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Concordance Between Recommendations From Multidisciplinary Molecular Tumor Boards and Central Consensus for Cancer Treatment in Japan

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Abstract

IMPORTANCE Quality assurance of molecular tumor boards (MTBs) is crucial in cancer genome medicine.

OBJECTIVE To evaluate the concordance of recommendations by MTBs and centrally developed consensus treatment recommendations at all 12 leading institutions for cancer genomic medicine in Japan using 50 simulated cases.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective quality improvement study of 50 simulated cancer cases. Molecular tumor boards from 12 core hospitals independently recommended treatment for 50 cases blinded to the centrally developed consensus treatment recommendations. The study's central committee consisted of representatives from all 12 core hospitals in Japan who selected the 50 simulated cases from The Cancer Genome Atlas database, including frequently observed genomic alterations. The central committee recommended centrally developed consensus treatment. The concordance rate for genomically matched treatments between MTBs and centrally developed consensus treatment recommendations was evaluated. Data analysis was conducted from January 22 to March 3, 2021.

EXPOSURES Simulated cases of cancer.

MAIN OUTCOMES AND MEASURES The primary outcome was concordance, defined as the proportion of recommendations by MTBs concordant with centrally developed consensus treatment recommendations. A mixed-effects logistic regression model, adjusted for institutes as a random intercept, was applied. High evidence levels were defined as established biomarkers for which the treatment was ready for routine use in clinical practice, and low evidence levels were defined as biomarkers for genomically matched treatment that were under investigation.

RESULTS The *Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment* (edition 2.1) was used for evidence-level definition. The mean concordance between MTBs and centrally developed consensus treatment recommendations was 62% (95% CI, 57%-65%). Each MTB concordance varied from 48% to 86%. The concordance rate was higher in the subset of patients with colorectal cancer (100%; 95% CI, 94.0%-100%), *ROS1* fusion (100%; 95% CI, 85.5%-100%), and high evidence level A/R (A: 88%; 95% CI, 81.8%-93.0%; R:100%; 95% CI, 92.6%-100%). Conversely, the concordance rate was lower in cases of cervical cancer (11%; 95% CI, 3.1%-26.1%), *TP53* mutation (16%; 95% CI, 12.5%-19.9%), and low evidence level C/D/E (C: 30%; 95% CI, 24.7%-35.9%; D: 25%; 95% CI, 5.5%-57.2%; and E: 18%; 95% CI, 13.8%-23.0%). Multivariate analysis showed that evidence level (high [A/R] vs low [C/D/E]: odds ratio, 4.4; 95% CI, 1.8-10.8) and

(continued)

Key Points

Question Is there concordance between cancer treatment recommendations of regional molecular tumor boards and those made by a central consensus of oncologists?

Findings In this quality improvement study of 50 simulated cancer cases, the concordance rate of recommendations by molecular tumor boards and centrally developed consensus treatment recommendations was 62%, consistently concordant for genomic alterations for which treatment was established as standard of care. However, discrepancies were found for genomic alterations wherein treatment was based on low-level evidence.

Meaning The findings of this quality improvement study suggest that discrepancies between regional molecular tumor board recommendations and central consensus were greater when evidence for treatment was limited.

+ Supplemental content

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Abstract (continued)

TP53 alteration (yes vs no: odds ratio, 0.06; 95% CI, 0.03-0.10) were significantly associated with concordance.

CONCLUSIONS AND RELEVANCE The findings of this study suggest that genomically matched treatment recommendations differ among MTBs, particularly in genomic alterations with low evidence levels wherein treatment is being investigated. Sharing information on matched therapy for low evidence levels may be needed to improve the quality of MTBs.

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Introduction

Cancer is the leading cause of death worldwide, accounting for approximately 10 million deaths throughout the world in 2020.[1,2] Cancer causality continues to be investigated, but genomic alterations are crucial in cancer development; genomic medicine plays a key role in precision oncology and is rapidly developing.

In Japan, 2 comprehensive cancer genomic profiling (CGP) tests (Oncoguide NCC Oncopanel System [NCCOP] and FoundationOne CDx Cancer Genomic Profile [F1CDx]) were approved in December 2018 and began to be reimbursed in June 2019.[3] As of August 2022, more than 36 000 cases of one of these CGP tests had been registered at the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), which acts as a case repository and provides C-CAT findings, which reports annotations for gene alteration–matched therapies.[4] Cancer genomic profiling tests must be conducted at 12 designated core hospitals, 33 hub hospitals, and 185 cooperative hospitals for genomic cancer medicine. Cancer genomic profiling test results must also be reviewed by the multidisciplinary molecular tumor board (MTB) at designated core or hub hospitals, which are called expert panels. Molecular tumor board recommendations are developed, and results are explained to the patients by treating physicians. Each MTB must include medical oncology, genetics, pathology, and bioinformatics experts.

The role of MTBs is increasing worldwide; MTBs examine CGP test quality and results, perform annotations, form recommendations for genomically matched treatment, and evaluate the need for genetic counseling.[5,6] The recommendations for genomically matched treatment are based on the treatment guidelines as the standard of care in some cases; however, for approximately two-thirds of cases, investigational new drugs (INDs) were recommended by MTBs in previous reports.[7] Several observational studies and integrated analyses of multiple phase 1 or 2 trials have demonstrated that genomically matched IND treatment improves outcomes.[8-15] Therefore, appropriate recommendations for IND trials are crucial for improving outcomes in cancer.

A previous report[7] noted that recommendations varied across MTBs, particularly in the number of recommended IND trials. However, few studies have evaluated MTB quality. Therefore, we aimed to evaluate MTB quality using 50 simulated cases with centrally developed consensus treatment recommendations (central TRs).

Methods

Study Design

This prospective observational quality improvement study evaluated MTB quality and diversity in the 12 core hospitals in Japan. This study examined the concordance of recommendations by MTBs and central TRs using 50 simulated cases and explored the factors that affected the discordance between recommendations by MTBs and central TRs. This study followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) reporting guideline.[16] The institutional review board at

the National Cancer Center was consulted for the study protocol; however, this study did not include actual patients and did not require approval. All 12 core hospitals approved this decision before study inception. Data analysis was conducted from January 22 to March 3, 2021.

Procedures

Development of Simulated Cases

Simulated cases were developed to explore MTB quality at all 12 core hospitals. The frequently reported cancer types (lung, breast, colon, prostate, stomach, liver, uterus, esophagus, central nervous system, skin, ovary, and soft-tissue cancers) based on the CONCORD-3 report[2] were selected. Thereafter, we obtained frequency information on genetic mutations in each cancer type from The Cancer Genome Atlas[17] and important genomic alterations leading to therapies were identified. In general, variants able to be treated with drug therapy were included as important genomic alterations as a consensus by experts selected as representatives at each MTB from the 12 core hospitals (central committee). The central committee was organized in December 2019.

Using these data, each simulated case was developed by the central committee. Each representative produced 4 to 7 simulated case drafts that were centrally reviewed by all other representatives who then evaluated whether the simulated cases were realistic. The patient characteristics (eg, Eastern Cooperative Oncology Group performance status, age, sex, cancer type, and family history), specimen information (eg, year of collection, collection method, and tumor cell proportion), and clinical course (eg, prior therapy) were developed. Subsequently, a simulated test report of the test company reports (NCCOP or F1CDx) was prepared for each simulated case. The simulated C-CAT findings were also prepared using C-CAT. **Table 1** presents a list of 50 cases. Clinical course, test report, typical examples of C-CAT findings, and results of recommendations by each MTB are listed in the Clinical Course of simulated 50 cases, typical examples of C-CAT findings and simulated test reports for each case are found in eAppendix 1, eAppendix 2, and eAppendix 3 in the Supplement.

Evidence Levels

In Japan, evidence levels for all matched treatments for genomic alteration are investigated based on the *Clinical Practice Guidelines for Next-Generation Sequencing n Cancer Diagnosis and Treatment* (edition 2.1)[6] (eTable 1 in the Supplement). Briefly, evidence levels A, B, and R are the established biomarkers for which the treatment is ready for routine use in clinical practice (high evidence level), and evidence levels C, D, and E are the biomarkers for which the genomically matched treatment is being investigated (low evidence level).

Development of Consensus Treatment Recommendations

Using the simulated test report and simulated C-CAT findings of the cases, the representatives from MTBs at all core hospitals (central committee) discussed evidence level determination and therapies recommended for each genomic alteration and summarized them as central TRs, which included genomically matched treatment recommendations, information for clinical trials, and consideration for genetic counseling (Table 1). In general, treatment recommendations were composed of standard treatment, such as treatment recommended by guidelines, and clinical trials in which the patient could participate based on the CGP test results.

Investigations by MTBs at the Core Hospitals

All MTB members at the 12 core hospitals except central TR developers (assigned to the central committee) held meetings to review the 50 simulated cases, recommend genomically matched treatment, and refer to genetic counseling. The reports of all 50 simulated cases were provided to the central committee, which investigated whether the MTB reports were concordant with the central TRs.

Table 1. List of the 50 Simulated Cases and Consensus Treatment Recommendations

Cancer type	Case No.[a]	Variants	Consensus recommendation
Lung	1	*KRAS G12C*, *TP53 T125T*	Sotorasib
	2	*EGFR L858R*	No recommendation
	3	*ERBB2 A775_G776insYVMA*	Trastuzumab deruxtecan
	4	TMB-high, *STK11 D53fs*11*, *TP53 R248W*	Adavosertib, *AMG650*
	5	*BRAF* G466A, *KEAP1* G477D	*LY3214996*
	6	*CD74-ROS1* fusion	Entrectinib, crizotinib
	7	*EML4-ALK* fusion	Ceritinib, lorlatinib
	8	*MET c.3028+2T>C*	Capmatinib, tepotinib
Breast	9	*PIK3CA H1047R*, *TP53 E339K*	No recommendation
	10	*AKT1 E17K*, *CDH1c.832+2T>C*, *PTEN E201fs*41*	No recommendation
	11	*ERBB2 L755S*, *GATA3 P409Fs*99*	Trastuzumab deruxtecan
	12	*PIK3CA* amp, *MAP3K1 R306H*, *TP53 C275Y*	Adavosertib, *AMG650*
Colorectal	13	*KRAS G12D*, *SMAD4 R361H*	Not recommended: cetuximab, panitumumab
	14	*BRAF V600E*, *TP53 R175H*	No recommendation
	15	*PIK3CA E545K*, *FBXW7 R465H*, *KRAS G12A*	Not recommended: cetuximab, panitumumab
	16	*APC R1450**, *RNF43 G659fs*41*, *KRAS G12S*	E7386, not recommended: cetuximab, panitumumab
	17	*MSI*-high, *MSH2 E580**	Pembrolizumab, nivolumab, nivolumab plus ipilimumab
Prostate	18	*ATM E2444**, *KMT2D E551**	*BAY1895344*
	19	*CHEK2 E275**, *PTEN* loss	Olaparib
Gastric	20	*PIK3CA H1047R*, *KMT2D P2354Lfs*30*, *FGFR3 K650M*	Erdafitinib, futibatinib, pemigatinib
	21	*ARID1A D1850Tfs*33*, *TP53 R175H*	Adavosertib, *AMG650*
	22	*ERBB2* A, *PTEN K267Rfs*9*	Trastuzumab deruxtecan
	23	*MYC* amp, *CCNE1 A*, *TP53 Y234C*	Adavosertib, *AMG650*
Liver	24	*CTNNB1 S33C*, *TP53 R249S*, *ARID1A Q1741**	*E7386*, *E7386* plus lenvatinib, adavosertib, *AMG650*
Cervix	25	*PIK3CA E545K*, *EP300 S24fs*14*, *KRAS G12V*	*LY3214996*
	26	*ERBB2 S310F*, *PRKCI* amp, *TP53 Q331**	Adavosertib, *AMG650*
	27	*KRAS G12D*, *FBXW7* R505G, *TP53 R175H*	*LY3214996*, adavosertib, *AMG650*
Esophagus	28	*FGF3*, *FGF4*, *FGF19* A, *TP53 R175H*	Adavosertib, *AMG650*
	29	*CDKN2A* loss, *CDKN2B* loss, *MTAP* loss	No recommendation
	30	*CCND1amp*, *TP53 R196**	Adavosertib, *AMG650*
Pancreas	31	*KRAS G12D*, *TP53 R196**, *SMAD4 D415fs*20*	Adavosertib, *AMG650*
	32	*gBRCA2* S2835*, *GNAS R201H*, *CDKN2A R80**	Platinum followed by olaparib
	33	*EGFR* amp, *EGFR* A289V	No recommendation
CNS	49	*TP53*	Adavosertib, *AMG650*
	34	*BRAF V600E*	Dabrafenib plus trametinib
	35	*IDH1 R132H*, *TP53 R273C*	Adavosertib, *AMG650*
	36	TMB-high, *TP53 I255del*, *ATM* splice site *6573-1G>A*	*BAY1895344*
Melanoma	37	*BRAF V600E*, *BRCA1 L63**	Dabrafenib plus trametinib, encorafenib plus binimetinib, olaparib
	38	*RAF1* rearrangement	Trametinib
	39	*NRAS Q61R*, *TP53 A189V*	*LY3214996*, adavosertib, *AMG650*
Ovary	40	*sBRCA1 L63**, *TP53 R248Q*	Adavosertib, *AMG650*
	41	*gBRCA2 G1892fs*17*, *TP53 R175H*	Adavosertib, *AMG650*
	42	*NF1 E1333fs*7*	No recommendation

(continued)

Table 1. List of the 50 Simulated Cases and Consensus Treatment Recommendations (continued)

Cancer type	Case No.[a]	Variants	Consensus recommendation
Soft tissue	43	*MDM2 A*, *CDK4 A*	*BI907828*
	44	*RB1* loss, *TP53 R248W*	Adavosertib, *AMG650*
	50	No significant genetic abnormalities detected	No recommendation
Cholangiocarcinoma	45	*FGFR2-BICC1* fusion	*FGFR* inhibitor
Thyroid	46	*CCDC6-RET* fusion	*LOXO 292*
Adrenal cortex	47	No significant genetic abnormalities detected	No recommendation
Bladder cancer	48	No significant genetic abnormalities detected	No recommendation

Abbreviations: amp, amplification; CNS, central nervous system; TMB, tumor mutational burden.

[a] The number of each case corresponds to the Clinical Course of simulated 50 cases in eAppendix 1 in the Supplement.

Study Outcome

The primary outcome was the concordance for simulated cases of the treatment recommendations by MTBs of core hospitals with the central TRs. The central committee decided whether all cases were concordant or discordant. Concordance was calculated for each simulated case and genomic alteration. Concordance definitions for simulated cases were as follows: among therapies recommended by the central TR, at least one must be recommended and, if the evidence level of R, which means the genomic alteration is resistant to specific treatment, was included in the simulated case, all treatments identified to be avoided are not recommended.

Statistical Analysis

Concordance and discordance were treated as 1 and 0 values, respectively, for each MTB recommendation for a case. A logistic mixed-effects model was used to evaluate the concordance rate for each end point and the factors affecting the concordance rate. To control for heterogeneity among MTBs, random intercepts were assumed in the model. Two-sided *P* values <.05 were considered statistically significant. In multivariate analysis, cancer type, whether the biomarker was established or investigational, multiple biomarkers in 1 case, and *TP53* were included as explanatory variables. Statistical analysis was performed using R, version 4.1.0 (R Foundation for Statistical Computing).

Results

Recommendations for genomically matched treatment and genetic counseling for 50 simulated cases were collected from all MTBs at the 12 core hospitals. The mean value of concordance for MTBs with central TRs was 62% (95% CI, 57%-65%) and varied for each MTB from 48% to 86% (**Table 2**). Concordance was higher in cases of colorectal cancer (100%; 95% CI, 94.0%-100%), *ROS1* fusion (100%; 95% CI, 85.5%-100%), and high evidence level A/R (A: 88%; 95% CI, 81.8%-93.0%; R: 100%; 95% CI, 92.6%-100%) (**Table 3**; eTables 2, 3, and 4 in the Supplement). Conversely, concordance was lower in cases of cervical cancer (11%; 95% CI, 3.1%-26.1%), *TP53* mutation (16%; 95% CI, 12.5%-19.9%), and low evidence level C/D/E (C: 30%; 95% CI, 24.7%-35.9%; D: 25%; 95% CI, 5.5%-57.2%; and E: 18%; 95% CI, 13.8%-23.0%). *TP53* was the most frequently included genomic alteration among the simulated cases (20 cases) (Table 1). Multivariate analysis showed that evidence level (high [A/R] vs low [C/D/E]: odds ratio, 4.40; 95% CI, 1.79-10.81) and *TP53* alteration (yes vs no: odds ratio, 0.06; 95% CI, 0.04-0.10) were significantly associated with concordance (**Table 4**).

Six cases had genetic alterations requiring referral for genetic counseling. The concordance for genetic counseling also differed among the MTBs (33%-100%).

Discussion

We evaluated the concordance of MTBs in leading cancer hospitals using 50 simulated cases and calculated the concordance as 62%. Consistent concordance was observed in established biomarkers with a high evidence level of A or R. Conversely, a substantial discrepancy was observed in low evidence-level biomarkers for which the genomically matched treatment is investigational. Most of the investigational biomarkers were *TP53*, and multivariate analysis revealed that established biomarker was the positive predictive factor and *TP53* was the negative predictive factor for concordance.

Table 2. Concordance of Recommendation Across Multidisciplinary MTBs

MTB institution	Concordance, % (95% CI)
1	56 (42-69)
2	56 (42-69)
3	82 (69-90)
4	58 (44-71)
5	86 (73-93)
6	54 (40-67)
7	54 (40-67)
8	50 (37-64)
9	74 (60-84)
10	48 (35-62)
11	68 (54-79)
12	52 (38-65)
Total	62 (54-69)

Abbreviation: MTB, molecular tumor board.

Table 3. Concordance Rate According to Cancer Type

Cancer type	No. of genomic alterations leading to recommendation	Concordance per genomic alteration, % (95% CI)
Colorectal	5	100 (94-100)
Adrenocortical	1[a]	100 (74-100)
Bladder	1[a]	100 (74-100)
Cholangiocarcinoma	1	92 (62-100)
Thyroid	1	92 (62-100)
Lung	8	73 (63-81)
Breast	4	65 (49-78)
Gastric	4	63 (47-76)
CNS	4	60 (45-74)
Prostate	2	54 (33-74)
Ovary	3	50 (33-67)
Esophagus	3	47 (30-65)
Melanoma	3	42 (26-50)
Pancreas	3	39 (23-57)
Soft tissue	3	33 (16-55)
Liver	1	17 (2-48)
Cervix	3	11 (3-26)

Abbreviation: CNS, central nervous system.

[a] No treatment was recommended in these cases. Therefore, the statement "there is no recommendation" was considered concordant.

Table 4. Multivariate Analysis for Predictive Factors for Concordance

Factor	OR (95% CI)	*P* value
Cancer type[a]	1.10 (0.70-1.72)	.67
Established biomarker[b]	4.40 (1.79-10.81)	<.001
Multiple biomarkers in 1 case[c]	0.85 (0.45-1.64)	.63
TP53	0.06 (0.04-0.10)	<.001

Abbreviation: OR, odds ratio.

[a] Breast, colorectal, gastric, liver, lung, prostate (n = 24), and other (n = 26).

[b] Evidence level A, B, or R (n = 9).

[c] Multiple biomarkers (n = 36); *TP53* (n = 17).

Two studies targeting *TP53* as an inclusion criterion are underway (JapicCTI-205332[18] and jRCT2031200176[19]). However, our results noted that some MTBs were not aware of these studies and therefore could not inform patients despite the fact that these hospitals were leading hospitals in Japan. Accessibility to genomically matched treatment depends largely on IND trials,[7,20] and because studies have demonstrated that genomically matched INDs improve outcomes, information on IND trials for which biomarkers are included as eligibility criteria is crucial. Some information can be provided on websites, such as ClinicalTrials.gov[21] and jRCT.[22] However, it is difficult to share the cohort status in a timely manner, and data on the website do not reflect the actual status of the trials. Therefore, interactive information sharing regarding IND studies could be established to improve patient accessibility, leading to improved outcomes. We explicitly simulated that if concordance for *TP53* variants improves to 100%, the total concordance will improve to 87%.

The number of 50 cases was not determined based on a prior statistical calculation. However, if we consider the statistical power for the level of evidence A/R in the multivariate analysis (odds ratio, 4.40; 95% CI, 1.79-10.81), we calculate that 50 cases (50 cases ×12 centers = 600 cases) would have a power of 89% for a 2-sided significance level of 5%.

Our study is unique because it investigated MTBs. Based on CONCORD-3[2] and The Cancer Genome Atlas,[17] the distribution of cancer type and genomic findings for each tumor was sufficient to evaluate MTB quality. The central TRs were reviewed by experts in medical oncology and genomic medicine from the leading core hospitals. Our first report may be validated by further studies that evaluate MTBs in hub hospitals.

We used the classification of clinical practice guidelines for next-generation sequencing in cancer diagnosis and treatment[6] at the evidence level. The classification is quite similar to those of the Joint Consensus Recommendation of the American Society of Clinical Oncology, College of American Pathologists, and Association for Molecular Pathology[23] or the European Society for Medical Oncology.[24] Therefore, our results can be extrapolated to other countries. In Japan, evaluation by MTBs was required for reimbursement purposes, which means that more than 36 000 cases were evaluated by MTBs at core or hub hospitals (currently only 45 hospitals). Core hospitals are the leading hospitals in Japan and are highly experienced. Therefore, our discrepancy results found in the low evidence level may be unsettling and warrant further investigation of MTB quality.

We estimated that if *TP53* concordance improves, overall concordance would be approximately 90%, suggesting that improving MTB quality by sharing information about low levels of evidence, such as for *TP53*, might be effective. Further investigation is warranted, and an educational program based on this study may be useful.

Recently, 2 reports also investigated the MTBs. Koopman and colleagues[25] reported that MTBs in the Netherlands reached high agreement in recommendations for genomic alterations. Rieke and colleagues[26] reported some heterogeneity in MTB recommendations. Our results further support these findings, with high concordance in high-level evidence. We also provide suggestions as to which points are likely to be in disagreement.

Limitations

This study has limitations. Consensus treatment recommendations developed centrally will change over time. Therefore, our investigation of concordance might have been chronologically different. However, the concordance for established biomarkers will not easily change.

The concordance for genetic counseling also differed among the MTBs. However, our simulated data set included few cases with germline findings, and it was difficult to assess the discordance and causality for genetic counseling recommendations.

Conclusions

In this study, recommendations for genomically matched treatment based on comprehensive genomic profiling tests differed among MTBs, particularly in genomic alterations with low evidence

levels for which the treatment was being investigated. Consistent concordance was observed in established biomarkers. To improve MTB quality, sharing information about low levels of evidence, such as *TP53*, might be useful.

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SUPPLEMENT.

eTable 1. Evidence Levels Based on Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment (Edition 2.1)
eTable 2. Concordance Rate According to Genomic Alterations
eTable 3. Recommendation by Each MTB
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