

For molecular pathologists

MOLECULAR HEALTH  
**GUIDE**



## Get ready for the future of gene variant interpretation with Molecular Health Guide

With MH Guide you get full access to the global clinical knowledge data platform Dataome, with today over 28,000 gene variant-drug relations.



# About MH Guide


MH Guide is an automated clinical interpretation software that accepts any variant list in VCF file format. These files contain structured information regarding the beginning and end positions of the genetic variant, a measure for the observation quality, the variant type, and copy number changes, total read count, and reference and alternate allele frequencies.

With MH Guide Premium, MH Guide can be expanded with a bioinformatic pipeline that accepts raw sequencing data (FASTQ files) or aligned sequencing data (BAM files).

MH Guide also supports output from non-NGS methods such as FISH, IHC, (q)PCR, and microarrays. Data that is not compatible with VCF format can be added manually (e.g. protein expression data).

Regardless of the origin of the VCF file, the MH Guide automated analysis interprets the patient’s genetic variants using data derived from the global clinical knowledge data platform, Dataome, containing up-to-date published scientific and biomedical evidence on cancer treatments, pathways, genes, variants, and clinical trials.

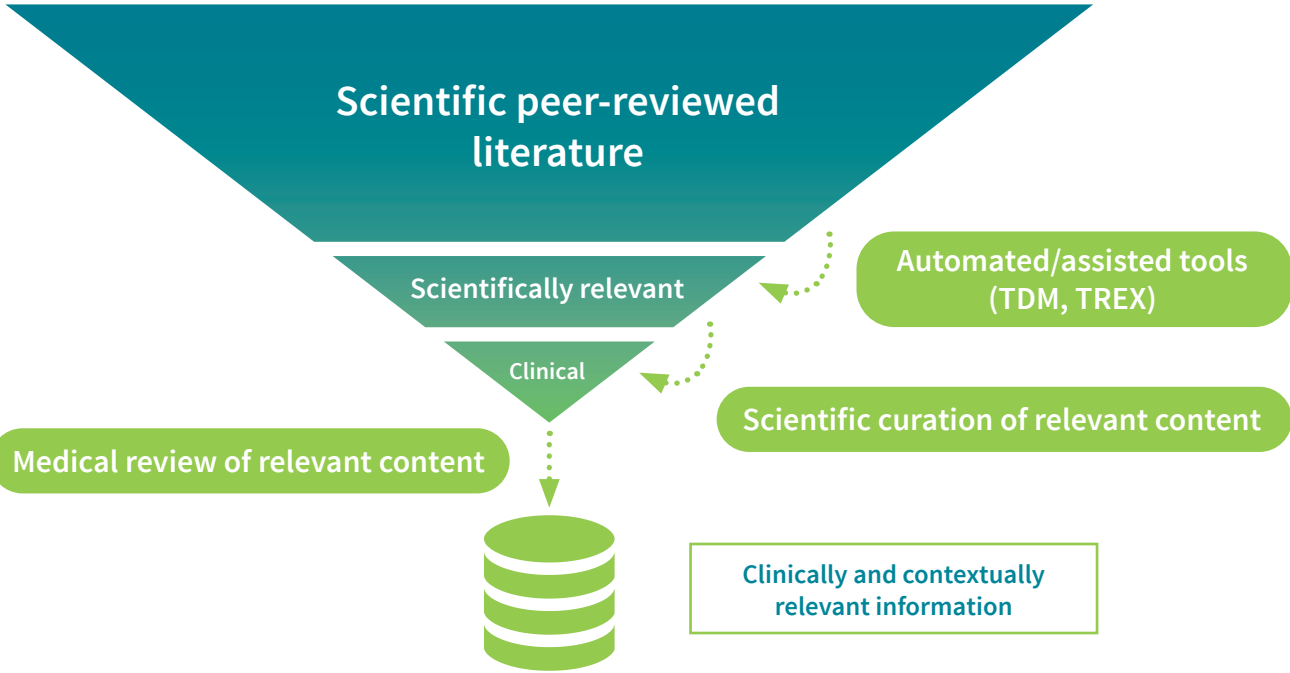
# Dataome, the backbone of MH Guide



**Dataome**, a global clinical knowledge data platform, is based on large biomedical and drug data sets combined with novel artificial intelligence and machine learning (AI/ML) technologies. It provides unparalleled evidence by connecting real-world patient outcome data to up-to-date state of clinical and molecular knowledge.

**28,000 curated gene variant ↔ drug relations**

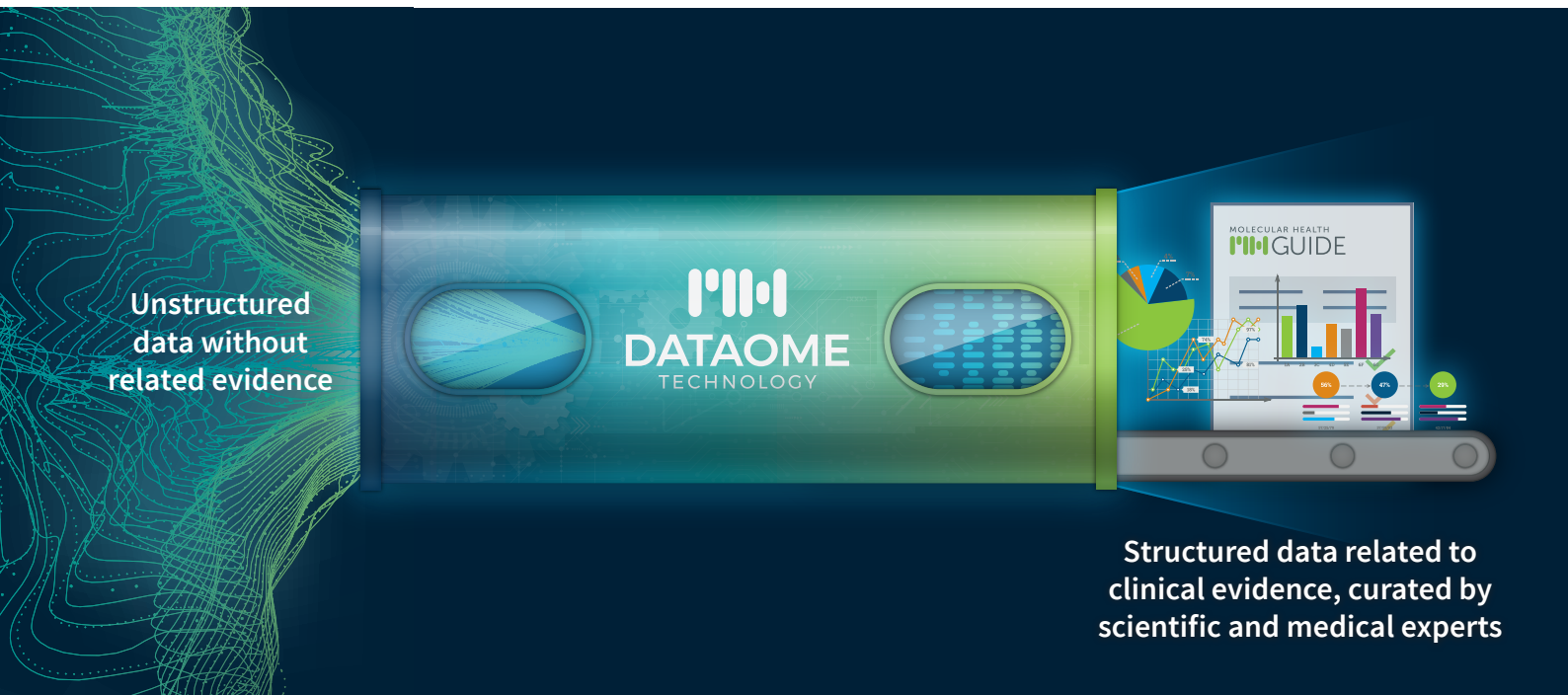
# Quality assurance by curation of data



Molecular Health provides quality assurance by curation of data – a sophisticated process, in which the data is regularly updated and finally curated by medical and scientific experts.

Our regular updates of MH Guide assure that information about new biomarkers and approved drugs is implemented quickly so that you get the information you need.

Dataome is the ultimate data source for MH Guide



Dataome integrates data from various data resources:

- **For variant identification and biomarker annotation:** ACMG variant classification<sup>1</sup>, COSMIC<sup>2</sup>, BRCA Exchange<sup>3</sup>, CVIs (proprietary of Molecular Health), AMP/CAP/ASCO classification<sup>4</sup>, GNOMAD based population frequencies<sup>5</sup>, and others
- **For recommendation of drugs and clinical trials:** WHO and NCT clinical trials, Drug Dev Stages (Global), NCCN guidelines, curated ESMO guidelines, Clinical Trial NGS Biomarker, and others

Dataome contains structured data that were integrated using ETL (extract, transform, load) processes, and data from unstructured sources (free text).

Interested in becoming a  
curation expert for MH Guide?  
Let us know!

From NGS data to treatment options:  
Clinical Variant Interpretation (CVI)

MH Guide analyzes NGS data from commercial or customized panels, and WES to identify and interpret relevant gene variants detected in the patient’s tumor. We call this clinical variant interpretation.



**Preferred CVI:**

System

**Impact:**

effective

**Match quality:**

✓

**Biomarker score:**

3 II D

**Narrative:**

The small GTPase KRAS activates the RAS/MAPK signaling pathway to promote cell proliferation and survival. In preclinical studies this variant promotes transformation due to enhanced downstream signaling. Preclinical models revealed that pancreatic cancer cells with KRAS codon 12 mutations were sensitive to MEK inhibitors trametinib, selumetinib, binimetinib, refametinib, or moderately sensitive to cobimetinib.

**Comment:**

**Impact**

- Predictive (effective, ineffective, safety)
- Diagnostic
- Prognostic

**Biomarker score**

- CVI score: preclinical (1-3), clinical (4-6), clinically approved (7)
- AMP score

**Narrative**

Summary of the CVI

**Variants**

- Gene name
- Variant name (HGVS)
- Somatic or germline
- Zygosity

**Diseases**

List of diseases related to the variant

**Treatments**

- List of treatments
- CVI score and AMP score

**References**

List of publications and their corresponding PubMed IDs

**Treatments**

Azd4785  
Binimetinib  
Cobimetinib  
Refametinib  
Selumetinib  
Trametinib

**References**

Liu P et al. Targeting the untargetable KRAS in cancer therapy. Acta pharmaceutica Sinica. B. 2019 Sep; 9(5) (PubMed ID: 31649840)

Waters AM, Der CJ. KRAS: The Critical Driver and Therapeutic Target for Pancreatic Cancer. Cold Spring Harbor perspectives in medicine. 2018 Sep; 8(9) (PubMed ID: 29229669)

Brauswetter D et al. Molecular subtype specific efficacy of MEK inhibitors in pancreatic cancers. PloS one. 2017; 12(9) (PubMed ID: 28357477)

Hamidi H et al. KRAS mutational subtype and copy number predict in vitro response of human pancreatic cancer cell lines to MEK inhibition. British journal of cancer. 2014 Oct; 111(9) (PubMed ID: 25167228)

Jing J et al. Comprehensive predictive biomarker analysis for MEK inhibitor GSK1120212. Molecular cancer therapeutics. 2012 Mar; 11(3) (PubMed ID: 22169769)

Each CVI is based on published biomedical knowledge.

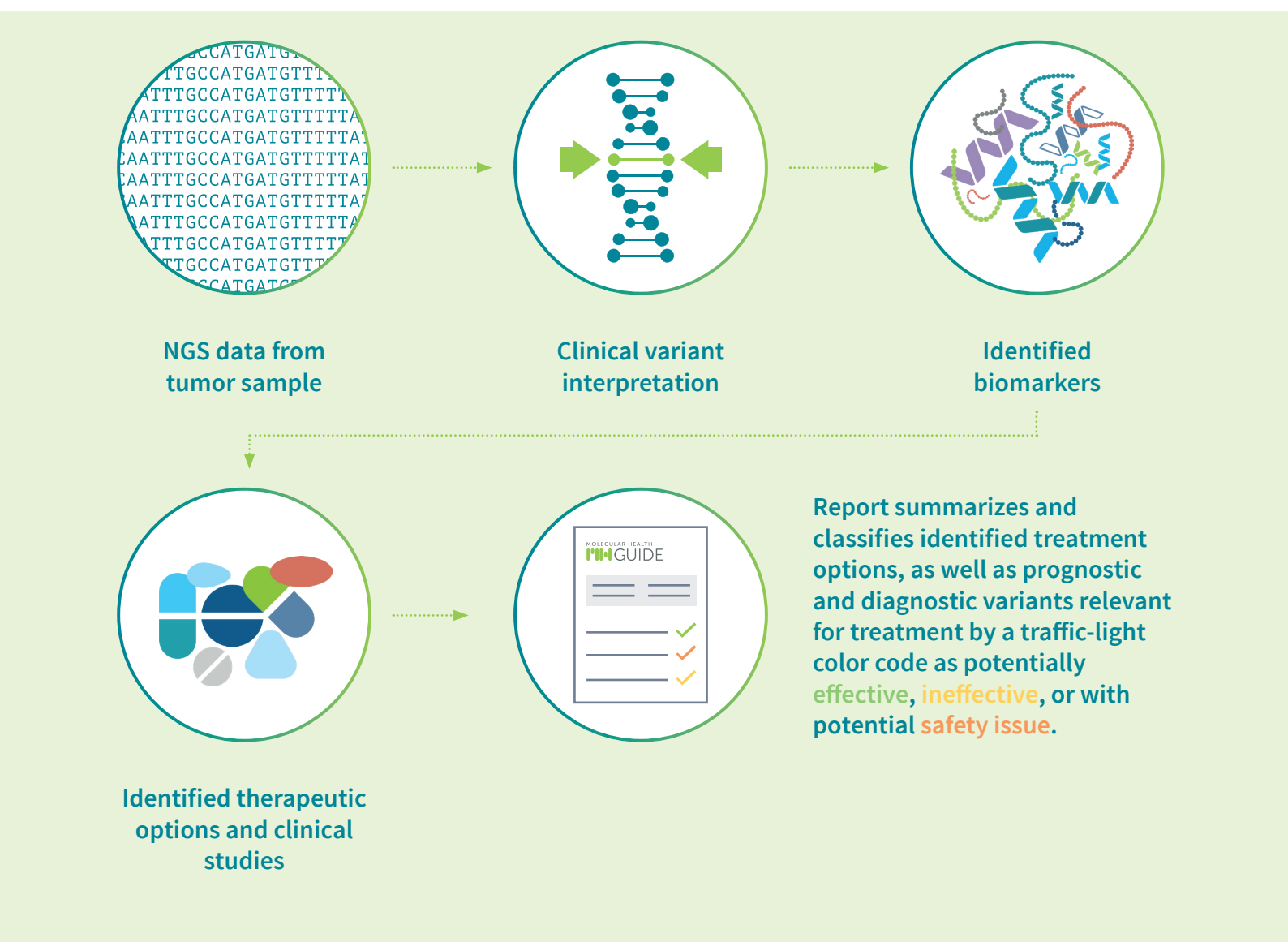
Each CVI lists the relevant information regarding the variant, lineage (germline or somatic), disease association, treatment (drug or drug combination), treatment impact (effective, ineffective, toxic), prognostic or diagnostic biomarkers, biomarker validity (preclinical, clinical, clinically approved), and a narrative summarizing the clinical knowledge available for the variant.

If relevant, information on developmental stage of the drug(s) and potentially recruiting clinical trials is added.

Any conflicting evidence is also reported. Standard output formats are PDF, JSON and XML. An adapter is available to adapt the output to other formats, if required.



# From NGS data to MH Guide report

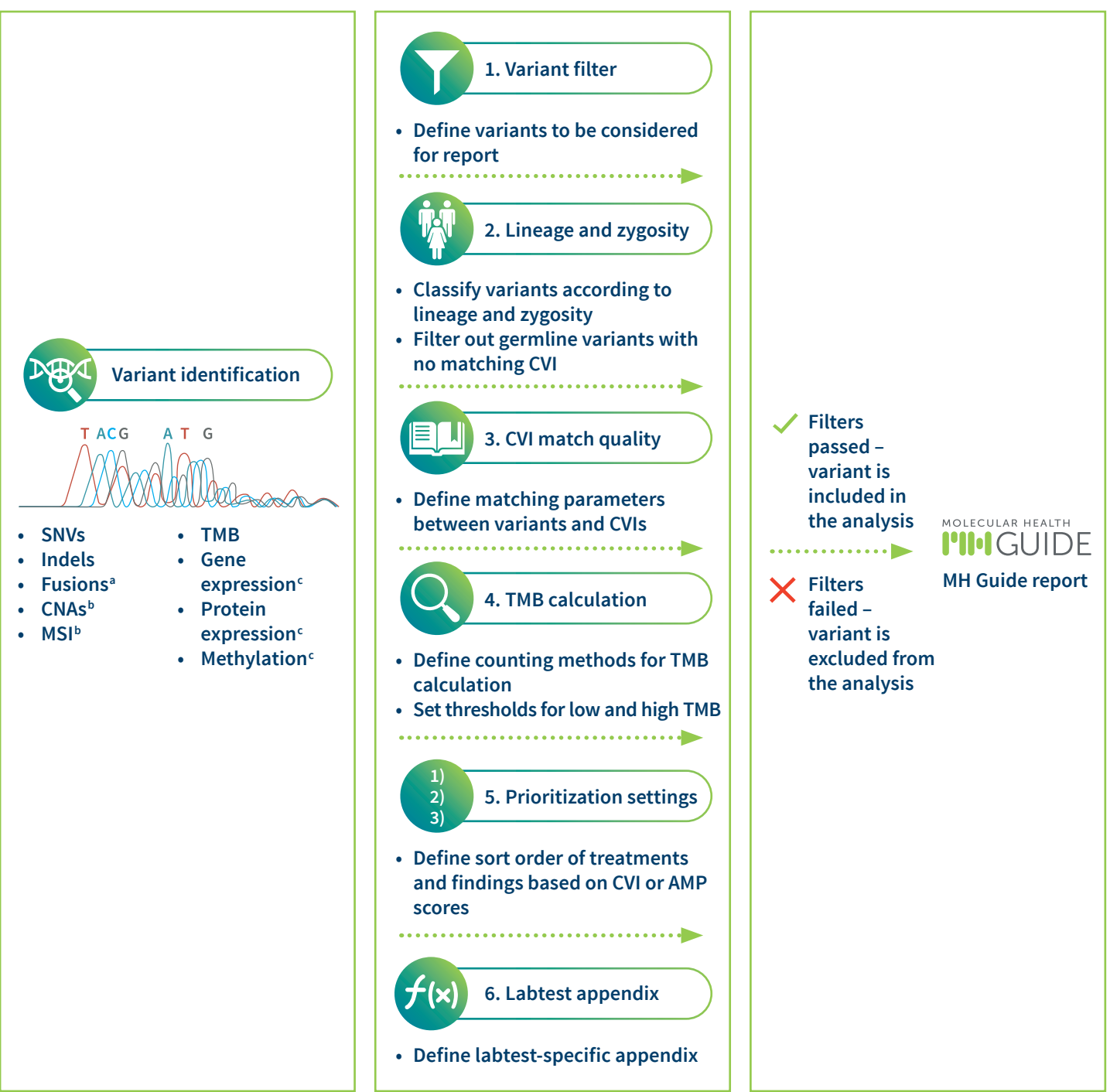


The CE-marked IVD software MH Guide and MH Guide Premium supply curated variant interpretations, which are reviewed by scientific and medical experts. These provide unparalleled evidence for treatment decisions by connecting real-world patient outcome data with up-to-date clinical and molecular knowledge.

**MH Guide** data analysis starts with the variant call format (VCF) of the NGS data, from either customized or commercial panels, or from WES. Moreover, MH Guide can analyze data from other assays that report detected variants in VCF format.

**MH Guide Premium** allows interpretation of NGS data from FASTQ files, from either customized or commercial panels, or from WES.

# You can use MH Guide default or customized filters and rule sets according to your needs



**Definitions and abbreviations:**  
a: detected in unpaired analyses or from RNAseq data, full suport from VCF input  
b: detected from FASTQ or BAM data for paired analyses, full suport from VCF input  
c: only possible via additional test result

SNVs: single nucleotide variants  
Indels: insertions-deletions (indels, ins, dels, frameshifts)  
CNAs: copy number alterations  
MSI: Microsatellite instability  
TMB: Tumor mutational burden

ETV6/NTRK3 fusion

Solid Tumors

Larotrectinib, Entrectinib, Selitrectinib

The neurotrophic receptor tyrosine kinase NTRK3 activates the PI3K/AKT and RAS/MAPK signaling pathways to promote cell survival and differentiation. ETV6-NTRK3 translocations were identified in several cancer types. Pan-NTRK inhibitors such as larotrectinib or entrectinib led to tumor responses in tumors that harbored the ETV6-NTRK3 fusion gene, regardless of tumor type. Larotrectinib and entrectinib are indicated for the treatment of patients with solid tumors who have an NTRK gene fusion. Entrectinib led to tumor responses in salivary gland, parotid, and neuroendocrine neoplasms. In a preclinical study, cells that harbored this translocation were sensitive to larotrectinib, entrectinib, and selitrectinib (LOXO-195).

MLH1 premature stop codon

Colorectal Cancer

Pembrolizumab

MLH1 is important for DNA mismatch repair, and mutations in this gene are frequently seen in colon adenocarcinomas. Although mutations in this gene are associated with Lynch syndrome, a majority of tumors that harbor these mutations are not the result of genetic predisposition but are acquired spontaneously. Mutations in this pathway prevent adequate DNA repair, and tumors that harbor these defects show microsatellite instability (MSI), meaning that DNA regions with single nucleotide repeats are expanded or contracted without control. This typically results in a higher-than-normal mutation rate. It may render such tumors susceptible to novel immune-modulating drugs like the PD-1 inhibitor pembrolizumab. Colon cancer patients with MSI have shown better overall survival than patients with colon cancers that are driven by other mechanisms. It remains controversial whether colon cancers with MSI show an increased sensitivity to 5-FU-based treatment regimens. MSI can be tested for MHL1, MSH2, or PMS2 by immunohistochemical staining.

EGFR p.L861Q

Lung Neoplasms

Afatinib

Erlotinib, Gefitinib

Osimertinib, Neratinib, Lazertinib

EGFR is a receptor tyrosine kinase that regulates the PI3K and RAS/MAPK pathways. In preclinical studies, the EGFR.L861Q mutation was shown to activate the PI3K and RAS/MAPK pathways. Afatinib is indicated for the treatment of non-small cell lung tumors that harbor this mutation. Patients with lung adenocarcinoma and this mutation showed response to erlotinib or gefitinib. In comparison to common EGFR mutations, the response to erlotinib or gefitinib was less favorable if L861Q occurred as a single mutation. However, when co-occurring with L858R, exon 19 deletion, or a G719X mutation, it led to a better response rate and progression-free survival. Preclinical data confirm the sensitivity of this variant to afatinib, osimertinib, neratinib, and lazertinib, but reduced sensitivity to erlotinib and gefitinib.

ERBB2 p.V659E

Lung Neoplasms

Afatinib, Lapatinib, Trastuzumab, Tesevatinib

The receptor tyrosine-protein kinase ERBB2 (HER2) activates the RAS/MAPK, PI3K/AKT, and JAK/STAT signaling pathways to promote cell proliferation and survival. The ERBB2.V659E mutation located in the transmembrane domain activates ERBB2 signaling. The tumor of a lung cancer patient with this mutation has been reported to show response to afatinib. Another patient whose lung cancer had this mutation was first treated with trastuzumab, achieving stable response for five months, followed by afatinib, achieving symptomatic improvement and metabolic response for five months. Preclinical studies have shown that cell lines with this mutation are sensitive to tesevatinib, afatinib, or lapatinib.

Variant evaluation

MH Guide gives you full access to the evidence underlying the analysis, and provides valuable additional information about annotated variants.

Variant

Variant information

CVIs

Consider for report

> KRAS  
p.G12D

SNV Missense

Effective 1 (1) Ineffective 1 (16) Safety 0 (0) Prognostic 0 (0) Diagnostic 0 (0)

Variant filter

Lineage and zygosity

CVI match quality

Allele frequency

Variant count

Coverage

Observation quality

Population frequencies

Filter failed

Conditional pass

Filter passed

Quality control of variants in NGS data

Differentiation between somatic and germline variants based on #COSMIC, PF, and VAF

Matching patient information to CVI description and variants

Variant tab: annotation, and classification of variants

Variant list

Review variants to identify potentially relevant variants

Gene filter TMB Additional test results Show variant details Show variant classification

47089 displayed 47089 in total

Variant

Variant information

CVIs

Consider for report

> KRAS  
p.G12D

SNV Missense

Effective 1 (1) Ineffective 1 (16) Safety 0 (0) Prognostic 0 (0) Diagnostic 0 (0)

Variant relevance details

Variant details

Variant annotations

ACMG criteria

Example of first page of our customizable MH Guide report

Header section with general case-specific information

Display of biomarkers and their validity

Drug approval state in patient indication/location

Options for the physicians to customize the report with their personal amendments

Summary and classification of identified treatment options by a traffic-light color code

Electronic signature of pathologist

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Patient ID EU000004  
Case ID  
Date of birth

Diagnosis Lung cancer  
ICD-10-CM code D002289 (Carcinoma, Non-Small-Cell Lung)  
MeSH ID/term  
Additional MeSH IDs D008175

Sex Ethnicity Country  
Primary tumor site Lung  
Surgical pathology  
Tissue type Metastatic  
Collected Tumor cellularity  
Barcode  
Sample type  
Labtest  
Software version  
Ordering physician  
Facility  
Email  
Phone  
Fax  
Product  
Report

SUMMARY

Overview of potential treatment impacts

6 Effective 2 Ineffective 13 Safety

Overview of prognostic and diagnostic findings

0 Prognostic 0 Diagnostic

Potential impact Treatment Drug approval\* Biomarker VAF Biomarker score

Effective Gefitinib Approved EGFR p.E746\_A750del (del) 29.52% AMP Tier I A 7 Clinically Approved

Effective Osimertinib Approved EGFR p.E746\_A750del (del) 29.52% AMP Tier I A 7 Clinically Approved

Effective Afatinib Approved EGFR p.T790M (SNV) 29.46% AMP Tier I A 7 Clinically Approved

Effective Erlotinib Approved EGFR p.E746\_A750del (del) 29.52% AMP Tier I A 7 Clinically Approved

Effective Dacomitinib Other EGFR p.E746\_A750del (del) 29.52% AMP Tier I A 7 Clinically Approved

Effective Azz3759 Other EGFR p.E746\_A750del (del) 29.52% AMP Tier II C 5 Clinical

Ineffective Erlotinib Approved EGFR p.T790M (SNV) 29.46% AMP Tier I B 6 Clinical

Ineffective Gefitinib Approved EGFR p.T790M (SNV) 29.46% AMP Tier I B 6 Clinical

Safety Cisplatin Approved TPMT p.Y240C (SNV) 100.00% AMP Tier I B 5 Clinical

Order date 23 May 2018  
Report Version 1  
Molecular Health GmbH, Kurfuersten-Anlage 21, 69115 Heidelberg | www.molecularhealth.com | +49 6221 43851-150

Signed by Dr. John Doe  
09 Apr 2019 12:23 (UTC+02:00)

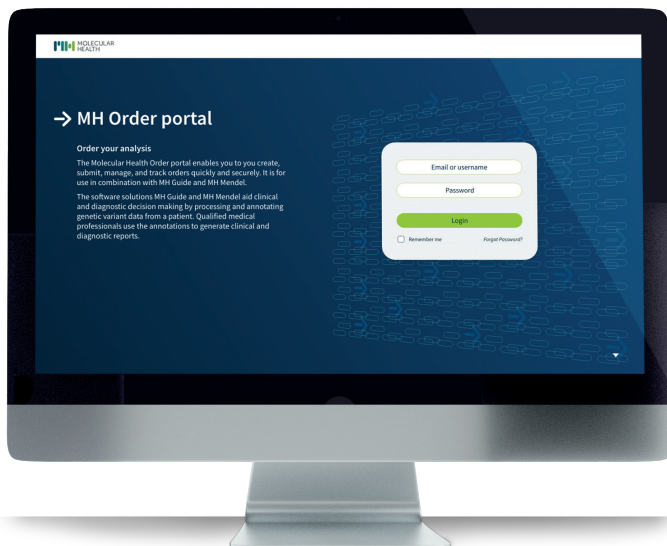
Phone 2266

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Customize your MH Guide report, add other lab results like IHC and FISH, or a specific appendix.

# How to order

## Molecular Health Order portal (MH Order portal)



Order MH Guide or MH Guide Premium using our user-friendly, browser-based MH Order portal. After uploading the patient's NGS data or VCF, and diagnosis, the analysis is performed and the individual molecular profile is generated. Once completed, you will be notified automatically. In your MH Guide account, you have full access to the data and the analysis. You can make amendments and add attachments, and sign the report.

### Literature:

- <sup>1</sup> Richards S, Aziz N, Bale S, et al. 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. *Genet Med.* 2015;17(5):405-424. doi:10.1038/gim.2015.30
- <sup>2</sup> Tate JG, Bamford S, Jubb HC, et al. COSMIC: the Catalogue Of Somatic Mutations In Cancer. *Nucleic Acids Res.* 2019;47(D1):D941-D947. doi:10.1093/nar/gky1015
- <sup>3</sup> Cline MS, Liao RG, Parsons MT, et al. BRCA Challenge: BRCA Exchange as a global resource for variants in BRCA1 and BRCA2. *PLoS Genet.* 2018;14(12):e1007752. Published 2018 Dec 26. doi:10.1371/journal.pgen.1007752
- <sup>4</sup> Li MM, Datto M, Duncavage EJ, et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn.* 2017;19(1):4-23. doi:10.1016/j.jmoldx.2016.10.002
- <sup>5</sup> Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature.* 2020;581(7809):434-443. doi:10.1038/s41586-020-2308-7