MAYO CLINIC LABORATORIES

# Test Definition: HSCHP

High Sensitivity Clonal Hematopoiesis Panel, Next-Generation Sequencing, Blood

## Overview

### Useful For

Evaluating clonal hematopoiesis (CH) prior to initiation of genotoxic therapy

Monitoring clonal evolution and the emergence of clinically relevant clones throughout the course of genotoxic treatment

Distinguishing tumor driver mutations from CH-associated variants

Evaluating patients with unexplained cytopenias persisting for greater than 4 months after secondary causes have been reasonably excluded

Providing molecular evidence, in conjunction with blood cell counts, morphology, and other clinical findings, to support ruling in or ruling out a suspected myeloid malignancy

### Genetics Test Information

This test utilizes highly sensitive next-generation sequencing to detect single nucleotide variants (SNVs) and small deletion-insertions (delins) in 37 genes associated with clonal hematopoiesis (CH). This panel identifies variants in: *ASXL1, ATM, BARD1, BCOR, BCORL1, BRAF, BRCA1, BRCA2, BRIP1, CBL, CHEK2, DNMT3A, EZH2, GATA2, IDH1, IDH2, JAK2, KRAS, NRAS, PALB2, PHF6, PPM1D, PTPN11, RAD21, RAD51C, RAD51D, RUNX1, SETBP1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1,* and *ZRSR2.* See Targeted Genes and Methodology Details for High Sensitivity Clonal Hematopoiesis Panel for details regarding the targeted gene regions evaluated by this test.

### Method Name

Targeted Next-Generation Sequencing (NGS)

### NY State Available

No

## Specimen

### Specimen Type

Varies

### Ordering Guidance

This test is **not** a prenatal screening test. For prenatal screening, consider QUAD1 / Quad Screen (Second Trimester) Maternal, Serum.

Multiple oncology (cancer) gene panels are available. For more information see Hematology and Oncology Test Selection

Guide.

## Specimen Required

**Patient Preparation:** A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.
**Specimen Type:** Whole blood
**Container/Tube:** Lavender top (EDTA) or yellow top (ACD)
**Specimen Volume:** 3 mL
**Collection Instructions:**
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
3. Whole blood collected postnatal from an umbilical cord is also acceptable. See Additional Information
**Specimen Stability Information:** Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days
**Additional Information:**
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. For postnatal umbilical cord whole blood specimens, maternal cell contamination studies are recommended to ensure test results reflect that of the patient tested. A maternal blood specimen is required to complete maternal cell contamination studies. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal blood specimens under separate order numbers.

## Specimen Minimum Volume

See Specimen Required

## Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

## Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| Varies | Ambient (preferred) | | |
| | Refrigerated | | |
| | Frozen | | |

# Clinical & Interpretive

## Clinical Information

Clonal hematopoiesis (CH) is an age-related condition in which certain hematopoietic stem cells acquire genetic changes that allow them to proliferate and expand. Clonal hematopoiesis of indeterminate potential (CHIP) is defined by somatic mutations with a variant allele fraction (VAF) greater than 2% in the absence of hematologic malignancy. CHIP is associated with increased inflammation and an elevated risk of developing myeloid neoplasms (MNs). CH can also occur

after exposure to chemotherapy or radiation. When this happens, it is referred to as therapy-induced CH (t-CH) or context-relevant CH (CR-CH). CR-CH can affect how patients with solid tumors respond to treatment and can influence overall outcomes.(1-3) Chemotherapy and radiation can drive the growth of existing or newly developed t-CH and increase the risk of therapy-related myeloid neoplasms.(4-6) CH may also be identified in patients with unexplained cytopenias persisting for greater than 4 months after other possible causes have been reasonably excluded and may contribute to the diagnostic evaluation of a suspected myeloid malignancy.(7,8)

This test analyzes peripheral blood to detect somatic mutations that are known to be associated with CH. The results can help a patient's healthcare professional make more informed decisions about the use of chemotherapy, radiation or radionuclide therapies. It can also help guide personalized monitoring strategies to reduce therapy-related hematologic toxicities. In patients with persistent unexplained cytopenias persisting for greater than 4 months after other possible causes have been reasonably excluded, results may provide molecular evidence of clonality that can be used in conjunction with blood counts, morphology, and other clinical findings to support ruling in or ruling out a suspected myeloid malignancy. The assay’s limit of detection may also enable detection of CHIP- or CCUS-associated variants. This test reduces the risk of false-positive liquid biopsy results that could lead to unnecessary PARP inhibitor treatment, reported in up to 10% of prostate cancer cases.(9)

In addition to helping guide treatment and monitoring, CH- or CHIP-related mutations, when identified, can offer valuable prognostic information, inform clinical trials eligibility, and support risk-adapted patient monitoring strategies. In patients with unexplained cytopenias persisting for greater than 4 months after other possible causes have been reasonably excluded, test results may also support further diagnostic evaluation of a suspected myeloid malignancy.

### Reference Values

An interpretive report will be provided.

### Interpretation

The interpretation of molecular biomarker analysis includes an overview of the results and the associated implications.

### Cautions

Test results should be interpreted in the context of clinical laboratory data. If results obtained do not match other clinical or laboratory findings, contact the laboratory for discussion. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

This test may not differentiate between somatic mutations and germline alterations.

This test does not detect large structural variants or copy number changes. This test does not reliably detect insertions larger than approximately 119 base pairs and deletions larger than approximately 129 base pairs

A negative (ie, wildtype) result does not rule out the presence of an alteration that may be present but below the limits of detection of this assay.

The presence or absence of a variant may not be predictive of response to therapy in all patients.

### Supportive Data

Validation studies demonstrated a limit of detection of 0.25% variant allele frequency (VAF) for single nucleotide

variants (SNVs) and deletion-insertions (delins), supported by a minimum deduplicated coverage depth of greater than or equal to 500× and a minimum DNA input of 40 ng. Variants with observed VAFs as low as 0.15% may be reported.

Analytical accuracy studies demonstrated 100% sensitivity for SNVs and 98.9% sensitivity for delins, with positive predictive value of 100% for SNVs and 99.0% for delins when compared with orthogonal next-generation sequencing methods and high-sensitivity confirmatory testing. Base-by-base sequencing accuracy assessed using well-characterized reference materials demonstrated greater than or equal to 99.99% accuracy.

### Clinical Reference

1. Diplas BH, Ptashkin R, Chou JF, et al. Clinical importance of clonal hematopoiesis in metastatic gastrointestinal tract cancers. JAMA Netw Open. 2023;6(2):e2254221doi:10.1001/jamanetworkopen.2022.54221
2. Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. Cell Stem Cell. 2017;21(3):374-382.e4. doi:10.1016/j.stem.2017.07.010
3. Mayerhofer C, Sedrak MS, Hopkins JO, et al. Clonal hematopoiesis in older patients with breast cancer receiving chemotherapy. J Natl Cancer Inst. 2023;115(8):981-988. doi:10.1093/jnci/djad065
4. Morton LM, Dores GM, Schonfeld SJ, et al. Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. JAMA Oncol. 2019;5(3):318-325. doi:10.1001/jamaoncol.2018.5625
5. Hsu JI, Dayaram T, Tovy A, et al. PPM1D mutations drive clonal hematopoiesis in response to cytotoxic chemotherapy. Cell Stem Cell. 2018;23(5):700-713.e6. doi:10.1016/j.stem.2018.10.004
6. Kahn JD, Miller PG, Silver AJ, et al. PPM1D-truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. Blood. 2018;132(11):1095-1105. doi:10.1182/blood-2018-05-850339
7. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228. doi:10.1182/blood.2022015850
8. Malcovati L, Gallì A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood. 2017;129(25):3371-3378. doi:10.1182/blood-2017-01-763425
9. Jensen K, Konnick EQ, Schweizer MT, et al. Association of clonal hematopoiesis in DNA repair genes with prostate cancer plasma cell-free DNA testing interference. JAMA Oncol. 2021;7(1):107-110. doi:10.1001/jamaoncol.2020.5161

## Performance

### Method Description

The high sensitivity clonal hematopoiesis panel is a capture-based next-generation sequencing assay designed to detect single nucleotide variants (SNVs) and small deletions-insertions (delins) across defined regions in 37 genes associated with clonal hematopoiesis using whole blood-derived genomic DNA. The human genome reference GRCh37/hg19 build was used for sequence read alignment. Refer to the final patient report for gene transcript information referenced at the time of testing. Confirmation of selected reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

See Targeted Genes and Methodology Details for High Sensitivity Clonal Hematopoiesis Panel for details regarding the

targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

### PDF Report
No

### Day(s) Performed
Varies

### Report Available
9 to 15 days

### Specimen Retention Time
Whole blood: 28 days (if available); Extracted DNA: 3 months

### Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

## Fees & Codes

### Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

### Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

### CPT Code Information
81479

### LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| HSCHP | HS Clonal Hematopoiesis Panel | In Process |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| 623138 | Result | 82939-0 |
| 623139 | Interpretation | 69047-9 |
| 623140 | Additional Information | 48767-8 |
| 623141 | Specimen | 31208-2 |
| 623142 | Method | 85069-3 |
| 623143 | Disclaimer | 62364-5 |

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|---|---|---|
| 623670 | Released By | 18771-6 |