MOLECULAR HEALTH
MENDEL

Date of birth	—	Patient ID	—
Suspected disease	Hereditary Cancer	ICD-10-CM	—

Case ID	—	Software version	—	Ordering physician	—
Ethnicity	—	General dataset ID	—	Email	—
Sex	Male	CVI dataset ID	—	Phone	—
Labtest	—	Collected	—	Fax	—
				Product	MH Mendel
				Report	—

Summary

Variants associated with the selected disease(s)

Disease / inheritance	Variant	Zygosity	Classification
Colorectal cancer, hereditary nonpolyposis, type 5 Autosomal dominant inheritance	MSH6 p.F1088fs	heterozygous	Pathogenic

Disease details

Colorectal cancer, hereditary nonpolyposis, type 5 — Autosomal dominant inheritance

Hereditary non-polyposis colorectal cancer 5: An autosomal dominant disease associated with marked increase in cancer susceptibility. It is characterized by a familial predisposition to early-onset colorectal carcinoma (CRC) and extra-colonic tumors of the gastrointestinal, urological and female reproductive tracts. HNPCC is reported to be the most common form of inherited colorectal cancer in the Western world. Clinically, HNPCC is often divided into two subgroups. Type I is characterized by hereditary predisposition to colorectal cancer, a young age of onset, and carcinoma observed in the proximal colon. Type II is characterized by increased risk for cancers in certain tissues such as the uterus, ovary, breast, stomach, small intestine, skin, and larynx in addition to the colon. Diagnosis of classical HNPCC is based on the Amsterdam criteria: 3 or more relatives affected by colorectal cancer, one a first degree relative of the other two; 2 or more generation affected; 1 or more colorectal cancers presenting before 50 years of age; exclusion of hereditary polyposis syndromes. The term 'suspected HNPCC' or 'incomplete HNPCC' can be used to describe families who do not or only partially fulfill the Amsterdam criteria, but in whom a genetic basis for colon cancer is strongly suspected.

Pathogenic MSH6 p.F1088fs heterozygous

Phenotype association based on ClinVar:89364

PubMed ID
28492532, 25741868, 26467025, 24033266, 26681312, 25980754, 21642682, 26845104, 23757202, 20028993, 12658575, 20487569, 20587412, 18301448, 28195393, 24689082, 17453009, 15483016, 17117178, 18809606, 16807412, 15365995, 26318770, 25117503, 24100870, 25110875, 20045164, 21674763, 28481244, 25194673, 9929971, 9307272, 24068316, 15837969

Molecular Health glossary

Biomarker:
In general, a biomarker is any characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological response to a therapeutic intervention. In the context of MH Guide, reported biomarkers predict a patient's response to therapy and are based on the characterization of the patient/tumor genomic DNA. Depending on the analysis type, such genomic characteristics can include single nucleotide variants (SNVs), insertions and deletions (indels), fusion genes, and copy number alterations (CNAs).

Classification:
The variants listed can either be unclassified or they can be assigned to an ACMG classification. ACMG classifications of variants can be Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, or Benign. Source: Richards S., Aziz N., Bale S., Bick D., Das S., Gastier-Foster J., Grody W.W., Hegde M., Lyon E., Spector E., Voelkerding K., Rehm HL.; ACMG Laboratory Quality Assurance Committee "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, " Genetics in Medicine, vol. 17, issue 5, pp. 405-24, 2015, doi: 10.1038/gim.2015.30.

Inheritance:
The inheritance type of a disease describes the circumstances under which a disease is passed from one generation to the next. Diseases with a dominant inheritance type are always passed on to the next generation, while diseases with a recessive type may not be passed on, if only a heterozygous variant associated with the disease is detected.

PubMed ID:
A PubMed identifier is a unique number assigned to each PubMed record - also termed PMID. A PMID can be used to retrieve a specific publication from the PubMed database by entering the PMID in the search box on the PubMed site at http://www.ncbi.nlm.nih.gov/pubmed.

Zygosity:
The zygosity of a variant can be homozygous, heterozygous, or hemizygous. Homozygous and hemizygous means the variant was detected on all copies of the gene, heterozygous means the variant was detected on only one of the copies of the gene, and one healthy copy of the gene is still present. Zygosity tells you more about the inheritance type of the variant.

Molecular Health disclaimer

Molecular Health Guide Mendel (MH Mendel) is a bioinformatics software for the annotation of genetic data. It provides variant annotation data to support physicians in classifying variants and storing variant classifications for future cases. It enables medical experts to generate a customizable clinical report that includes a list of annotated variants they identified as clinically relevant and a conclusion explaining the reasoning behind this decision.

The MH variant detection pipeline covers:

1. Processing of a patient's genetic alterations
2. Aggregation, integration, collation, and maintenance of up-to-date biomedical reference information.
3. Mapping of the patient's genetic alterations to the biomedical reference information.
4. Integration of the patient's genetic alterations based on the mapping to biomedical reference information.
5. Generation of a customizable clinical report by a trained user (an MH-certified physician), providing links to the sources of evidence of the information displayed, for full traceability.

The information consolidated into the clinical report is the result of comprehensive filter settings based on values defined by the MH-certified physician. The MH-certified physician is neither a contractor nor an employee of MH. The information provided in the report must be evaluated in conjunction with all other relevant clinical information of the patient.

The information provided in this disclaimer may not be applicable when the product is used in other configurations than the MH standard configuration.

The contents of the clinical report, a result of mapping patient data against the MH Guide database, followed by the selection of diagnosis- and phenotype-relevant information by the MH-certified physician, are for use only as additional assistance for diagnosing. Interpretation of the report contents must occur in consultation with a medical expert. Decisions on patient diagnosis, care, and treatment must be based on independent medical judgment, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the applicable standard of care. Decisions regarding diagnosis, care, and treatment should not be based solely on the information contained in this report.

The identification of a genomic alteration does not necessarily imply a definite diagnosis. Also, the absence of a reported diagnosis does not necessarily invalidate a suspected diagnosis.

The following phenotypes are excluded from the intended use: blood groups; infections and infectious diseases; irregular anti-erythrocytic antibodies; the hereditary disease phenylketonuria; the HLA tissue groups DR, A, and B; the tumoral marker PSA, and the risk of trisomy 21.

MH Mendel supports annotation of single nucleotide variants (SNVs), insertions, deletions, and indels, copy number alterations (CNAs), and fusion genes from VCF data. MH Mendel also supports annotation of manually added wild-types, methylation, gene expression, protein expression, microsatellite instability, and tumor mutational burden data.

MH Mendel can detect single nucleotide variants (SNVs), insertions and deletions (indels).

The quality of the results from MH Mendel depends on the quality of the input data submitted by a lab on behalf of the MH-certified physician. The accuracy, analytic sensitivity, and specificity of the variant lists is the sole responsibility of the MH-certified physician.

For ethnicity Japanese (JPT) a population-specific reference genome based on ToMMo 3.5KJPNv2 (MAF>=1%) is used for sequencing alignment. Additionally, population frequencies from ToMMo 3.5KJPNv2 (MAF>=1%) are available in the application for display and filtering.

MH Mendel uses and contains data and information obtained from third-party sources. Molecular Health GmbH (MH) uses reasonable efforts to ensure that this information is as accurate as possible in a tightly controlled QA process. However, MH cannot guarantee that data from any third party are accurate, comprehensive, and complete. Thus, MH Mendel may not contain all relevant or all up-to-date information. Third-party databases or other sources in MH Mendel may only be updated from time to time with new or revised information.

MH Mendel has not been cleared or approved by the U.S. Food and Drug Administration (FDA). However, MH Mendel using VCF as input is offered as a bioinformatics service under CLIA.
In the European Union, MH Guide Mendel (MH Mendel) is registered as an in vitro diagnostic medical device (IVD).

MH is the legal manufacturer of MH Mendel as a stand-alone software, the statutory provisions of the German Medical Devices Act (MPG) and the European Directive 98/79/EC apply to MH. We therefore maintain a quality management system according to EN ISO 13485 for the scope of "Design, Development and Manufacture of software systems for the integrated analysis of clinical and genomic patient data to support treatment decisions and provision of related services." MH has also received CLIA certification and CAP accreditation for the provision of MH Mendel as a dry lab service to clinical laboratories in the US.

MH Guide is a registered trademark of Molecular Health GmbH.