Germline DNA mutations that increase the susceptibility of a patient to certain cancers have been identified in specific genes. Patients can be screened for mutations in these genes to assess their level of risk for developing cancer. In the era of preventive medicine, the detection of germline mutations in blood samples from patients can be extremely useful for identifying patients at high risk of developing a malignancy.

Circulogene has developed and validated a 30-gene hereditary panel to assess genetic risk for cancer or familial hypercholesterolemia (FH) using next generation sequencing (NGS) techniques. This genetic information can be used to guide medical management as well as genetic counseling for at-risk family members. The earlier the information can be provided to the patients; the more options can be explored.

Clinical utilization of this test could increase the identification of patients at high risk for these diseases and potentially improve care by changing surveillance procedures and/or treatment of malignancies at a cost that is comparable to that of a single gene test.

The genes in the panel were selected because they could provide clinically significant data, not just an assessment of risk.

Test Performance

The intra-assay precision for hereditary genetic test is >99%. The inter-assay precision for hereditary genetic test is >99%.

### Test Accuracy

Overall test accuracy of Circulogene’s Hereditary Gene Panel Test assessed by comparing with results from Sophia Genetics’ 27-gene NGS test (another CLIA lab using different library chemistry and different sequencing platform) was >99%.

Traditional methods using Sanger sequencing focus on small groups of genes and therefore are unable to screen for numerous genes from multiple patients simultaneously. The Hereditary Gene Panel Test by next-generation Sequencing is a laboratory-developed test for the detection and genotyping of 30 well-characterized and well-documented cancer- and FH-associated genes in high-risk population.

**DNA sequences used as references for this panel of genes can be found at** http://www.ncbi.nlm.nih.gov/refseq/rsg/. Variants were classified using methods consistent with American College of Medical Genetics and Genomics Guidelines and the Human Genome Variation Society (http://www.hgvs.org/mutnomen/).
In hereditary cancers, insight into genomic risk factors helps steer improved patient care. Circulogene’s cutting-edge bioinformatics applies artificial intelligence, machine-learning and database-driven algorithms to deliver highest quality and most accurate SNV, INDEL and structural variant analysis and classification to clinic.

Aggregated Data From Diverse, First-Class Sources
- Automated, validated and up to date with built-in quality systems
- Data from diverse, first-class data sources aggregated, organized, aligned, annotated and classified
- Constant variant reclassification every 3 weeks

Advanced and Fully Integrated AI Greatly Enhances Confident Calls.
- Machine-educated variant calling of pathogenic, likely pathogenic, VUS variants, including automatic pre-classification
- Approx. 200,000 “global inter-lab” calling data sets, on top of eight major public databases to achieve unparalleled accuracy

Big Data-Sharing With Global Medical Community
- Fast, accurate raw data analysis and data sharing with variant calling and annotation
- Regular upload of our reported variants to share with broader medical community

Comprehensive Intuitive Report
- Variant details
- Clinically relevant and actionable information
- Follows ACMG and AMP guidelines for all mutation types
- Simplified data mining correlates millions of internal and external medical data sources, (both public & private)

Complete End-to-End Solution
- Patient centric
- Data analysis
- Classification
- Interpretation and reporting

Security and Privacy
- HIPAA compliant
- Long-term cloud storage
- Clinical grade security, privacy and compliance

OVER 2 MILLION VARIANT CALL DATA
Unlike most labs that use free, public databases, or rely on their own public-inaccessible databases, Circulogene has built a proprietary aggregate integrating the 8 largest public databases with a global community variant-calling atlas.

HUMAN GENETIC VARIANT DATABASES:

- **The Genome Aggregation Database (gnomAD)**
  Variants of 15,496 genomes and 123,136 exomes from seven populations worldwide

- **ClinVar**
  Currently holds >160,000 submitted interpretations, representing >130,000 variants, affecting >26,000 genes

- **COSMIC**
  >170,000 mutations, >2.9 million experiments, >500,000 tumors

- **ExAC**
  60,706 exomes from seven populations

- **ESP**
  6,503 exomes from European Americans and African Americans

- **1000 Genomes Project**
  Genomic data for 2,504 individuals from five populations

- **CG69**
  69 individuals with complete genomes

- **dbNSFP**
  83,422,341 nsSNVs and ssSNVs (splicing-site SNVs)