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Evaluation of annotations for cancer gene panel testing using a genome-guided system

Yu Sunakawa[1,2], Peter Koch[3], Hiroyuki Yamamoto[2,4], Ai Motoyoshi[2,5], Kiyomi Imoto[2], Martin Maerz[3], and Yoshihisa Yamano[2,6,7]

1 Department of Clinical Oncology, St. Marianna University School of Medicine, 2 Center for Genomic Medicine, St. Marianna University Hospital, 3 Molecular Health Inc., 4 Department of Bioinformatics, St. Marianna University Graduate School of Medicine, 5 Division of Breast and Endocrine Surgery, Department of Surgery, St Marianna University School of Medicine, 6 Division of Neurology, Department of Internal Medicine, St. Marianna University School of Medicine, 7 Department of Rare Diseases Research, Institute of Medical Science, St. Marianna University School of Medicine

Conflict of Interest disclosure slide for representative speakers or investigators

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Name of lead presenter	Yu Sunakawa	Institution or company/position	St. Marianna University School of Medicine

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contributions or endowed chair	☐	
fees of testimony, judgment, comment, etc.	☐	
presents or other payment	☐	
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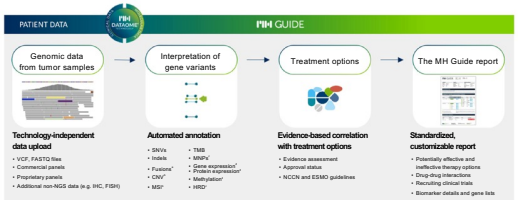
Background

- In Japan, oncogene panel testing is covered by public insurance since June 2019, and it is now mandatory to explain to the patients the results of testing, after interpretation by an Expert Panel (EP) at cancer genomic medicine hospitals.
- Therefore, the work-load for interpreting genomic data and proposing treatments based on the results is tremendous for clinicians, making an automated annotation system desirable.

Methods

- This trial evaluated the clinical utility of a treatment decision support software soon to become IVD approved in Japan and used in clinics world-wide. MH Guide from Molecular Health Inc. (MH, Heidelberg, Germany) interpretes NGS data generated from patients who underwent cancer gene panel testing and who gave consent to secondary use of the test results at St. Marianna University Hospital.
- XML files of Foundation One CDx and NCC Oncopanel testing were sent to the MH, then the annotation success rate was investigated.
- In addition, we exploratively compared the results of the expert panel with those of the MH Guide system.

Analysis Flow



MH Guide system

MH Guide transforms NGS data from the patient's tumor into clinically actionable information, helping you to select the most effective and safe treatment options for individual cancer patients.

Profiling: MH Guide generates a comprehensive molecular tumor profile. This includes analysis of drug safety risk factors, including resistance mechanisms and toxicity (treatment side effects).

Matching: The genetic profile of the patient's tumor is annotated with the most recently published biomedical peer reviewed evidence. MH Guide also provides information about potentially relevant active clinical trials.

Reporting: The report includes information about approved drugs and biomarkers, as well as lists of drugs in clinical trials.

Results: patient characteristics

- Six patients were enrolled from March 2021 to November 2021: male/female 2/4, esophageal cancer/colon cancer/renal cell carcinoma/cancer of unknown primary 3/1/1/1. Foundation One CDx and NCC Oncopanel were performed in 5 and 1 patients, respectively.

	Cancer type	Age	Gender	Type of panel testing
1	Esophageal	58	Female	Foundation One CDx
2	Esophageal	48	Male	Foundation One CDx
3	Primary unknown	67	Female	Foundation One CDx
4	Esophageal	78	Female	NCC oncopanel
5	Kidney	42	Male	Foundation One CDx
6	Colon	57	Female	Foundation One CDx

No.1: Esophageal cancer

	Expert Panel Gene ➡ drug (evidence of clinical practice guidance)	MH Guide Gene ➡ drug (AMP/ASCO/CAP category)<CVI score>
Genomic testing report: Actionable genes	ATM Y2019C, CCND1 amp, CDKN2A M53fs*67, CRKL amp. FGF19 amp, FGF3 amp, FGF4 amp, MAPK1 amp, SPEN Q1564*, TP53 L130V	
Druggable gene with evidence D or higher	ATM Y2019C ➡ olaparib(C) FGF19 amp ➡ sorafenib(D) CCND1 amp ➡ palbociclib(D) CDKN2A M53fs*67 ➡ CDK4/6 inhibitor(D)	ATM Y2019C ➡ olaparib(Tier IIC)<6> FGF19 amp ➡ sorafenib(Tier IID)<3> erdafitinib(Tier IID)<3> CCND1 amp ➡ palbociclib(n/a)<1> CDKN2A M53fs*67 ➡ CDK4/6 inhibitor (n/a)<2>
Druggable gene with evidence C or higher	ATM Y2019C ➡ olaparib(C)	ATM Y2019C ➡ olaparib (Tier IIC)<6>

No.2: Esophageal cancer

	Expert Panel Gene ➡ drug (evidence of clinical practice guidance)	MH Guide Gene ➡ drug (AMP/ASCO/CAP category)<CVI score>
Genomic testing report: Actionable genes	BRCA2 S492fs*17, CCND1 amp, FGF19 amp. FGF3 amp. FGF4 amp, MLL2 E3562fs*97, NFE2L2 E82A, TP53 Y163C	
Druggable gene with evidence D or higher	FGF19 amp ➡ sorafenib(D) CCND1 amp ➡ palbociclib(D) BRCA2 S492fs*17 ➡ PARP inhibitor(C)	FGF19 amp ➡ sorafenib(Tier IID)<3> erdafitinib(Tier IID)<3> CCND1 amp ➡ palbociclib(n/a)<1> BRCA2 p.S492fs*17 ➡ PARP inhibitor(Tier IIC)<6>
Druggable gene with evidence C or higher	BRCA2 S492fs*17 ➡ PARP inhibitor(C)	BRCA2 S492fs*17 ➡ PARP inhibitor (Tier IIC)<6>

No.3: Carcinoma of unknown primary

	Expert Panel Gene ➡ drug (evidence of clinical practice guidance)	MH Guide Gene ➡ drug (AMP/ASCO/CAP category)<CVI score>
Genomic testing report: Actionable genes	BRCA1 L63*, PIK3CA amp, SOX2 amp, C11orf30 amp, CRKL amp, PRKCI amp, TERC amp, TP53 Q331fs*14	
Druggable gene with evidence D or higher	BRCA1 L63* ➡ PARP inhibitor(C)	BRCA1 L63* ➡ PARP inhibitor(Tier IIC) <6>
Druggable gene with evidence C or higher	BRCA1 L63* ➡ PARP inhibitor(C)	BRCA1 L63* ➡ PARP inhibitor(Tier IIC) <6>

No.4: Esophageal cancer

	Expert Panel Gene ➡ drug (evidence of clinical practice guidance)	MH Guide Gene ➡ drug (AMP/ASCO/CAP category)<CVI score>
Genomic testing report: Actionable genes	TMB 10.9Muts/Mb, RB1 K844*, TP53 H179R, TP53 P85fs*38	
Druggable gene with evidence D or higher	TMB-High ➡ pembrolizumab(A)	TMB-High ➡ pembrolizumab(Tier IA) <7>
Druggable gene with evidence C or higher	TMB-High ➡ pembrolizumab(A)	TMB-High ➡ pembrolizumab(Tier IA) <7>

No.5: Renal cell cancer

	Expert Panel Gene ➡ drug (evidence of clinical practice guidance)	MH Guide Gene ➡ drug (AMP/ASCO/CAP category)<CVI score>
Genomic testing report: Actionable genes	CD274 amp, CDKN2A loss, CDKN2B loss, SETD2 E1749*, TP53 V173L, VHL F136S	
Druggable gene with evidence D or higher	CD274 amp ➡ ICI(D) VHL F136S ➡ everolimus, sunitinib(D) CDKN2A loss ➡ CDK4/6 inhibitor(D)	CD274 amp ➡ ICI(Tier IID)<4> VHL F136S ➡ belzutifan(n/a)<2> CDKN2A loss ➡ CDK4/6 inhibitor (Tier IID)<3>
Druggable gene with evidence C or higher	none	none

No.6: Colon cancer

	Expert Panel Gene ➡ drug (evidence of clinical practice guidance)	MH Guide Gene ➡ drug (AMP/ASCO/CAP category)<CVI score>
Genomic testing report: Actionable genes	FGFR4 N535K, PTEN loss, APC rearrangement exon 16, FAS loss, TP53 E171*	
Druggable gene with evidence D or higher	FGFR4 N535K ➡ erdafitinib(D)	PTEN loss ➡ Capivasertib(Tier IID)<3>
Druggable gene with evidence C or higher	none	none

Results:

- The annotation success rate of MH Guide was 100% while the time for analysis was a few minutes only.
- In 5 out of 6 patients, MH Guide showed 100% of druggable gene alterations which were picked up in the EP, with evidence D or higher of clinical practice guidance for next-generation sequencing conducted by 3 Japanese academic societies.
- MH Guide recommended the same treatment option as initially identified in the EP for gene alterations with evidence C or higher in all patients.

Conclusions

- The IVD approved treatment decision support software MH Guide was significantly faster in generating comprehensive patient reports.
- Treatment options identified with MH Guide were evaluated as equally good in comparison to original findings by the Expert Panel.