Molecular Health Guide 4.3

Product Description and Intended Use

MOLECULAR HEALTH GUIDE

including

MOLECULAR HEALTH MENDEL and MOLECULAR HEALTH BRCA

Manufacturer:

MOLECULAR HEALTH

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Table of Contents

1 Overview

MH Guide, MH Mendel, and MH BRCA

Molecular Health Guide (MH Guide) is a bioinformatics software application that supports trained medical experts in the creation of clinical reports by annotating and reporting genetic alterations in the human genome. *MH Guide* maps the patient's genetic alterations to biomedical reference information and uses this as the basis for automated and integrated annotation. *Molecular Health Guide Mendel (MH Mendel)*, and *Molecular Health Guide BRCA (MH BRCA)* are part of the MH Guide system registered as IVD in the EU and support trained medical experts in the creation of clinical diagnostic reports.

As input information, *MH Guide* uses genome sequencing data from an individual patient together with clinical and demographic patient parameters. Reports created with *MH Guide* summarize the genetic alterations detected in the patient's genome and highlight the potential effects of these alterations, including predictive, prognostic and diagnostic biomarker information. For *MH Mendel* and *MH BRCA* diagnostic information for hereditary diseases are provided.

The *MH Guide* system provides different products for analysis of variants from cancer samples (hereafter referred to as *MH Guide*), hereditary diseases (*MH Mendel*), or hereditary breast and ovarian cancer (HBOC) predispositions (*MH BRCA*). *MH Guide* can be used as an in vitro diagnostic (IVD) in the EU to create the reports for clinical use with the products *MH Guide* and *MH Guide Premium*. Additionally, the non-IVD reports for non-clinical use *MH Guide Onco Report, MH Guide Onco Report+ and MH Guide Onco Report Premium* are available. The reports can be created in PDF format and in the form of a Clinical Molecular Report (MH CMR) in JSON or XML format.

MH Guide, *MH Mendel*, and *MH BRCA* are not registered as IVD in markets outside of the EU. In the US, *MH Guide* offers a workflow solution to analyze oncology data from VCF files and generate a comprehensive final clinical oncology report in PDF, XML or JSON formats. *MH Guide Premium* is an expanded offering of *MH Guide*. It accepts FASTQ input and analyses oncology data through the MH Variant Detection Pipeline. It offers an application to create a final CAP/CLIA compliant clinical report for non-clinical use only.

MH Guide, MH Mendel, and *MH BRCA* provide a mode that can be used to automatically create an MH CMR and PDF report based on user defined rules. The MH CMR contains all annotations matched to the patient case.

For analysis of germline variants, *MH Mendel*, *MH Mendel Premium, MH BRCA,* and *MH BRCA Premium* can be ordered as part of the IVD in the EU. Users can select the appropriate report (product) when ordering an *MH Guide*, *MH Mendel* or *MH BRCA* analysis.

In the US, *MH Mendel Premium* is an expanded offering from *MH Mendel*. It processes hereditary disease data from a FASTQ file and analyses the data through the MH Mendel Variant Detection Pipeline (MH Mendel VDP). It offers an application to create a final CAP/CLIA compliant diagnostic report for non-clinical use only. *MH BRCA Premium* is an expanded offering from *MH BRCA*. It processes Hereditary Breast and Ovarian Cancer (HBOC) syndrome disease data from a FASTQ file and analyses the data through the MH BRCA Variant Detection Pipeline (MH BRCA VDP). It offers an application to create a final CAP/CLIA compliant diagnostic report for non-clinical use only.

MH Guide, *MH Mendel*, and *MH BRCA* are designed for different user groups and the access to them is strictly controlled by MH, for regulatory reasons. *MH Guide* is optimized for efficient creation of a

treatment-centric report to aid personalized treatment decision support for cancer patients, while *MH Mendel* and *MH BRCA* are optimized for creation of a clinical report for germline diagnostics.

MH Guide Premium uses MH Guide's Variant Detection Pipeline (MH Guide VDP) for variant detection from raw (FASTQ format) or aligned (BAM format) sequencing data. All other MH Guide cancer products are based on genomic (VCF format), which can be submitted directly for analysis by *MH Guide*. Data from patient samples for *MH Mendel* or *MH BRCA* analyses can be submitted in VCF, FASTQ, or BAM format. For the *MH Mendel* or *MH BRCA* FASTQ or BAM format analyses, an extension of the MH Mendel VDP is available for detection of germline variants.

In the US, the *MH Guide VDP*, *MH Mendel VDP* and *MH BRCA VDP* are not intended for clinical use. Genomic variants detected by the MH Guide VDP and variants provided via VCF input are mapped to transcript and protein level in a form that is compliant with the recommendations of the Human Genome Variation Society (HGVS) using ENSEMBL transcript and UniProt protein data.

All data required for analyses can be uploaded to *MH Guide, MH Mendel*, and *MH BRCA*, either using the *MH Order Portal* or via an MH SFTP server. The *MH Order Portal* may not be available as part of standard contracts in all countries.

MH Drug Explorer is available as an optional module that can be accessed from *MH Guide* depending on the customer contract. *MH Drug Explorer* is for non-clinical use only and allows users to browse, search, and compare clinical trial outcome measures, important for evaluating the effect of cancer treatments. Outcomes data are made available for a growing number of cancer entities.

Depending on the customer contract, protected health information (PHI)-relevant data can be securely encrypted using a customer-defined encryption key. Encrypted PHI information can be decrypted in *MH Guide*, *MH Guide Onco Report+*, *MH Mendel* and *MH BRCA* reports. Reports created with the product *MH Guide Onco Report*, or with the automated mode of *MH Guide, MH Mendel* or *MH BRCA,* will contain encrypted PHI, i.e., the patient name and date of birth will not be visible in the PDF-output. Encrypted information in MH CMR, can be decrypted by the customer.

System and Application Availability SLA

MH Guide with its components *MH Mendel and MH BRCA* is provided as a software as a service (SaaS) on a secure, cloud-based platform. The information in this chapter applies to all components of the *MH Guide* system.

Application Availability SLA (Service Level Agreement) is defined as follows:

- *MH Guide* has a general annual availability of at least **98%** (calculated on a hypothetical continuous uptime 24/7 all year long). Unplanned and planned (scheduled) downtimes, e.g., for system and application upgrades, are considered in (and cumulatively added to) this general availability value. Uptime is measured using external probes logging into the system regularly and availability is defined as such.
- Molecular Health will deliver an annual availability report showing the measured uptime which shall be the basis for calculating the service level.

The platform is operated at a HIPAA-compliant, professional hosting center. Login to the system is *via* an encrypted connection for data security reasons. *MH Guide* offers PHI encryption.

MH Guide is a multi-user software application that use the data platform SAP HANA and EnterpriseDB (PostGres) and provide a variety of interfaces for data exchange and integration into third-party applications.

Molecular Health reserves the right to define the number of user licenses provided per user role for each customer account.

MH Guide was tested on Google Chrome (Version 83.0.4103.116 (Official Build) (64-bit)) using Windows 10 (64-bit). We therefore recommend Google Chrome (Version 83.0.4103.116 (Official Build) (64-bit))) for best performance. Based on published browser compatibility comparisons, Opera is expected to be fully compatible as well. Other browsers such as Safari or Internet Explorer may not support all *MH Guide* functionalities, as they do not comply with the latest HTML5 and Java Script standards.

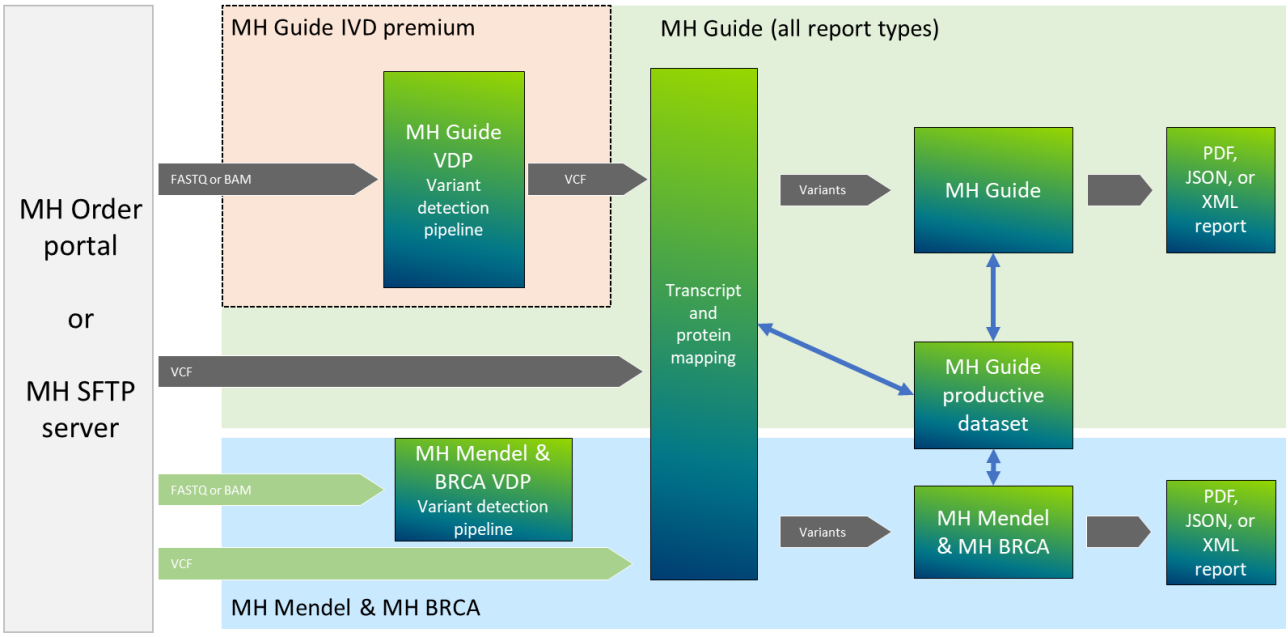
The local and the wide area network at the customer side needs to support the worldwide internet protocol standard HTTPS and a corresponding connectivity to Germany.

Partner Labs need to establish a secure ftp connection (SFTP) between their local IT systems (or sequencing machines) and MH's hosting center in Germany to transfer files. Alternatively, MH Order Portal can be used for file upload via the web browser.

Access to the following URLs and ports must be allowed by the customer:

- Standard use of MH Guide
  - Port 80 (http) and port 443 (https)
  - URLs:
    - https://eu.mh.guide/reporter
    - https://eu.mh.guide/orderportal
    - https://upload-eu.mh.guide
    - https://download-prod.mh.guide
- Usage of the embedded IGV viewer
  - Port 443 (https)
  - URLs:
    - https://s3.amazonaws.com/igv.org.genomes/genomes.json
    - https://s3.dualstack.us-east-1.amazonaws.com/igv.broadinstitute.org/genomes/seq/hg19/hg19.fasta.fai
    - https://s3.dualstack.us-east-1.amazonaws.com/igv.broadinstitute.org/genomes/seq/hg19/cytoBand.txt
    - https://igv.org/genomes/locus.php
    - https://s3.dualstack.us-east-1.amazonaws.com/igv.broadinstitute.org/genomes/seq/hg19/hg19.fasta
    - https://data.broadinstitute.org/igv/projects/current/counter_igvjs.php
- SFTP upload
  - Port 22 (SFTP)
  - ftp.de.molecularhealth.com

2 Provided products



MH Guide

MH Guide aims to support clinical laboratories, physicians, physician assistants, treating physicians, board-certified molecular pathologists, or molecular geneticists in their preparation of clinical reports for their patients. *MH Guide* uses Molecular Health's proprietary expert-curated and reviewed database to annotate genomic information, with a focus on treatment-related predictive biomarkers. Training and certification are mandatory for access to *MH Guide* to create reports covered by the *MH Guide* IVD.
MH Guide provides a mode that is designed for high-volume, automated processing of cancer-relevant variants from VCF input using predefined filters and rulesets, providing variant annotations in the form of a Clinical molecular record (MH CMR) in JSON and XML format and optionally as PDF. Depending on the contract, filters and rulesets can be configured for variant filtering, and a conversion of the MH CMR to a customer defined XML format can be offered. This mode is designed for easy integration into existing lab processes.

MH Guide cancer products:

- *MH Guide Premium*:
  MH Guide Premium allows users to prioritize treatment options automatically identified by *MH Guide* using customer-defined filters and rulesets. Reports can be created in PDF or XML format. *MH Guide* is covered by the *MH Guide* IVD registered in the EU. *MH Guide Premium* uses the MH Guide VDP for variant detection from FASTQ or BAM input. In the US, the *MH Guide VDP* is not intended for clinical use.
- *MH Guide*:
  Ordering an *MH Guide* report allows users to prioritize treatment options automatically identified by *MH Guide* using customer-defined filters and rulesets. Reports can be created in

PDF or XML format. *MH Guide* is a registered IVD in the EU. *MH Guide* report supports VCF variant input and does not use the MH Guide VDP.

- *MH Guide Onco Report*:
  MH Guide Onco Report is designed for high-volume, automated processing of cancer-relevant variants from VCF input using predefined filters and rulesets, providing treatment-centric variant annotations in PDF format. Users can view the Report tab in read-only mode; other tabs are not available. *MH Guide Onco Report* is not part of the registered IVD and is therefore not for clinical use. Certification of the user by Molecular Health is not mandatory for use of this product. *MH Guide Onco Report* is designed for easy integration into existing lab processes.
- *MH Guide Onco Report+:*
  MH Guide Onco Report+ allows users to view the Variants-, CVIs- and Report tabs and modify the list of patient variants and CVIs to report treatment options automatically identified by *MH Guide* using customer-defined filters and rulesets. Reports can be created in PDF or XML format. *MH Guide Onco Report+* is not part of the registered IVD and is therefore not for clinical use. Certification of the user by Molecular Health is not mandatory for use of this product.
  MH Guide Onco Report+ supports VCF variant input and does not use the MH Guide VDP.
- *MH Guide Onco Report Premium:*
  MH Guide Onco Report Premium is an expanded offering of *MH Guide Onco Report*. It processes molecular data in a FASTQ format through MH Guide Variant Detection Pipeline (MH Guide VDP) and generates a final variant annotation summary in an XML, JSON and PDF format. It is intended for non-clinical use only.

MH Mendel

MH Mendel aims to support human geneticists in their preparation of diagnostic reports for their patients. *MH Mendel* uses Molecular Health's proprietary database to annotate genomic information, with a focus on diagnostic biomarkers. Training and certification are mandatory for access to *MH Mendel* to create reports covered by the *MH Guide* IVD.
MH Mendel provides a mode that is designed for high-volume, automated processing of cancer-relevant variants from VCF input using predefined filters and rulesets, providing variant annotations in the form of a Clinical molecular record (MH CMR) in JSON and XML format and optionally as PDF. Depending on the contract, filters and rulesets can be configured for variant filtering, and a conversion of the MH CMR to a customer defined XML format can be offered. This mode is designed for easy integration into existing lab processes.

MH Mendel germline diagnostic products:

- *MH Mendel*, using FASTQ input:
  MH Mendel with FASTQ input uses the MH Mendel VDP for variant detection and allows users to annotate and classify variants and prioritize phenotypes automatically identified by *MH Mendel* using customer-defined filters and rulesets. Reports can be created in PDF or XML format. *MH Mendel* is covered by the *MH Guide* IVD registered in the EU. *MH Mendel* is aimed at human geneticists and genetic counsellors trained for use of the *MH Mendel* IVD. Training and certification are mandatory for operating *MH Mendel* as an in vitro diagnostic medical

device in the EU, as the same regulations apply as for the *MH Guide* IVD. In the US, the *MH Mendel VDP* is not intended for clinical use.

- *MH Mendel*, using VCF input:
  MH Mendel with VCF input allows users to annotate and classify submitted variants, and to prioritize phenotypes automatically identified by *MH Mendel* using customer-defined filters and rulesets. Reports can be created in PDF or XML format. *MH Mendel* is covered by the *MH Guide* IVD registered in the EU. *MH Mendel* is aimed at human geneticists and genetic counsellors trained for use of the *MH Mendel* IVD. Training and certification are mandatory for operating *MH Mendel* as an in vitro diagnostic medical device in the EU, as the same regulations apply as for the *MH Guide* IVD.

MH BRCA

MH BRCA aims to support human geneticists in their preparation of diagnostic reports for their patients. *MH BRCA* uses Molecular Health's proprietary database to annotate genomic information, with a focus on diagnostic biomarkers. Training and certification are mandatory for access to *MH BRCA* to create reports covered by the *MH Guide* IVD.
MH BRCA provides a mode that is designed for high-volume, automated processing of cancer-relevant variants from VCF input using predefined filters and rulesets, providing variant annotations in the form of a Clinical molecular record (MH CMR) in JSON and XML format and optionally as PDF. Depending on the contract, filters and rulesets can be configured for variant filtering, and a conversion of the MH CMR to a customer defined XML format can be offered. This mode is designed for easy integration into existing lab processes.

- *MH BRCA*, using FASTQ input:
  MH BRCA with FASTQ input uses the MH BRCA VDP for variant detection and allows users to classify and report identified variants in genes related to Hereditary Breast and Ovarian Cancer (HBOC) syndrome using customer-defined filters and rulesets. Reports can be created in PDF or XML format. *MH BRCA* is covered by the *MH Guide* IVD registered in the EU. *MH BRCA* is aimed at human geneticists and genetic counsellors trained for use of the *MH BRCA* IVD. Training and certification are mandatory for operating *MH BRCA* as an in vitro diagnostic medical device in the EU, as the same regulations apply as for the *MH Guide IVD*. In the US, the *MH BRCA VDP* is not intended for clinical use.
- *MH BRCA*, using VCF input:
  MH BRCA with VCF input and allows users to classify and report submitted variants in genes related to HBOC syndrome using customer-defined filters and rulesets. Reports can be created in PDF or XML format. *MH BRCA* is covered by the *MH Guide* IVD registered in the EU. *MH BRCA* is aimed at human geneticists and genetic counsellors trained for use of the *MH BRCA* IVD. Training and certification are mandatory for operating *MH BRCA* as an in vitro diagnostic medical device in the EU, as the same regulations apply as for the *MH Guide IVD*.

3 Components

MH Guide Variant Detection Pipeline (MH Guide VDP) for somatic variants

The MH Guide Variant Detection Pipeline (MH Guide VDP) is optimized for identification of variants from cancer samples using NGS panels, as well as for the identification of variants from cancer samples and control samples using a whole exome sequencing (WES) approach. The performance of the MH Guide VDP is validated and depends to a large extent on the quality of the sample and the data provided by the sequencing lab. The MH Guide VDP is used by *MH Guide Premium*. Samples must comply with the current MH sequencing guidelines. MH reserves the right to inform the Lab and/or the Hospital (Physician) about QC issues and to reject processing of samples that do not comply with the then current MH sequencing guidelines.
The MH Guide VDP provides the following core functionality:

- Read alignment based on standard (HG19, GRCh37).
- Unpaired analyses:
    - Variant calling for SNVs, Indels, Fusions
- Paired analyses:
    - Variant calling for SNVs, Indels, CNAs, and MSI**

The MH Guide VDP does not automatically identify and report wild type positions.

The MH Guide VDP consists of two pipelines: the DNAseq for general variant calling and the RNAseq pipeline for fusion calling.

In the US, the *MH Guide VDP* is not intended for clinical use.

*CNA calling from capture-based approaches has technical limitations. MH recommends that CNA variants shall be orthogonally validated before a treatment recommendation is based on such variants.

**MSI identification was validated with 100% precision, but sensitivity between 60% and 100%. As the determinants for the difference in sensitivity are unknown, MH strongly recommends that the MSI status of unclassified cases or MSS cases should be assessed with orthogonal methods before a treatment decision is made based on the MSI status.

MH Guide RNAseq pipeline (MH Guide Premium only)

The MH RNAseq pipeline enables comprehensive and high-quality detection of fusions from FASTQ data. Fusions detected by the RNAseq pipeline are integrated into the list of variants in MH Guide and available for CVI matching. The MH RNAseq pipeline is a component of the MH Guide VDP and can optionally be used for higher fusion detection quality or fusion detection in combination with WES assays.

MH Mendel & MH BRCA Variant Detection Pipeline (MH Mendel VDP / MH BRCA VDP) for germline variants

The MH Mendel and MH BRCA Variant Detection Pipelines (MH Mendel VDP / MH BRCA VDP) issue an identical setup and are optimized for identification of germline variants from genomic samples using NGS panels, as well as for the identification of variants from a whole exome sequencing (WES) approach. The performance of the MH Mendel VDP and MH BRCA VDP is validated and depends to a large extent on the quality of the sample and the data provided by the sequencing lab. Samples must comply with the current MH sequencing guidelines.

The MH Mendel VDP and MH BRCA VDP provides the following core functionality:

- Read alignment based on standard (HG19, GRCh37).
- Variant calling for SNVs, Indels

The MH Mendel VDP and MH BRCA VDP does not automatically identify and report wild type positions.

In the US, the *MH Mendel and MH BRCA VDPs* are not intended for clinical use.

Transcript and protein mapping

Transcript and protein mapping are done for all reports created with *MH Guide* and *MH Mendel.* Genomic variants from VCF input are mapped to transcript and protein level in HGVS compliant form using ENSEMBL transcript and UniProt protein data. The transcript and protein mapping supports non-coding and coding SNVs, Indels (del, ins, del-ins), Fusions and copy number alterations (CNAs) from VCF input. The pipeline can be configured to only report variants based on a provided gene list and/or to filter out all non-coding variants without relevant information available in the *MH Guide* dataset.

Copy number alterations are mapped to all genes fully covered by the genomic region submitted in the VCF input.

Fusions are mapped to all genes covering the fusion breakpoints submitted in the VCF input.

Core features provided in *MH Guide* cancer products

Users creating the reports *MH Guide Onco Report+, MH Guide,* and *MH Guide Premium* access MH's fully interactive applications that include a web-based reporting interface. Users can create a report based on a customizable ruleset that is applied to all detected variants. Use of the default ruleset and automated ACMG pre-classification, or any change made to them, is on the user's sole responsibility. The user can include all matched CVIs and the associated information in reports. The web-based user interface leads the user through the steps required to create a report.

In contrast, users of the *MH Guide* automated annotation mode can view and download reports or pick up analysis results in terms of XML, JSON or VCF files from the MH SFTP server. Users of *MH Guide Onco Report* cannot use below features of the fully interactive user interface but only download PDF reports from within the user interface.

MH Guide provides the following core functionalities:

- **Case management:** users can sort, search, and filter cases in a list, change case status, and download the report for a case after it has been set to status signed off, with an electronic signature, if wished. This feature is available with *MH Guide Onco Report+*, *MH Guide*, and *MH Guide Premium* reports.
- **Patient information management:** the information for the patient provided at the time the analysis was ordered can be edited in the interactive user interface. If information that affects knowledge matching is modified, the knowledge matching is automatically adjusted to reflect the new information.
- **Filter and ruleset management:** filters and rulesets are automatically applied to cases. They include variant filters, lineage and zygosity classification and filter, CVI matching parameters, pre-selection and sort order of reported treatments and findings, and labtest target region size. Rulesets and filters define the content initially included in the report, before it is modified by the user. Use of provided default rulesets and filters, and use of use of custom rulesets and filters, are at the sole responsibility of the customer. Rulesets can be configured by authorized users. This feature is available with *MH Guide Onco Report+*, *MH Guide*, and *MH Guide Premium*.
- **Variant management:** users can browse a list of all detected variants, search for specific variants or genes, assess variant relevance based on information about variant type, matching CVIs, an automated and editable ACMG classification, gene properties, correlated variants, detection quality, and variant annotations from a number of external resources. In addition, users can define and apply gene filters that exclude variants in genes that are not in the scope of their current analysis. This feature is available with *MH Guide Onco Report+*, *MH Guide*, and *MH Guide Premium* reports.
- **Manual addition and interpretation of variants and genomic findings from other assays:** users can manually add information on SNVs (HGVS protein level only), Indels (HGVS protein level only), fusions, CNAs, protein expression, gene expression, methylation, wild types, tumor mutational burden, and microsatellite instability. This feature is available with *MH Guide* and *MH Guide Premium* reports.
- **Variant browser:** this is a separate variant detail view with case-specific filters and scores that helps users to interpret protein variants in complex and rare cancer types and provides access to detailed gene and variant information. This feature is available with *MH Guide* and *MH Guide Premium* reports.
- **CVI management:** for each detected variant, users can create custom CVIs, either from scratch or based on an existing CVI (e.g., a CVI provided by MH). CVIs are shared within an organizational unit; all changes are tracked and traceable in the system history. CVI biomarker validity scores (MH score and AMP score) and match quality details help users to assess the relevance of a CVI. Users can create custom CVIs for single variants or combinations of variants. Although *MH Guide* does not support automated detection of wild-type biomarkers, users can choose to report wild-type CVIs provided by

MH. This is done on the sole responsibility of the user. Manually created CVIs can be inactivated to exclude them from use in future cases. This feature is available with *MH Guide* and *MH Guide Premium.* Detailed information on medications: drug and CVI information are shown in separate views for potentially effective medications and medications with potential for adverse reaction or ineffectiveness, and users can browse all medications associated with CVIs that were selected for reporting. If there is contradicting evidence about the effectiveness and safety of a treatment, this is highlighted, and users can select which medications to include in their report. Users can prioritize treatment recommendations by modifying the sort order. This feature is available with *MH Guide* and *MH Guide Premium* reports.

- **Access to *MH Drug Explorer:*** an optional module that can be accessed from *MH Guide* depending on the customer contract. *MH Drug explorer* is for non-clinical use only and allows users to browse, search, and compare clinical trial outcome measures, important for evaluating the effect of cancer treatments. Outcomes data are made available for a growing number of cancer entities.
- **Access to *MH Pathway Viewer:*** that can be accessed from Molecular Health Guide (MH Guide) patient cases, is for non-clinical use only, that can be used to better understand a patient's tumor and where in a pathway treatment relevant biomarker are located.
- **Clinical trials:** potentially relevant recruiting clinical trials are shown for each selected potentially effective medication, taking the patient demographics and the primary and secondary diseases into account. Trial selection for the report can be edited by the user. This feature is available with *MH Guide* and *MH Guide Premium* reports.
- **Medical guidelines:** treatments and related information such as recommended use and evidence levels from NCCN and a selection ESMO guidelines are available and displayed in the context of the patient's disease based on assigned MeSH terms. Biomarkers matched to the molecular profile of the patient are displayed to provide information about the potential impact of the treatment for the patient. Guideline information can be selected by users for the report. This feature is available with *MH Guide* and *MH Guide Premium* reports.
- **Prognostic and diagnostic findings:** separate views allow users to browse all prognostic and diagnostic findings associated with relevant variants and select which prognostic and diagnostic findings to include in the report. This feature is available with *MH Guide* and *MH Guide Premium* reports.
- **Interactive report preview:** in the report view, users can write a clinical impression and choose which attachments to include in the final report. Available attachments include a list of all variants identified as relevant, a list of potentially relevant recruiting clinical trials, a list of all publications cited in reported CVIs, a list of all drug class members of reported drug classes, treatment details, the filters and ruleset settings used, and a summary of the mutational load. A lab-specific disclaimer can be attached to reports. Depending on the *MH Guide* report, not all sections and attachments may be available. For *MH Guide Onco Report+*, the attachments cannot be changed. For *MH Guide Onco Report*, the clinical report can be viewed and downloaded without modification.
- **Report management:** all changes made to reports are tracked and traceable in the system history. Reports can be signed, and if required, electronic signatures can be used. A copy of each signed report is automatically stored in the system and provided for download. Reissued reports can be assigned a

label indicating the reason they were reopened; the label and the reason given are printed on the report.

- **Automated CMR output:** The system can be configured to automatically create an MH CMR file on the SFTP server for signed cases. This is available for all *MH Guide* reports.
- **Software version management:** A UDI code for each component relevant for identification of the system is provided on the user interface to ensure full traceability according international regulatory provisions.

Core features provided in *MH Mendel*

MH Mendel is a fully interactive application that includes a web-based reporting interface. It applies a customizable ruleset and automated ACMG pre-classification to all detected variants to support the user in creating a clinical diagnostic report. Use of the default ruleset and automated ACMG pre-classification, or any change made to them, is on the user's sole responsibility. The user can include all matched CVIs and the associated phenotype information in reports.

The following core functionalities are available for *MH Mendel* and are available for FASQ and VCF input:

- **Case management:** users can sort, search, and filter cases in a list, change case status, and download the report for a case after it has been set to status signed-off (with an electronic signature, if wished).
- **Patient information management:** the information for the patient provided at the time the analysis was ordered can be edited in the interactive user interface.
- **Filter and ruleset management:** filters and rulesets are automatically applied to cases. They include variant filters, zygosity classification, CVI matching parameters, and labtest target region size. Rulesets and filters define the content initially included in the report, before it is modified by the user. Use of provided default rulesets and filters, and use of use of custom rulesets and filters, are at the sole responsibility of the customer. The rulesets can be configured by authorized users.
- **Variant management:** users can browse a list of all detected variants including automated variant pre-classifications based on ACMG, editable ACMG criteria and variant classifications, an MH-calculated ACMG and consensus classifications, annotation data from external sources, search for specific variants or genes, assess variant relevance and store their variant classification based on information about variant type, matching CVIs, gene properties, correlated variants, detection quality and variant annotations from a variety of external resources. Users can permanently store variant classifications to build a variant knowledge base for their OrgUnit. In addition, users can define and apply gene filters that exclude variants in genes that are not in the scope of their current analysis.
- **Manual addition and interpretation of variants and genomic findings from other assays:** Users can manually add information on SNVs, Indels, fusions, CNAs, protein expression, gene expression, methylation, wild types, tumor mutational burden, and microsatellite instability.
- **Variant browser:** this is a separate variant detail view with case-specific filters and scores that helps users to interpret protein variants in complex cases and provides access to detailed gene and variant information.
- **CVI management:** for each detected variant, users can create custom CVIs, either from scratch or based on an existing CVI (e.g., an automatically generated uncurated diagnostic CVI provided by MH). A CVI is automatically created for variants from ClinVar that matches a phenotype described in HPO (Human Phenotype Ontology). If no phenotype association with a variant could be established, no CVI

is automatically created for this variant. CVIs are shared across an organizational unit; all changes are tracked and traceable in the system history. Match quality details help users to assess the relevance of a CVI. Users can create custom CVIs for single variants or combinations of variants (variant combination CVIs). Manually created CVIs can be inactivated to exclude them from use in future cases.

- **Phenotypes tab:** this tab provides detailed information on phenotypes associated with detected variants. It shows all the variants associated with each potentially applicable phenotype and provides a phenotype description, inheritance information, and associated symptoms. On the Phenotypes tab, users can select which phenotypes should be included in the diagnostic report. Phenotypes associated with pathogenic or likely pathogenic variants will be automatically preselected for reporting.
- **Interactive report preview:** users can write a case summary and choose which attachments to include in the final report. Available attachments include a list of all variants identified as relevant, a list of all publications cited in reported CVIs, and the filters and ruleset settings used. A lab-specific disclaimer can be attached to reports.
- **Report management:** all changes made to reports are tracked and traceable in the system history. Reports can be signed, and, if required, electronic signature can be used. A copy of each signed report is automatically stored in the system and provided for download. Reissued reports can be assigned a label indicating the reason they were reopened; the label and reason given are printed on the report.
- **Automated CMR output:** The system can be configured to automatically create an MH CMR file on the SFTP server for signed cases.
- **Software version management:** A UDI code for each component relevant for identification of the system is provided on the user interface to ensure full traceability according international regulatory provisions.

Core features provided in *MH BRCA*

MH BRCA is a fully interactive application that includes a web-based reporting interface. It applies a customizable ruleset and automated ACMG pre-classification to all detected variants to support the user in creating a diagnostic report. Use of the default ruleset and automated ACMG pre-classification, or any change made to them, is on the user's sole responsibility.

The following core functionalities are available for *MH BRCA*:

- **Case management:** users can sort, search, and filter cases in a list, change case status, and download the report for a case after it has been set to status signed-off (with an electronic signature, if wished).
- **Patient information management:** the information for the patient provided at the time the analysis was ordered can be edited in the interactive user interface.
- **Filter and ruleset management:** filters and rulesets are automatically applied to cases. They include variant filters, zygosity classification, CVI matching parameters, and labtest target region size. Rulesets and filters define the content initially included in the report, before it is modified by the user. Use of provided default rulesets and filters, and use of use of custom rulesets and filters, are at the sole responsibility of the customer. The rulesets can be configured by authorized users.
- **Variant management:** users can browse a list of all detected variants including automated variant pre-classifications based on ACMG, editable ACMG criteria and variant classifications, an MH-calculated ACMG and consensus classifications, annotation data from external sources, search for specific variants or genes, assess variant relevance and store their variant classification based on information

about variant type, matching CVIs, gene properties, correlated variants, detection quality and variant annotations from a variety of external resources. Users can permanently store variant classifications to build a variant knowledge base for their OrgUnit. In addition, users can define and apply gene filters that exclude variants in genes that are not in the scope of their current analysis.

- **Variant browser:** this is a separate variant detail view with case-specific filters and scores that helps users to interpret protein variants in complex cases and provides access to detailed gene and variant information.
- **Interactive report preview:** users can write a case summary. The report contains a disease description, reported variants and a list of cancer risk of pathogenic variants per analyzed gene.
- **Report management:** all changes made to reports are tracked and traceable in the system history. Reports can be signed, and, if required, electronic signature can be used. A copy of each signed report is automatically stored in the system and provided for download. Reissued reports can be assigned a label indicating the reason they were reopened; the label and reason given are printed on the report.
- **Automated CMR output:** The system can be configured to automatically create an MH CMR file on the SFTP server for signed cases.
- **Software version management:** A UDI code for each component relevant for identification of the system is provided on the user interface to ensure full traceability according international regulatory provisions

Core content provided in *MH Guide*

The following main content components form the basis of the processing and analysis steps by which the genome sequencing data of a patient is translated into clinically actionable information:

- Variant annotations:
    - Variant classifications, functional impact scores, phenotype associations, references to databases, and population frequencies from a variety of external resources. Curated information about functional variant effects.
- ACMG classifications:
    - Automatically calculated ACMG pre-classifications based on available variant annotations
- Clinical variant interpretations (CVIs):
    - CVIs are curated and reviewed by a team of biomolecular and medical experts based on published peer-reviewed evidence. CVIs link information on drug, disease, variant, lineage and zygosity. Additionally, CVIs with CVI scores 4-7 (clinical and approved evidence levels) undergo a final review and approval by oncologists and pathologists before being included in the MH database.
    - Depending on the target regions of a labtest and the input format, not all CVIs provided in MH Guide may be available for matching to a patient case. A positive list with matchable variants per input format is provided by MH for each content release. On request, this list can also be provided in a labtest-specific manner.
    - To ensure standardized disease information nomenclature, CVI diseases and patient diseases are mapped using the widely accepted MeSH codes categorized by the U.S. National Library of Medicine. The selection of appropriate MeSH terms for the patient disease is critical for the result of analyses with *MH Guide* and is at the sole responsibility of a customer.
    - CVIs are based on either a single variant, a variant combination, or a wild type or wild type combination, and include lineage and zygosity information.

- CVIs contain a narrative description, in which knowledge of the clinical significance of the mutation within the context of the patient disease is summarized.
- CVIs either contain predictive information about a treatment effect (effective, ineffective or safety), or provide diagnostic or prognostic information.
- CVIs contain references to the underlying publications.
- CVIs provide validity information depending on the underlying published evidence. For this purpose, MH CVI scores and AMP guideline scores are used.
    - MH CVI scores:
        - MH score 7: Clinically approved. The biomarker has been validated in a clinical context (FDA, EMA, or NCCN).
        - MH scores 4-6: Different levels of clinical evidence.
        - MH scores 1-3: Different levels of pre-clinical evidence. The biomarker has been tested non-clinically, in an in vitro or animal model, or it was inferred from information available for other biomarkers with potentially similar implications.
    - AMP guideline scores:
        - Biomarker scores from Tier I to Tier IV according to the published consensus guidelines for somatic variant interpretation from AMP, ASCO, and CAP.

- Drug development stages:
    - Information on drug development stages for treatments described in matching CVIs. Drug development stage information in the context of a disease is mapped to MeSH terms and provided in the context of the patient's disease and country. Drug development stages are mapped to the following terms:
        - Approved: registered or launched for the patient disease
        - Off-label: approved for another disease
        - Investigational: The drug is being tested in pre-clinical and clinical studies, but has not been launched for any disease
        - Other: The drug is neither approved, nor off-label, nor investigational (e.g., no detailed drug development data is available)
    - The drug development information provided in *MH Guide* is country specific. If no geographic information is available, the drug development stages valid for the US are shown for all drugs.
    - If the drug patent protection period has expired, drug developmental stage information may no longer be accurate.
- Medical guidelines:
    - Treatments and related information such as recommended use and evidence levels from NCCN and a selection of ESMO guidelines are available and displayed in the context of the patient's disease based on assigned MeSH terms.
- Clinical trials:
    - Clinical trials from clinicaltrials.gov are mapped to the patient based on disease, age, gender, country, and effective treatment options identified by *the software*. Disease terms from clinicaltrials.gov are mapped to MeSH terms for mapping to the patient disease.

Core content provided in *MH Mendel*

MH Mendel provides the following main content components on which processing and analysis steps to support human geneticists in variant classification and report generation are based.

- Variant annotations:
  - Variant classifications, functional impact scores, phenotype associations, references to databases, and population frequencies from a variety of external resources. Curated information about functional variant effects.
- ACMG classifications:
  - Automatically calculated ACMG pre-classifications based on available variant annotations
- Variant to phenotype associations:
  - Automatically generated CVIs that include phenotype information extracted from external data sources such as ClinVar, ARUP BRCA Mutation Database and ENIGMA via BRCA exchange and can be used by users as templates to generate, store and reuse their own variant interpretations. In contrast to *MH Guide,* the automatically generated CVIs are not intended for use as variant interpretations and direct reporting by users. They are a starting point for users who wish to create their own variant interpretations.

Core content provided in *MH BRCA*

MH BRCA provides the following main content components on which processing and analysis steps to support human geneticists in variant classification and report generation are based.

- Variant annotations:
  - Variant classifications, functional impact scores, phenotype associations, references to databases, and population frequencies from a variety of external resources. Curated information about functional variant effects.
- ACMG classifications:
  - Automatically calculated ACMG pre-classifications based on available variant annotations
- Cancer risk of pathogenic variants per analyzed gene:
  - A summary of implications of pathogenic variants on cancer risks per analyzed gene

Performance of MH Guide VDP, MH Mendel & MH BRCA VDP

Product	Pipeline	Variant Type	Precision*	Sensitivity*	Validation based on
MH Mendel, MH BRCA, MH Guide	Germline (used for panel and Exome analyses)	SNV	≥99%	≥99%	VAF ≥10%, ≥38x coverage at variant position
		Indel	≥98%	≥98%	VAF ≥10%, ≥38x coverage at variant position (measured on whole exome samples with 100x average coverage)
MH Guide	Panel	SNV	≥99%	≥99%	Tumor content ≥20%, VAF ≥5%, ≥95x coverage at variant position
		Indel	≥99%	≥97%	Tumor content ≥20%, VAF ≥5%, ≥95x coverage at variant position
		Fusion**	≥100%	≥100%	Tumor content ≥20%, supporting read pairs ≥10
	Exome (Tumor and control sample)	SNV Tumor: Control:	 ≥97% ≥98%	 ≥97% ≥99%	Tumor content ≥20%, VAF ≥5%, ≥20x coverage at variant position, and a 100x average coverage control sample.
		Indel Tumor: Control:	 ≥99% ≥98%	 ≥95% ≥98%	Tumor content ≥20%, VAF ≥5%, ≥20x coverage at variant position, and a 100x average coverage control sample.
		CNA loss**	95%	95%	≥ 50% tumor content. Detection only for genes with MH CVI for CNA loss
		CNA gain**	99%	71%	≥ 50% tumor content. Detection only for genes with MH CVI for CNA gain and copy number ≥4
		MSI-H	100%	88%	Samples without sequencing QC warnings
	RNASeq	Fusion	≥83%	≥94%	Supporting reads ≥2
	Panel & Exome	TMB**	n/a	n/a	TMB-H detection is not clinically validated. No precision and sensitivity can be provided due to the specifics of this biomarker type.

*Performance and limits of detection of the MH Guide VDP and MH Mendel VDP were calculated using validation cases with a defined minimum sequencing coverage at variant positions. These values are meant as a reference point. Depending on the design of the customer's assay, the required average coverage to ensure the specified coverage at variant positions may strongly vary. Similar performance is expected for

data from panel and WES analyses that fulfill requirements and recommendations from MH sequencing guidelines and pass the sample QC checks within the software.

Higher sequencing coverage will result in higher precision and sensitivity, and improved limits of detection (better detection for variants with lower Allele Frequency).

Lower sequencing coverage will result in lower precision and sensitivity and will worsen detection of variants with lower Allele Frequency. In general, our MH Sequencing Guidelines need to be considered by the Lab.

**DNA-based fusion detection, CNAs, and TMB must be orthogonally validated before any treatment decision is made based on this information.

Accuracy and performance of MH Guide cannot be guaranteed, if the Lab is delivering incorrect or incomplete sequencing data, patient data or auxiliary files, such as BED files.

Data foundation, data & software updates, and their impact on reporting

MH Guide, *MH Mendel*, and *MH BRCA* content is derived from *MH Dataome* and comprises multiple databases, both internal and external. This database represents a semantic, unified, and correlated dataset of variant annotations for cancer and hereditary diseases. This dataset is updated, quality-assured, and tested at regular intervals.

When a dataset update is provided by MH, it is fully reflected in all cases that are processed after the update. CVI content available in previously processed cases is not changed until the user chooses to apply the changes and recalculates the case. Other content, such as annotations from external sources, clinical trials, and drug development stages, is automatically updated for all cases. Data displayed in the Variant browser is not updated for existing cases. Signed reports stored in the system are not affected by data updates.

MH regularly updates the content with new CVIs, drugs, clinical trial information, variant annotations, and other information. These updates are performed on a regular basis, independent of the software updates. Important content updates (e.g., due to regulatory reasons) can be provided at shorter intervals. For *MH Guide,* a list of new and updated CVIs is provided with each dataset.

MH Guide, *MH Mendel*, and *MH BRCA* are based on a pre-integrated, quality-approved data set that draws from more than 30 external databases with different update frequencies. This means that some of the information provided may not be up-to-date, due to inconsistencies between these external database versions.

Software and Content updates and hotfixes may be applied to the system without prior notification of users.

Software and Content upgrades (new major releases) will only be applied after user notification, 5 business days ahead of time.

Input formats

Analyses with *MH Guide*, *MH Mendel*, and *MH BRCA* require genetic or molecular alterations from a patient as input. Depending on the product, germline alterations (*MH Mendel* and *MH BRCA*), somatic alterations (NGS panel analyses in *MH Guide*), or a combination of both (analyses with control sample in *MH Guide*) can be used as input.

MH Guide Onco Report, MH Guide Onco Report+, MH Guide, and *MH Mendel* accept genetic alterations (SNVs, Indels, Fusions, CNAs, MSI) provided in accordance with the VCF format standards defined by Molecular Health (hereafter MH VCF).

Other types of molecular alterations identified for a patient can be added manually within the user interface for *MH Guide, MH Guide Premium, MH Mendel,* or *MH Mendel Premium.*

MH Guide Premium, MH Mendel Premium, and *MH BRCA Premium* with FASTQ input use the MH Variant Detection Pipeline (MH Guide VDP, MH Mendel VDP, or MH BRCA VDP) to identify genomic alterations in either cancer and control samples, cancer samples, or in germline samples.

For data provided in MH VCF format, submitted genomic alterations are provided on chromosomal level (HGVS g.-notation), transcript level (HGVS c.-notation, based on ENSEMBL transcript data) and protein level (HGVS p.-notation based on UniProt Canonical Isoform). Non-coding alterations are not available in HGVS p.-notation and intergenic non-coding alterations are only available in g.-notation.

Genomic alterations are only accepted when they are compliant with MH standards in terms of file formats, variant types, and data quality.

Sufficiently good quality of the input data and especially of the underlying lab analyses and variant calls submitted to MH is essential for every analysis and must be assured by the submitting user or lab.

Organizations must define filtering criteria for every labtest they use to filter data according to their limits of detection and to exclude potential false positives or polymorphisms. When using VCF input, it is in the sole responsibility of the organization that uses *MH Guide, MH* Mendel, or *MH BRCA* to either provide only true positive variant calls, or to filter the data according to their established limits of detection.

Inbound interfaces

Users can easily and securely upload the files containing variant information and patient metadata using SFTP or via the optional accessory the *MH Order Portal*. The *MH Order Portal* is not part of the standard offering in the US.

Due to its open nature on the inbound and outbound side, *MH Guide*, *MH Mendel*, and *MH BRCA* can be integrated into external systems and can process variants detected by an external genomic pipeline.

A master adapter for transformation of VCF-formatted variant lists into MH VCF formats is available from Molecular Health as a consulting service. Such transformations are not part of the product and must be run outside of the MH cloud by the customer, prior to uploading files.

Note for the VCF input channel:

Only fusion breakpoints that lie within gene start and end positions used by the system are reported as fusion genes, and only genes for which the coding regions fully reside within a defined CNA region are reported as CNAs. If a different coordinate system is used, the data must be transformed before sending it to *MH Guide* or *MH Mendel*. A list of gene boundaries used by MH is provided with every release of the software.

Patient data

For the analysis, the software requires basic clinical and demographic information, such as the patient's sex, MeSH disease term, and cancer type (not required for *MH Mendel* and *MH BRCA*). The user can choose to send additional patient data.

The quality of the analysis depends on the completeness and correctness of the patient data provided. If an incorrect patient MeSH disease term is provided for an *MH Guide* analysis, or if an inappropriate labtest configuration is associated with a case, this can lead to incorrect CVI matches, or incorrect filters for limits of detection may be applied to a case. The submission of correct and complete patient data is at the sole responsibility of the customer. Patient data can be edited during the process of report creation by the user. Any changes made, in particular changes that affect the analysis results, are done on the responsibility of the user.

Organizations needing to encrypt protected health information (PHI) can encrypt PHI-relevant data before uploading it to MH (patient name and date of birth). Each organizational unit uses their own encryption key, to ensure privacy of the data in *MH Guide*, *MH Mendel*, and *MH BRCA*. The key required for decryption can be safely stored in a HANA SecureStore within the system, and used to make critical patient information visible during analysis in *MH Guide* and in the final report. The encryption of the PHI data can be done in the *MH Order Portal* or on the customer side using a command line interface tool provided by MH. This availability of the encryption functionality can be configured per organizational unit of the customer.

Analysis turnaround time

- Analysis of MH VCF files:
    - Below five minutes. Exceptional cases with large numbers of variants, for extremely hyper-mutated-samples, analysis may take up to 4 hours.
- Analysis of FASTQ or BAM files*:*
    - For identification of variants from FASTQ or BAM input in *MH Guide Premium* cases, and *MH Mendel* or *MH* BRCA cases with FASTQ input, the network transfer time to the MH Cloud and the turnaround time of the respective VDP must be taken into consideration. Depending on the target region size and coverage of the NGS experiment, the *MH Guide*, *Mendel* and *BRCA* VDPs (without the network time) typically takes less than 1-2 days if processes and standards are met by the customer, and the input files comply with MH quality standards. As an example, our reference sample based on an unpaired 600+ gene panel, runs approx. 8h until the report is completed. Smaller panels may be processed significantly faster. Experiments with extensive target regions such as WES analyses might run significantly longer. However, this is still less than the usual wet lab NGS processing turnaround time.
    - Turnaround time is heavily influenced by the network bandwidth of the uploading party and is outside of MH's responsibility.

Output formats

Depending on the *MH Guide, MH Mendel,* or *MH BRCA* configuration, the report resulting from the analysis can be in PDF format, in the form of an MH CMR.

- PDF: Signed reports can be downloaded in PDF format for *MH Guide*, *MH Mendel*, and *MH BRCA*. On request, the appearance and content of PDF format reports can be customized by MH as a consulting service.

  The template for the report in PDF format can include sections for information on the experimental and technical quality, on CVIs and their clinical relevance, and links to the sources of evidence of the information displayed, for full traceability. The system can be configured to produce a Clinical molecular record (MH CMR) output on the SFTP server in addition to the PDF report.
  When using PHI encryption, PDF reports automatically created with the automated annotation mode of *MH Guide, MH Mendel or MH BRCA* will always contain encrypted PHI, i.e., the patient name and date of birth will not be visible in the PDF-output.
- MH CMR: For the MH CMR can be produced in JSON and XML format for easy incorporation into an organization's existing processes. The MH CMR is a standard defined by MH for reporting molecular and genetic information on an individual patient. The MH CMR is available to the user for download via SFTP for 30 days after the analysis is completed. The CMR can be automatically converted by a customer specific adapter to other data formats on request, e.g. to VCF format.
- MH Guide, MH Mendel, and MH BRCA support processing of up to 100,000 variants per case.
- *MH Guide*, *MH Mendel*, and *MH BRCA* do not support creation of clinical reports and MH CMRs with more than 10,000 reported variants.

Data storage

All necessary information and files are stored in compliance with applicable federal or state regulations.

Molecular Health is not taking responsibility for FASTQ and BAM file storage.

VCF input is stored for 2 years.

Analysis results are stored for 10 years according to GenDG §12.

Limitation of user numbers per role and contract

MH Guide, MH Mendel, MH BRCA, and *MH Order Portal* are multi-user software applications. Users are configured as named users and can have different user roles. User roles are described in detail under Intended user group in EMEA. Since the offered products are analytical applications and typically charged per patient case, the total number of user accounts per role is limited per contract. In the standard configuration, a contract is limited to the following number of users per role:

Product	**Role**	**Max. Number of Users**
MH Guide	Certified Physician (CP)	2
MH Guide	Certified Physician Oncologist (CPO)	5
MH Guide	Certified Physician Assistant (CPA)	10
MH Guide	Research physician (RP)	10
MH Mendel & MH BRCA	Human Geneticist (HG)	5
MH Order Portal	MH Order Portal-only user (OPO)	10
MH Order Portal	Lab user (LU)	10

In addition to these roles, *MH Guide, MH Mendel,* and *MH BRCA* users can share read-only access to an individual case for a limited time with a colleague, provided a patient agreement is in place. This limited access role is entitled **guest user (GU)**.

4 Intended use

MH Guide is a bioinformatics software application to aid clinical decision-making and patient diagnosis based on genetic and molecular alteration data from a patient sample. It enables the intended user group to generate a customizable clinical report.

The *MH Guide* system including *MH Mendel* and *MH BRCA* is designed to accept input data in form of FASTQ, BAM or VCF that was either generated with an approved IVD or was generated in the responsibility of the trained user.

MH Guide is composed of a web-based graphical user interface that provides a workflow for creating reports with *MH Guide*, *MH Mendel* and *MH BRCA*. The reporting workflows enable the trained user to process sequence data in a workflow that can include the manual annotation of data, the filtering of variant information, and report composition.

The automated mode provided by *MH Guide, MH Mendel* and *MH BRCA* provides variant annotations in the form of a MH CMR and in PDF format.

MH Guide Onco Report, MH Guide Onco Report+, and *MH Guide Onco Report Premium* are for non-clinical use only.

In the reports created with *MH Guide Onco Report+, MH Guide*, and *MH Guide Premium*, a summary of potentially effective medications, potentially ineffective medications, and medications that may pose a higher risk of adverse reactions is provided, based on the user-defined input, the user's selection of CVIs, and the prioritization settings chosen by the user. The summary also includes information on reportable variants that may be predictive of an increased risk for cancer progression. All MH data collated in the summary are gathered from a database based on information in peer-reviewed and published evidence, curated by MH biomedical experts.

In *MH Mendel,* users can store their own variant classifications, phenotypes, and treatment associations. Based on these data, users can create a clinical diagnostic report for hereditary diseases.

In *MH BRCA,* users can store their own variant classifications, phenotypes, and treatment associations. Based on these data, users can create a clinical diagnostic report for hereditary breast and ovarian cancer (HBOC) predispositions.

MH Guide, *MH Guide Premium*, and *MH Mendel, MH Mendel Premium,* and *MH BRCA* and *MH BRCA Premium* are only for use by trained medical experts. No other use of the in vitro diagnostic medical device is intended.

Some of the components, functions, and features described here may not be available in the current software release or in all sales regions.

Intended user groups

MH Guide is intended to assist clinical laboratories, human geneticists, board-certified molecular pathologists, medical specialists in pathology, medical specialist in laboratory medicine, oncologist, or molecular geneticists in their preparation of patients' clinical reports.

For *MH Mendel* and *MH BRCA*, the intended user group is typically limited to medical specialist in human genetics, human geneticists, or genetic counselors.

We distinguish between the following intended user groups to reflect differing regulatory frameworks, country-specific conditions for scientific education, and the usage context.

1. Intended user group in EMEA

Medical professionals using *MH Guide*, *MH Mendel* or *MH BRCA* access the software from a desktop or mobile device using a web browser. The software is designed for use by the following user groups.

MH Guide:

- **MH-certified physician (CP):** CP users can sign off *MH Guide, MH Guide Premium, and MH Guide Onco Report+* cases, and access *MH Guide Onco Report* cases. CP users can modify lab test-specific filters and rulesets. They can place orders using the *MH Order Portal*. A CP typically has a special qualification as a Molecular Pathologist, Molecular Geneticist, or Oncologist and is trained in the use of the MH Guide software. Other expert users such as molecular pathologists that do not have a qualification as physician, may also take the role of a CP at the discretion of a responsible physician that is identified in the master service agreement.
- **MH-certified physician oncologist (CPO):** A CPO has the same rights as a CP but **cannot** modify lab test-specific filters and rulesets.
- **MH-certified physician's assistant (CPA):** CPA users typically prepare reports for review and sign off by a CP or CPO, as described above. CPA users **cannot sign** *MH Guide* and *MH Guide Premium* cases but can sign *MH Guide Onco Report+* cases and access *MH Guide Onco Report* cases. They can place orders using the *MH Order Portal*.
- **Research physician (RP)**: RP users have full access to *MH Guide Onco Report,* and *MH Guide Onco Report+* cases as Research Use only cases, without full *MH Guide* claims on an CE marked IVD. They can place orders using the *MH Order Portal*.
- **Guest user (GU)**: Guest user denotes a user invited to collaborate on a single case by a colleague responsible for this case (Case sharing). Guest user access is granted on an individual case with read-only rights and expires after 30 days.

MH Mendel:

- **Human Geneticist (HG**): HG users have full access to *MH Mendel* and *MH Mendel Premium*. They can place orders using the *MH Order Portal*. Users with this role are typically human geneticists or genetic counselors.
- **Guest user (GU)**: Guest user denotes a user invited to collaborate on a single case by a colleague responsible for this case (Case sharing). Guest user access is granted on an individual case with read-only rights and expires after 30 days.

MH BRCA:

- **Human Geneticist (HG**): HG users have full access to *MH BRCA* and *MH BRCA Premium*. They can place orders using the *MH Order Portal*. Users with this role are typically human geneticists or genetic counselors.
- **Guest user (GU)**: Guest user denotes a user invited to collaborate on a single case by a colleague responsible for this case (Case sharing). Guest user access is granted on an individual case with read-only rights and expires after 30 days.

MH Order Portal:

- **CP, CPO, RP and HG users:** These user roles can use the full functionality of the *MH Order Portal*
- **MH Order Portal-only user (OPO):** This user group can use the full functionality of the *MH Order Portal*, but has no tasks in *MH Guide*, *MH Mendel*, or *MH BRCA*, and in consequence no access rights to the respective user interfaces.
- **Lab user (LU):** this user is a member of a lab registered in the *MH Order Portal*. The lab user can update the status of cases ordered at his lab and trigger an *MH Guide, MH Mendel, or MH BRCA* analysis by uploading the required sequencing files.

2. Intended user group in the US

MH Guide, MH Mendel, and *MH BRCA* allow the trained user group of Molecular Pathologists or Molecular Geneticists to identify genetic variant data from a patient's cancer sample.

MH Guide provides trained users with a database of medically and scientifically curated, peer-reviewed, and published evidence to enable them to generate a summary, based upon the published literature, of potentially effective medications, potentially ineffective medications, and medications that may pose a higher risk of adverse reactions, for the user-defined list of reportable variants. Information on reportable variants that the literature identifies as predictive of an increased risk for cancer progression is also provided.

MH Mendel allows the trained user group of Molecular Pathologists or Molecular Geneticists to identify genetic variant data from a patient germline sample. *MH Mendel* provides trained users with annotations from external databases to support them in classification and interpretation of their reportable variants and the creation of their diagnostic report.

MH BRCA allows the trained user group of Molecular Pathologists or Molecular Geneticists to identify genetic variant data from a patient germline sample in genes associated with hereditary breast and ovarian cancer. *MH BRCA* provides trained users with annotations from external databases to support them in classification and interpretation of their reportable variants and the creation of their diagnostic report.

Patients and diseases

MH Guide allows trained physicians, molecular pathologists, or molecular geneticists to interpret genetic variant data from a patient's cancer sample. It is designed to analyze molecular data from patients diagnosed with any cancer. Diseases beyond this are out of the scope of this workflow.

MH Guide requires a defined diagnostic MeSH code as input. However, as the analysis encompasses the entire biomedical reference information available in the system, data from a patient with an unspecified cancer type can be interpreted.

MH Mendel allows human geneticists to classify and interpret genetic variant data from a patient sample. It is designed to analyze molecular data from patients potentially suffering from hereditary diseases or disease predispositions that are not listed in the section 'Exclusions for intended use' of this document. Diseases beyond this are out of the scope of this workflow.

MH BRCA allows human geneticists to classify and interpret genetic variant data from a patient sample. It is designed to analyze molecular data from patients potentially suffering from hereditary breast and ovarian cancer predispositions. Diseases beyond this indication, including diseases listed in the section 'Exclusions for intended use' of this document, are out of the scope of this workflow.

MH Guide, *MH Mendel* and *MH BRCA* analyses are not limited by patient age, gender, ethnicity, disease stage, or by previous treatments. For regulatory reasons, it is current practice to not represent the exact age of patients over 90 years of age.

Foreseeable misuse

MH Guide is a software that can be used to analyze a wide range of genomic input data.

If *MH Guide* is used for any disease other than cancer, the output information may be incomplete and therefore misleading. Since *MH Guide* requires a cancer-related disease code for a successful analysis, one situation in which misuse could occur is if an incorrect disease code is provided with the order. The same applies for erroneously paired input data, e.g., from two different patients, or from submission of a germline sample as input for an unpaired cancer analysis.

If *MH Guide Mendel* is used for other purposes than analysis of hereditary diseases and disease predispositions, e.g., for tumor analyses, the output information may be incomplete and therefore misleading.

If *MH Guide BRCA* is used for other purposes than analysis of hereditary breast and ovarian cancer predispositions, e.g., for tumor analyses or other hereditary diseases, the output information may be incomplete and therefore misleading.

The medical professional could in theory grant the patient access to *MH Guide*, *MH Mendel, or MH BRCA*, or use the unsigned report or the uninterpreted data as a means of communication with the patient. Such unintended and unsupervised access by untrained users could lead to inaccurate interpretations of the patient's status and treatment options.

Exclusion for intended use

- The software will not be made accessible to or operated by untrained personnel.
- The software will not be used by patients.
- The prefilled report as provided by *MH Guide, MH Mendel,* or *MH BRCA* is not intended to be shared directly with a non-trained physician. A CP may however share a specific case with a colleague who is a qualified physician for the purpose of gaining a second opinion, before the CP completes and signs the report
- *MH Guide* does not provide an automatically generated treatment recommendation. *MH Guide* supports the clinical decision-making process, analogous to a medical handbook, scientific literature, treatment guideline, or a diagnostic test. *MH Guide* provides annotations for genomic alterations detected in a patient's genome and provide a clinical annotation of this information. Although *MH Guide* automatically correlates the detected genetic variants with clinical information about potential drug response, resistance, or toxicity, this information must always be interpreted and adapted by a specially trained medical professional. The information provided by *MH Guide* is only suitable for use to support the process of treatment prioritization in the context of this medical interpretation and adaption.
- *MH Mendel* and *MH BRCA* do not provide an automatically generated diagnosis. They rather support human geneticists by providing them with a means to save and reuse variant classifications and interpretations (CVIs). CVIs provided by MH for these products are automatically generated based on variant to-phenotype associations from external databases such as the ClinVar database. These CVIs are not curated or approved by MH experts and are not intended for direct inclusion in reports by the user. These CVIs are meant as a template for users to facilitate the efficient generation of custom CVIs. The information provided by *MH Mendel* and *MH BRCA* is only suitable for use to support the process of diagnosing a patient.

- *MH Guide, MH Mendel* and *MH BRCA* cannot be used to automatically compare multiple patient data sets ('cohort analysis')
- Sequencing data, for example from whole exome sequencing, may contain additional variant data that is not part of *MH Guide, MH Mendel* or *MH BRCA*
- The following indications and markers are excluded from clinical reporting with MH Guide, MH Mendel and MH BRCA even though genetic and annotation data may support this. Therefore, diagnoses of the following nature shall not be reported with *MH Guide, MH Mendel, or MH BRCA*:
    - Blood groups
    - Infections and infectious diseases
    - Irregular anti-erythrocytic antibodies
    - Hereditary disease phenylketonuria
    - HLA tissue groups: DR, A, B
    - Tumoral marker: PSA
    - Risk of trisomy 21

5 Combination with other products

MH Guide, MH Mendel and *MH BRCA* can optionally be combined with *MH Order Portal*. The *MH Order Portal* is an optional accessory that fulfills customers' needs in the pre- and post-analysis phases in the ordering and supply chain processes.

MH Guide can process patient genetic data or next-generation (NGS) sequencing data of various analysis types. As described in the section 'Input formats', MH Guide analyses can be either paired (comparing a cancer sample with a control sample) or unpaired (cancer sample only), and the analyzed sample can be of a targeted gene panel or of the whole exome (WES).

MH Guide is designed to analyze genetic input data from an IVD in a format accepted by *MH Guide*, or data generated as directed by the trained physician ordering the analysis.

The administration of the users and organizational units, the labtests and configuration settings of *MH Guide, MH Mendel,* and *MH Order Portal* is managed using the *MH Admin portal*. *MH Admin portal* is provided as a SaaS and it is intended to be used only by internal MH users. Further details are described in the product description of *MH Admin portal*.

The interoperability of each accessory with *MH Guide* and internal subcomponents is part of the relevant verification and validation phase and is included in the overall assessment of each release decision.

6 Regulations

Molecular Health GmbH is certified according to ISO 13485 for the 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. Molecular Health is accredited according to the CLIA/CAP (Clinical Laboratory Improvement Amendments/College of American Pathologists).

The *MH Guide* system fulfills the requirements of an in vitro diagnostic device (IVD), is registered as an in vitro diagnostic medical device (IVD) in Europe, and is CE-marked in compliance with the European Union's Directive on in vitro diagnostic medical devices 98/79/EC.

MH Guide is designed to analyze genetic input data from an IVD in a format accepted by *MH Guide*, or data generated as directed by the trained physician ordering the analysis. Specifically, given NGS sequencing data in FASTQ format that meet the QC criteria of *MH Guide*, *MH Guide* produces variant calls of sufficient accuracy, precision, and sensitivity (recall) and its results were validated with synthetic and clinical data. The estimated average precision and sensitivity for unpaired (panel) and paired analyses (whole exome) for the variant types that can be called by the MH Guide and MH Mendel Variant Detection Pipelines are available as summative evaluation results upon written request. *MH Guide* meets the requirements of HIPAA in the US (Health Insurance Portability and Accountability Act), and in the EU it complies fully with the requirements of the GDPR (General Data Protection Regulation) and GenDG (Gendiagnostik-Gesetz, German Genetic Diagnostic Law).

MH Guide Onco Report, MH Guide Onco Report+ and *MH Guide Onco Report Premium* are explicitly non-IVD related reports for non-clinical use, as described in the Section ‚Intended use'.