overall positive call rate for all variants analyzed across the 12 FFPE clinical samples and one commercial cell line was 2607/2650, or 98.4% (97.8-98.8% CI). Three-hundred and ninety-eight (398) of 521 (76%) mutations in the clinical specimens had %CV ≤ 10%; 91 of 521 (17%) were between 10 and 20%; and 32 of 521 (6%) were > 20%. Precision – Per Specimen: Per specimen variant analysis for 12 clinical specimens and a commercial cell line demonstrated consistent repeatability and reproducibility by showing 100% concordance for 511 out of 530 unique mutations, or 96.4% (94.5%-97.8% CI). Precision – Well Characterized Reference Material: Analysis of the well characterized sample demonstrated consistent repeatability and reproducibility by achieving an overall positive call rate of 99.86% (99.75%-99.93% CI). Precision – TMB: TMB precision analysis was based on 12 clinical samples and 1 commercial cell line. The tumor purity for these samples ranged from 25% to 90%. The per sample TMB analysis demonstrated repeatable and reproducible TMB rates with a %CV <10% for all 13 samples.
Analytical Sensitivity – Limit of Detection	LoD – SNVs and Indels: The results from 13 FFPE clinical samples demonstrated the ability to detect and reliably call each variant class at the 5% mutant allele frequency with a success rate of ≥ 95%, with SNVs called at 96.7% (82.8%-99.9% CI), insertions at 100% (83.2%-100.0% CI) and deletions at 100.0% (78.2%-100.0% CI). LoD – TMB: Ten (10) FFPE tumor specimens, with tumor purities ranging from 10 to 20%, demonstrated consistent repeatability and reproducibility as all samples evaluated had a %CV < 10%. The Omics Core assay will evaluate and report TMB rates for clinical samples with tumor purities ≥ 20%.

Characteristic	Performance Specifications
Accuracy – Comparison To Orthogonal Method	<u>Accuracy – SNVs and Indels:</u> Accuracy was assessed by comparing Omics Core results to results obtained from the orthogonal method in a total of 401 FFPE tumor samples representing mutations covering 2,634 SNVs, 125 small insertions and 313 small deletions. Omics Core successfully detected mutations in all 401 samples assessed, representing accuracy of 100% (99.08-100% CI). • 2634 unique SNVs demonstrated PPA of 99.76% (99.50-99.90% CI), PPV of 99.93% (99.75-99.99% CI) • 125 unique small insertions demonstrated PPA of 100% (97.20-100.00% CI), PPV of 100% (97.20-100.00% CI) • 313 unique small deletions demonstrated a PPA of 99.71% (98.38-99.99% CI), PPV of 99.71% (98.38-99.99% CI) <u>Accuracy – TMB:</u> TMB accuracy was assessed by comparing the TMB rates generated by Omics Core and the orthogonal method. A linear regression demonstrated high correlation between the two methods ($R^2 = 0.9899$).
Accuracy – Supplemental Method Comparisons Study for Wildtype Calls	An analysis of 220 positive mutations and 12,612 wildtype calls demonstrated a PPA of 99.54% (97.48-99.99%) and NPA of 99.99% (99.99-100%).
Traceability	Omics Core assay is not traceable to any known standard. The assay uses matched normal whole blood as a matched normal control, a No Template Control (NTC), and positive and negative controls to monitor the ongoing performance of the assay.
Stability	Reagent stability is based on manufacturer expiration dating and supported by NantHealth verification. Stability of the reagent is monitored through the use of consistent controls.
Expected Values	The Omics Core assay does not use calibrators; however, the verification of mutant allele frequency is maintained by analysis of a positive control with expected allele frequencies.
Analytical Specificity	High analytical specificity is maintained by paired tumor/matched normal sequencing, and established during assay optimization. Interference is minimized with pre-analytic steps. Invalid rates in historical testing from >2,000 samples support that any interference from any challenging tissues is minimized.
Assay Cut-Off	Omics Core does not report mutations below 2% MAF. Mutations included in the calculation of TMB must be present at 5% allele frequency or greater.

Characteristic	Performance Specifications
Clinical Performance	The genes in the panel include those that play a role in cancer pathogenesis and tumor suppression, or for clinical or mechanistic information of relevance in the management of cancer patients. The assay reports mutations under two categories: "Cancer Mutations with Evidence of Clinical Significance" and "Cancer Mutations with Potential Clinical Significance" consistent with the intended use clinical settings. Mutations with evidence of clinical significance are represented in professional guidelines as established by consensus opinion of experts in the healthcare community.
Software Verification and Validation Testing	Software level of concern: MODERATE Verification and validation testing conducted as per FDA's Guidance for Industry and FDA Staff, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" and "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices"

7. SUMMARY

The submitted information in this 510(k) notification supports the Indications For Use for Omics Core and demonstrates that the Omics Core assay is as safe and effective as the predicate device and therefore supports a substantial equivalence conclusion.