Product Description

Including

For software version 5.0

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1 Product overview

MH Guide/BRCA, *MH Guide/Mendel*, and *MH Order Portal* are part of *MH Guide*, and provided as Software as a Service (SaaS). *MH Guide, MH Guide/BRCA*, and *MH Guide/Mendel* can be used for analysis of next-generation sequencing (NGS) data in FASTQ format, or genetic and molecular alteration data in VCF format. They can be used in an interactive mode and can provide analysis results as a digital Clinical Molecular Record (MH CMR) in JSON or XML format, and as a report in PDF format.

MH Guide

MH Guide is a stand-alone software as a service (SaaS) used for *in vitro* examination of next-generation sequencing (NGS) data or genetic and molecular alteration data to provide information to aid in the determination of treatment options based on genetic biomarkers and medical guidelines for patients diagnosed with cancer (solid and hematological cancers). *MH Guide* is used as an expert system for patient management by trained healthcare professionals qualified in genetics and oncology.

Core Features of MH Guide

- **Case management:** users can sort, search, and filter cases in a list, change case status, and download signed case reports.
- **Case quality control (QC) and file download:** users can access QC information per analyzed case, and download results, log files and intermediate files.
- **Audit trail:** an audit trail is available for all editing actions that affect reports.
- **Case metadata management:** case metadata can be edited, and cases are automatically re-calculated based on the updated information.
- **Filter and ruleset management:** filters and rulesets are automatically applied to processed cases. They include technical and non-technical variant filters, lineage and zygosity classification and filter, matching parameters for Clinical Variant Interpretations (CVIs), pre-selection and sort order of reported treatments and findings, and calculation of Tumor Mutational Burden (TMB). Use of provided defaults, or modified rulesets and filters are at the sole responsibility of the customer. Technical filters and CVI matching parameters can only be modified on request by MH personnel for regions in which *MH Guide* is provided as an IVD.
- **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. In addition, users can define gene filters that exclude variants in genes that are not in the scope of their current analysis.
- **Variant classification:** variants are automatically pre-classified based on ACMG rules. Variant classifications can be modified and stored for future use, either by changing ACMG criteria, or by directly assigning a variant classification (Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, Benign).
- **Variant annotation and interpretation:** for each detected variant, available annotations and interpretations are automatically identified and displayed. This includes proprietary curated variant

classification data, functional variant effect data, and CVIs, as well as a wide range of external data sources such as gnomAD, ClinVar, COSMIC, and dbNSFP.

- **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, microsatellite instability, and homologous recombination deficiency.
- **Clinical Variant Interpretation (CVI) management:** for each detected variant, users can create their own CVIs for future use. User-created CVIs are shared within an organizational unit and are not part of the CE-marked product. User-created CVIs can be inactivated to exclude them from use in future cases.
- **Treatment-centric tabs:** 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. Users can prioritize treatment recommendations by modifying the sort order or (de-)select them for the report. Treatment-centric tabs are not CE-marked.
- **Access to *MH Drug Explorer*:** a product 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:*** a product that can be accessed from MH Guide patient cases, is for non-clinical use only, and can be used to better understand a patient's tumor and where in a pathway treatment-relevant biomarkers are located.
- **Clinical trials tab:** 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. The Clinical trials tab is not CE-marked.
- **Medical guidelines tab:** 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. 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. The Medical guidelines tab is not CE-marked.
- **Prognostic and diagnostic tab:** 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. The Prognostic and Diagnostic tabs are not CE-marked.
- **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, a summary of the mutational load, and information from manually added additional test results. A lab-specific disclaimer can be attached to reports. The interactive report preview is not CE-marked.
- **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. The report is not CE-marked.

- **Automated CMR output:** The system can be configured to automatically create an MH CMR file in JSON or XML format for signed cases. The MH CMR is not CE-marked.

MH Guide/BRCA

MH Guide/BRCA is a stand-alone software as a service (SaaS) used for *in vitro* examination of next-generation sequencing (NGS) data or genetic and molecular alteration data to provide information to determine hereditary cancer predisposition for patients suspected of being at risk of a hereditary predisposition to breast and ovarian cancer syndrome (HBOC). *MH Guide/BRCA* is used as an expert system by trained healthcare professionals qualified in molecular diagnostics.

Core Features of MH Guide/BRCA

- **Case management:** users can sort, search, and filter cases in a list, change case status, and download signed case reports.
- **Case quality control (QC) and file download:** users can access QC information per analyzed case, and download results, log files and intermediate files.
- **Audit trail:** an audit trail is available for all editing actions that affect reports.
- **Case metadata management:** case metadata can be edited, and cases are automatically re-calculated based on the updated information.
- **Filter and ruleset management:** filters and rulesets are automatically applied to processed cases. They include technical and non-technical variant filters, and zygosity classification. Use of provided defaults, or modified rulesets and filters are at the sole responsibility of the customer. Technical filters can only be modified on request by MH personnel for regions in which *MH Guide/BRCA* is provided as an IVD.
- **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. In addition, users can define and gene filters that exclude variants in genes that are not in the scope of their current analysis.
- **Variant classification:** variants are automatically pre-classified based on ACMG rules. Variant classifications can be modified and stored for future use, either by changing ACMG criteria, or by directly assigning a variant classification (Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, Benign).
- **Variant annotation:** for each detected variant, available annotations are automatically identified and displayed. This includes proprietary curated variant classification data and functional variant effect data, as well as a wide range of external data sources such as gnomAD, ClinVar, COSMIC, and dbNSFP.
- **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. The interactive report preview is not CE-marked.
- **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. The report is not CE-marked.

- **Automated CMR output:** The system can be configured to automatically create an MH CMR file in JSON or XML format for signed cases. The MH CMR is not CE-marked.

MH Guide/Mendel

MH Guide/Mendel is a stand-alone software as a service (SaaS) used for *in vitro* examination of next-generation sequencing (NGS) data or genetic and molecular alteration data to provide information to aid in the diagnosis of hereditary diseases or disease predispositions for patients suspected of being at risk of these diseases. *MH Guide/Mendel* is used as an expert system by trained healthcare professionals qualified in molecular diagnostics.

Core Features of MH Guide/Mendel

- **Case management:** users can sort, search, and filter cases in a list, change case status, and download signed case reports.
- **Case quality control (QC) and file download:** users can access QC information per analyzed case, and download results, log files and intermediate files.
- **Audit trail:** an audit trail is available for all editing actions that affect reports.
- **Case metadata management:** case metadata can be edited, and cases are automatically re-calculated based on the updated information.
- **Filter and ruleset management:** filters and rulesets are automatically applied to processed cases. They include technical and non-technical variant filters, and zygosity classification. Use of provided defaults, or modified rulesets and filters are at the sole responsibility of the customer. Technical filters can only be modified on request by MH personnel for regions in which *MH Guide/Mendel* is provided as an IVD.
- **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. In addition, users can define and gene filters that exclude variants in genes that are not in the scope of their current analysis.
- **Variant classification:** variants are automatically pre-classified based on ACMG rules. Variant classifications can be modified and stored for future use, either by changing ACMG criteria, or by directly assigning a variant classification (Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, Benign).
- **Variant annotation:** for each detected variant, available annotations are automatically identified and displayed. This includes proprietary curated variant classification data and functional variant effect data, as well as a wide range of external data sources such as gnomAD, ClinVar, COSMIC, and dbNSFP.
- **CVI management:** for each detected variant, users can create their own CVIs for future use. User-created CVIs are shared within an organizational unit and are not part of the CE-marked product. CVIs are automatically prefilled based on available annotation data and current variant classification. User-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 in user-created CVIs. A phenotype description, inheritance information, and associated

symptoms are provided per phenotype. Users can select which phenotypes should be included in the report. The Phenotypes tab is not CE-marked.

- **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. The interactive report preview is not CE-marked.
- **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. The report is not CE-marked.
- **Automated CMR output:** The system can be configured to automatically create an MH CMR file in JSON or XML format for signed cases. The MH CMR is not CE-marked.

MH Order Portal

MH Order Portal is provided as software as a service (SaaS) and can be used for the ordering of *MH Guide, MH Guide/BRCA,* and *MH Guide/Mendel* analyses. *MH Order Portal* provides a graphical user interface for input case metadata and sequencing data upload. Alternatively, case metadata and FASTQ or VCF files can be uploaded using the MH SFTP servers (Secure Shell file transfer protocol). The *MH Order Portal* is a non-medical device module of MH Guide.

Core Features of MH Order Portal

- **Order management:** users can sort, search, filter ordered cases in a list, and check and change case status.
- **Case quality control (QC) and file download:** users can access QC information per analyzed case, and download results, log files and intermediate files.
- **Order creation:** users can create orders for *MH Guide, MH Guide/BRCA*, and *MH Guide/Mendel* lab tests assigned to their organization.
- **Case metadata input:** users can enter mandatory and optional case metadata for their orders. Completeness and correctness of the provided case data and lab test selection are critical for the analysis results. The correctness and completeness of data entered using *MH Order Portal* is at the sole responsibility of the customer.
- **File upload:** users can upload next-generation sequencing (NGS) data or genetic and molecular alteration data and start the analysis after successful file upload. MD5 checksums can be used to verify correctness and completeness of the uploaded files. The correctness and completeness of uploaded data is at the sole responsibility of the customer.

2 Regulatory status

European Union

MH Guide/BRCA and MH Guide/Mendel, and *MH Order Portal* are part of *MH Guide*,. In the European Union, *MH Guide* is registered as an in vitro diagnostic medical device (IVD). Molecular Health GmbH is the legal manufacturer of *MH Guide* as a stand-alone software, and the statutory provisions of the German Medical Devices Act (MPG) and the European Directive 98/79/EC apply. Molecular Health therefore maintains a quality management system according to EN ISO 13485 for the scope of "Design, Development and Manufacture of software systems for the integrated analysis of clinical and genomic patient data to support treatment decisions and provision of related services".

USA

MH Guide/BRCA and *MH Guide/Mendel,* and *MH Order Portal* are part of *MH Guide*. *MH Guide* has not been cleared or approved by the U.S. Food and Drug Administration (FDA). *MH Guide* with VCF input is offered as a bioinformatics service under CLIA. *MH Guide* using FASTQ input is not offered for clinical use in the USA. Molecular Health GmbH (MH) has received CLIA certification and CAP accreditation for the provision of MH Guide as a dry lab service to clinical laboratories in the US.

Other regions

MH Guide/BRCA, MH Guide/Mendel, and *MH Order Portal* are part of *MH Guide*. *MH Guide* is offered by Molecular Health GmbH as an off-shore service. *MH Guide* has not been cleared or approved as an in vitro diagnostic medical device (IVD) by regulatory authorities outside of the European Union.

3 Variant detection from FASTQ input

For FASTQ input, the MH Variant Detection Pipeline (MH VDP) is provided for GRCh37-based identification of variants and other biomarkers with *MH Guide, MH Guide/BRCA*, and *MH Guide/Mendel*. The MH VDP can process sequencing data from commercial panels, custom panels, and whole exome sequencing (WES). The MH VDP is validated for processing hybrid-capture based sequencing data from Illumina sequencing platforms. MH reserves the right to inform customers and data providers about QC issues, and to reject processing of data that does not comply with the current MH sequencing guidelines.

Supported variant types and validated analytical performance

The validated analytical performance and limits of detection of the MH VDP vary per product, assay type, and variant type. The performance is highly dependent on the quality of sample and sequencing data. Uploaded sequencing data must comply with the current MH sequencing guidelines. ***Table 1*** provides an

overview of supported assay types, variant types, validated analytical performance, limits of detection and relevant specifics of the used validation samples.

Table 1: Overview of supported assay and variant types, validated analytical performance, limits of detection and relevant validation sample specifics per product. *Precision, Sensitivity, and limits of detection of the MH VDP were calculated using validation samples 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.*

Product	Assay type	Variant Type	Sensitivity	Precision	Limits of detection and validation sample specifics
MH Guide/BRCA, MH Guide/Mendel	DNA sequencing panel and WES analyses (germline sample)	SNV	≥99%	≥99%	VAF ≥10%, ≥38x coverage at variant position, in samples with 100x average sequencing coverage.
		Indel	≥98%	≥98%	VAF ≥10%, ≥38x coverage at variant position, in samples with 100x average sequencing coverage.
MH Guide	DNA sequencing panel analyses (tumor sample only)	SNV	≥99%	≥99%	Tumor content ≥20%, VAF ≥5%, ≥95x coverage at variant position, in samples with 500x average sequencing coverage.
		Indel	≥97%	≥99%	Tumor content ≥20%, VAF ≥5%, ≥95x coverage at variant position, in samples with 500x average sequencing coverage.
		Fusion	≥100%	≥100%	Tumor content ≥20%, supporting read pairs ≥10.
	DNA sequencing WES analyses (tumor + germline control sample)	SNV Tumor: Control:	≥97% ≥99%	≥97% ≥98%	VAF ≥5%, ≥20x coverage at variant position, in tumor samples with 200x average coverage and tumor content ≥20%, and control samples with 100x average coverage.
		Indel Tumor: Control:	≥95% ≥98%	≥99% ≥98%	VAF ≥5%, ≥20x coverage at variant position, in tumor samples with 200x average coverage and tumor content ≥20%, and control samples with 100x average coverage.
		CNA loss	95%	95%	Tumor samples with 200x average coverage and tumor content ≥50%; control samples with 100x average coverage. Detection only for genes with MH CVI for CNA loss.

Product	Assay type	Variant Type	Sensitivity	Precision	Limits of detection and validation sample specifics
		CNA gain	71%	99%	Tumor samples with 200x average coverage and tumor content ≥50%; control samples with 100x average coverage. Detection only for genes with MH CVI for CNA gain and copy number ≥4.
		MSI-H	88%	100%	Samples without sequencing QC warnings.
	RNA sequencing panel and whole transcriptome analyses (tumor sample)	Fusion	≥94%	≥83%	Supporting reads ≥2
	DNA sequencing panel and WES analyses (tumor, or tumor + control sample)	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.
MH Guide, MH Guide/BRCA, MH Guide/Mendel	Protein mapping	SNV/Indel	99%	97%	n/a
	Transcript mapping	SNV/Indel	99%	90%	n/a
	Variant annotation	All supported types	99%	100%	n/a
	Variant ACMG classification	SNV/MNP/ Indel	75%	99%	n/a

4 Transcript and protein mapping

Transcript and protein mapping is done for FASTQ and VCF input. Genomic variants 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) and can process TMB, MSI, and HRD status from VCF. The system 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 annotation dataset. Copy number alterations are mapped to all genes fully covered by the genomic region submitted in the VCF input, if no gene is provided. Fusions are mapped to all genes covering the fusion breakpoints submitted in the VCF input, if no genes are provided.

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

The data used in *MH Guide*, *MH Guide/BRCA*, and *MH Guide/Mendel* 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 in regular intervals.

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

MH Guide, *MH Guide/BRCA,* and *MH Guide/Mendel* are based on a pre-integrated, quality-approved data set that draws from more than 30 external databases. Due to different update frequencies of the data sources, some of the information provided may not be fully up-to date.

Major software upgrades will only be applied after user notification, 5 business days ahead of time.

6 Input formats

Analyses with *MH Guide*, *MH Guide/BRCA*, and *MH Guide/Mendel* require next-generation sequencing (NGS) data or genetic and molecular alteration data and accompanying case metadata. Raw NGS data can be provided in FASTQ format for analysis. Pre-processed genetic and molecular alteration data for SNVs,

Indels, Fusions, CNAs, MSI, HRD, and TMB can be provided in VCF format for analysis. Uploaded VCF files must comply with the VCF standard defined by MH (MH VCF).

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 qualified lab.

For VCF based lab tests, organizations must define filtering criteria for every lab test 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 customers to only provide true positive variants, or to to provide MH with the technical filter parameter based on the established and validated performance characteristics and limits of detection of the variant detection pipeline with which the VCF was created.

Other types of molecular alterations identified for a patient from validated assays can be added manually within the user interface for *MH Guide* and *MH Guide/Mendel*.

7 Inbound interfaces

Users can easily and securely upload the files containing variant information and patient metadata using SFTP or via *MH Order Portal*.

Due to its open nature on the inbound and outbound side, *MH Guide*, *MH Guide/BRCA*, and *MH Guide/Mendel* can be integrated into external systems.

Adapters for transformation of VCF files from various tests into the MH VCF format are available from Molecular Health as a consulting service. Such transformations are not part of the product and must be run in the customer's local environment, prior to uploading files.

8 Output formats

Depending on the *MH Guide, MH Guide/BRCA,* and *MH Guide/Mendel* configuration, the analysis results can be provided in PDF format, as MH CMR in JSON or XML format, or in other customized output formats.

- **PDF Report:** Standard report templates are available for *MH Guide, MH Guide/BRCA,* and *MH Guide/Mendel*. On request, the appearance and content of PDF format reports can be customized by MH as a professional service. PDF reports are available for download in the user interface and via SFTP.
- **MH CMR:** the MH CMR can be produced in JSON and XML format for easy incorporation into other systems and databases. 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.

- **Customized output formats:** customized output formats (e.g., XLSX format), can be provided on request by MH as a professional service. Customized output files are available for download in the user interface and via SFTP.
- The system can support processing of up to 100,000 variants per case. Creation of clinical reports and MH CMRs with more than 10,000 reported variants is not supported.

9 Analysis turnaround time

Analysis of MH VCF files: Below five minutes. In exceptional cases with large numbers of variants, for extremely hyper-mutated-samples, analysis may take up to 2 hours.

Analysis of FASTQ files: Typical turnaround times from FASTQ input are below one day but are highly dependent on the target region size and coverage of the NGS experiment. The MH VDP typically takes less than 1 day if MH's processes and quality standards are met by the customer. As an example, our reference sample based on an unpaired 600+ gene panel with 500x coverage is processed in less than 4 hours. Smaller panels may be processed significantly faster. Experiments with extensive target regions such as WES analyses might run significantly longer.

The network transfer time from the customer to MH servers is not included in the turnaround time since the local and geographic bandwidth is in the sole responsibility of the customer.

If the customer or geographic network is limited, we provide a consulting solution called "MH VDP in a box" which contains the MH VDP and additional components for creating a VCF locally from a FASTQ file.

10 Data storage

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

VCF input is stored for 2 years. Molecular Health does not take responsibility for FASTQ and BAM file storage.

In the EU, analysis results like reports are stored for 10 years according to GenDG §12. In other regions, analysis results are also stored for 10 years.

11 Limitation of user numbers per role and contract

MH Guide, MH Guide/BRCA, MH Guide/Mendel, and *MH Order Portal* are multi-user software applications. Users are configured as named users and can have different user roles depending on their professional working role. 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 Guide/BRCA & MH Guide/Mendel	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 Guide/BRCA,* and *MH Guide/Mendel* 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)**.

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

12 System Description and Requirements

MH Guide, MH Guide/BRCA, MH Guide/Mendel, and *MH Order Portal* are provided as a software as a service (SaaS) on a secure, cloud-based platform.

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

- 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 on request - showing the measured uptime which shall be the basis for calculating the service level.

The platform is operated by Molecular Health following the IVD/HIPAA regulations at a HIPAA-compliant, and TSI certified professional hosting (housing) center. Login to the system is via an encrypted connection for data security reasons, and encryption of Protected Health Information (PHI) is offered.

MH Guide, MH Guide/BRCA, MH Guide/Mendel, and *MH Order Portal* were tested on Google Chrome (Version 91.0.4472.114 (Official Build) (64-bit)) using Windows 10 (64-bit). We therefore recommend this browser version for best performance.

Based on published browser compatibility comparisons, Edge and Opera are expected to be compatible as well. Other browsers such as Safari or Internet Explorer may not support all *MH Guide* functionalities, as they may 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 (Hypertext Transfer Protocol Secure) and a corresponding connectivity to Germany.

For data upload, the SSH file transfer protocol is used (SFTP) between the customer's local IT systems (or sequencing machines) and MH's hosting center in Germany needs to be established to transfer files. Alternatively, *MH Order Portal* can be used for data input and file upload via the web browser. A hybrid approach combining MH Order Portal (for entering patient data) and SFTP (for uploading sequencing files) is also available.