Acta Med. Okayama, 2022
Vol. 76, No. 6, pp. 673-678

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Handling of Germline Findings in Clinical Comprehensive Cancer Genomic Profiling

Mika Okazawa-Sakai[a,b,c*§], Yasuko Yamamoto[c,d§], Mashu Futagawa[a], Miki Okamura[d], Satoko Miyawaki[c,d], Tomohiro Nishina[c,d], Kazuhiro Takehara[b,d], Toshiyuki Kozuki[e], Shuta Tomida[f], Ichinosuke Hyodo[c], Shozo Ohsumi[d], and Akira Hirasawa[a,f]

[a]Department of Clinical Genomic Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, [f]Center for Comprehensive Genomic Medicine, Okayama University Hospital, Okayama 700-8558, Japan, Departments of [b]Gynecologic Oncology, [c]Cancer Genomic Medicine, [d]Hereditary Tumors, [e]Clinical Research Center, National Hospital Organization Shikoku Cancer Center, Matsuyama 791-0280, Japan

Patients found to have presumed germline pathogenic variants (PGPVs) during comprehensive genomic profiling (CGP) require genetic counseling (GC) referrals. We retrospectively investigated the outcomes of patients with PGPVs. Among 159 patients who underwent CGP, we recommended GC for the 16 patients with PGPVs (3 with [FG group] and 13 without [G Group] a family/personal history of hereditary cancer) as well as for the 8 patients with no PGPVs, but a history (F group); 2 (67%), 5 (38%), and 3 (38%) patients received GC in the FG, G, and F groups, respectively. Germline testing results were positive in 1 and 2 patients of the FG and G groups, respectively. Among the patients recommended for GC, 58% did not receive GC due to lack of interest, poor performance status, or death. CGP contributes to the identification of germline variants in patients without a history of hereditary cancer. However, the proportion of patients who undergo GC should be improved.

Key words: comprehensive genomic profiling, hereditary cancer, germline findings, presumed germline pathogenic variant(s), genetic counseling

Comprehensive genomic profiling (CGP) potentially detects pathogenic variants associated with hereditary cancer. These presumed germline pathogenic variants (PGPVs) are difficult to determine from tumor-only sequencing assays because their somatic or germline origins remain unclear [1]. Discussion on how to evaluate PGPVs detected in CGP for somatic variants is ongoing.

Several guidelines have been published to assist clinicians in determining which patients should be referred to genetic specialists, based on their CGP results [1,2,and Kyoto University Genetic Counseling Course: <http://sph.med.kyoto-u.ac.jp/gccrc/kouroukosugi.html>]. The American College of Medical Genetics and Genomics (ACMG) proposed a minimum list of genes for which germline variants should be reported to patients (updated to version 3.0 in 2021 [3]). The European Society of Medical Oncology (ESMO) presented the criteria for confirmatory germline testing through tumor-only testing in 2019 [2]. The ESMO guideline was established to optimize the identification of actionable pathogenic germline variants and to achieve a greater than 10% germline-conversion rate per gene; targeted variants considered as germline

Received March 25, 2022; accepted June 13, 2022.
*Corresponding author. Phone: +81-86-235-7436; Fax: +81-86-235-7437
E-mail: sakai.mika.jt@mail.hosp.go.jp (M. Okazawa-Sakai)
[§]These authors contributed equally to this work.

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

findings were restricted to those with variant allele frequency (VAF) >30% (single nucleotide variants) or >20% (small insertions/deletions) [2]. Moreover, the National Comprehensive Cancer Network (NCCN) guidelines specify the genes for which the presence of germline pathogenic variants requires specific management for hereditary cancer [NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Colorectal Version 1.2021 and Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 1.2022, <https://www.nccn.org/professionals/physician_gls>]. These strategies were adopted in Japan (Kyoto University Genetic Counseling Course: http://sph.med.kyoto-u.ac.jp/gccrc/kouroukosugi.html, accessed June, 2022).

We established a board to evaluate the germline findings for a genetic counseling (GC) referral in October 2019. In the current study, we retrospectively investigate the outcomes of patients with PGPVs found in clinical CGP over the past 2 years at our institution, and identify issues associated with handling germline findings in clinical practice.

Patients and Methods

In this retrospective study, we included cancer patients who underwent CGP at the National Hospital Organization (NHO) Shikoku Cancer Center between October 2019 and October 2021. Clinical and CGP data of the patients were retrospectively collected from the charts and analyzed. The cut-off date for data collection was January 2022.

This study was approved by the Institutional Ethics Review Committee of the NHO Shikoku Cancer Center (approval nos. 2019-20 and 2021-01) and was performed according to the Ethical Guidelines for Medical and Health Research involving Human Subjects (<https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278>.pdf, accessed June, 2022). Informed consent was obtained via opt-out through an Okayama University website (<https://cgm.hsc.okayama-u.ac.jp/>, accessed June, 2022).

CGP testing was performed as per clinical practice using one of the following next-generation sequencing (NGS)-based panels: FoundationOne® CDx Cancer Genomic Profile (Foundation Medicine, MA, USA), OncoGuide™ NCC Oncopanel System (Sysmex, Kobe, Japan), FoundationOne® Liquid CDx (Foundation Medicine, MA, USA), or Guardant360® (Guardant Health, CA, USA).

The GC board consisted of 2 medical geneticists and 2 medical oncologists who discussed which patients should be recommended for GC, with consideration for several guidelines, such as the Proposal Concerning the Information Transmission Process in Genomic Medicine [Kyoto University Genetic Counseling Course: <http://sph.med.kyoto-u.ac.jp/gccrc/kouroukosugi.html>], the ESMO guideline [2], and the statement of ACMG [1]. Briefly, i) the pathogenicity of somatic or germline variants in genes for which germline variants should be reported to patients was annotated using public databases; ii) the possibility of germline origin was evaluated according to an algorithm derived from the above-mentioned guidelines; and iii) any patient whose personal or family history met the criteria for germline genetic testing was referred to genetic specialists, regardless of the presence of PGPVs [4 and NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Colorectal Version 1.2021 and Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 1.2022, <https://www.nccn.org/professionals/physician_gls>].

Results

A total of 159 patients underwent CGP using the following panels: FoundationOne CDx Cancer Genomic Profile (n=108, 68%), Guardant360 (n=33, 21%), OncoGuide NCC Oncopanel System (n=12, 8%), and FoundationOne Liquid CDx (n=6, 4%). The median age at the time of testing was 63 years (range, 16-85 years). All patients were Japanese and 49% were women. The most common primary tumor sites were bile duct (9%), ovary (9%), pancreas (9%), lung (8%), and prostate (8%). The median turnaround time from ordering a CGP test to the disclosure of CGP results was 37 days (range, 13-90 days).

After a discussion among board members, 18 sequence variants in 16 patients were considered PGPVs: *BRCA2* (n=5), *ATM* (n=4), *PTEN* (n=3), *MSH6* (n=2), *BAP1* (n=1), *BRCA1* (n=1), *TP53* (n=1), and *RET* (n=1) (Table 1). They were detected using the FoundationOne CDx Cancer Genomic Profile (n=11) or Guardant360 (n=5). The frequency of

Table 1 Patients recommended for genetic counseling

Patient No.	Gender	Age	Disease	NGS-panel	Presumed germline pathogenic variants	Variant allele frequency (%)	Genetic counseling	Reasons for not receiving GC	Germline genetic testing
FG1	Female	67	Ovarian cancer	F1CDx	*ATM* c.748C>T	50.6	Received		Negative
FG2	Female	53	Ovarian cancer	G360	*BRCA2* c.3703C>T	45.8	Received		Positive
FG3	Female	39	Osteosarcoma	F1CDx	*TP53* c.376-2_380del	57.6	Not received	Poor PS	Not received
G1	Male	64	Bile duct cancer	G360	*ATM* c.4776+2T>A	47.3	Received		Positive
G2	Male	71	Prostate cancer	G360	*BRCA2* c.5773C>T	73.6	Received		Negative
G3	Female	50	Endometrial cancer	G360	*BRCA2* c.5576_5579del	50.4	Received		Positive
G4	Female	66	Cancer of unknown primary	F1CDx	*PTEN* c.159_164+12del	49.4	Received		Negative
G5	Male	72	Prostate cancer	F1CDx	*ATM* c.5188C>T *MSH6* c.3261_3262insC *MSH6* c.3495del	47.7 44.4 53.6	Received		Negative
G6	Male	56	Renal cancer	F1CDx	*BAP1* c.1098T>A	30.2	Not received	Not interested	Not received
G7	Male	65	Pleura mesothelioma	F1CDx	*BRCA1* c.427G>T	55.2	Not received	Not interested	Not received
G8	Female	68	Endometrial cancer	F1CDx	*PTEN* c.335T>C	61.2	Not received	Not interested	Not received
G9	Female	59	Breast cancer	F1CDx	*PTEN* c.368A>G	50.6	Not received	Poor PS	Not received
G10	Male	80	Prostate cancer	F1CDx	*ATM* c.8645C>G	64.8	Not received	Poor PS	Not received
G11	Male	77	Prostate cancer	F1CDx	*BRCA2* Loss	NA	Not received	Poor PS	Not received
G12	Female	60	Uterine sarcoma	F1CDx	*RET* c.2410G>A	81.8	Not received	Poor PS	Not received
G13	Male	79	Prostate cancer	G360	*BRCA2* c.9653del	32.0	Not received	Death before receiving CGP results	Not received
F1	Female	63	Uterine sarcoma	F1CDx	Negative		Received		Negative
F2	Male	77	Gastric cancer	F1CDx	Negative		Received		Not received
F3	Male	66	Prostate cancer	F1CDx	Negative		Received		Not received
F4	Male	71	Gastric cancer	F1CDx	Negative		Not received	Poor PS	Not received
F5	Female	64	Ovarian cancer	F1CDx	Negative		Not received	Poor PS	Not received
F6	Female	53	Ovarian cancer	F1CDx	Negative		Not received	Not interested	Not received
F7	Male	69	Colorectal cancer	F1CDx	Negative		Not received	Not interested	Not received
F8	Female	36	Salivary gland cancer	F1CDx	Negative		Not received	Not interested	Not received

Note: FG, G, and F in Patient No. column indicate the family/personal history+gene variant, gene variant only, and family/personal history only groups, respectively. NGS-panel F1CDx and G360 indicate the FoundationOne CDx Cancer Genome profile and Gauardant360, respectively. Patient FG1, FG2, F1, F3, F5, and F6 had history that met the testing criteria for hereditary breast and ovarian cancer. Patient FG3 had a personal history that met the diagnostic criteria for Li-Fraumeni syndrome. Patients F2, F7, and F8 had a family history of Lynch syndrome-related cancers. Patient F4 had a family history of suspected hereditary diffuse gastric cancer.
CGP, comprehensive genomic profiling; NGS, next-generation sequencing; GC, genetic counseling; PS, performance status; NA, not available.

PGPVs was 9% (11/120) in patients undergoing the tissue-based tests and 13% (5/39) in those undergoing the liquid-based tests ($p=0.51$, Chi-squared test). The median VAF of PGPVs was 52.1% (range, 30.2-81.8%) through the tissue-based tests and 47.3% (range, 32.0-73.6%) through the liquid-based tests ($p=0.61$, Student's *t*-test).

The patients were divided into three groups (Fig. 1): those with both family or personal history of hereditary cancer and PGPVs (FG group), those with only PGPVs (G group), and those with only history (F group).

In the FG group, patients FG1 and FG2 had a personal history that met the testing criteria for hereditary breast and ovarian cancer (HBOC), and patient FG3 had a personal history meeting the diagnostic criteria for Li-Fraumeni syndrome (Table 1). Two of these three patients (66%) underwent GC and confirmatory germline testing. In the G group, germline genetic testing after GC was performed in 5 of 13 patients (31%). Among 16 patients who had tumors harboring PGPVs, 7 patients (44%) underwent confirmatory genetic testing and 3 (19%) were positive for *BRCA2* (patients FG2 and G3) or *ATM* (patient G1) (Table 1 and Fig. 1). Patient FG2 was treated with the poly (ADP-ribose) polymerase (PARP) inhibitor Niraparib, but the disease

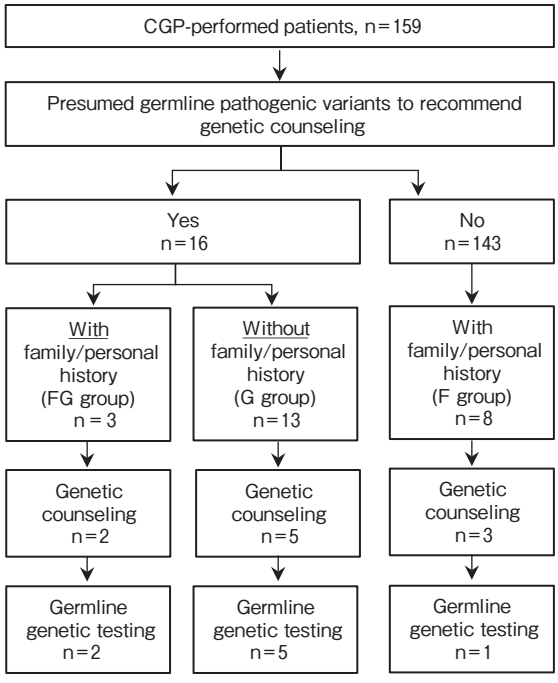

Fig. 1 Flow chart for recommending germline genetic testing to patients. In total, 159 patients underwent comprehensive genomic profiling (CGP). Presumed germline pathogenic variants (PGPVs) were found in 16 patients who were recommended for genetic counseling (GC): 3 patients with a family or personal history of hereditary cancer (FG group) and 13 patients without a history (G group). In the FG and G groups, germline genetic testing after GC was performed in 2 and 5 patients, respectively, and the germline origin was confirmed in 1 and 2 patients, respectively. Meanwhile, 143 patients with no PGPVs included 8 patients who were recommended for GC due to their familial or personal history (F group); only 3 of these 8 patients received GC.

progressed in 3 months. Patients G1 and G3 did not receive the treatment with PARP inhibitors, because these agents were not approved for cancer treatment in Japan at the time that these patients were assessed.

In the F group, 8 patients with no PGPV tumors were recommended for GC because their personal or family history met the testing criteria for HBOC (patients F1, F3, F5, and F6), because they had a family history of Lynch syndrome-related cancers (patient F2, F7, and F8), or because they had a family history suspicious for hereditary diffuse gastric cancer (patient F4) (Table 1). Among these patients, 3 (38%) received GC. One HBOC-suspected patient (13%) underwent germline genetic testing for *BRCA1/2* and no pathogenic variants were detected (patient F1).

Among the 24 patients for whom GC was recommended, 14 (58%) did not receive GC due to poor performance status (n=7), lack of interest in knowing their germline status (n=6), or death due to disease progression while awaiting CGP results (n=1) (Table 1).

Discussion

We recognized PGPVs in 10% (16/159) of the CGP-tested cancer patients. Germline pathogenic variants of *BRCA2* and *ATM* were found in 3 patients with ovarian, endometrial, and bile duct cancers. This finding led to the application of treatments with PARP inhibitors, identification of family members at risk, and discussion of preventive cancer-management strategies. The results in this patient group suggested that the identification of PGPVs was a step toward identifying patients with hereditary cancer, especially those without a personal or family history. Nonetheless, more than half of the patients were not referred for GC due to a deterioration of general health or a general lack of interest in GC.

Previous studies revealed that 3-17% of patients undergoing CGP tests carried germline pathogenic variants, indicating our results are plausible, but the exact prevalence of PGPVs detected in tumor-only sequencing in CGP remains unclear [5-9]. The detection of PGPVs fluctuates according to the cancer type, testing method of CGP, tumor sample quality, tumor purity, somatic copy number alterations, genes analyzed in CGP, and variant type [1,9,10]. A recent large cohort study analyzed tumor and blood massively parallel sequencing data from 21,333 cancer patients and demonstrated that tumor-only sequencing failed to detect 10.5% of clinically actionable pathogenic germline variants in cancer susceptibility genes [9]. Therefore, germline genetic testing should be considered for patients with a personal and family history of hereditary cancer but no PGPVs.

Generally, pathogenic variants detected in *BRCA1/2* or mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) through CGP are considered as PGPVs because of their high germline-conversion rates [2]. If pathogenic variants are detected in genes other than *BRCA1/2* and mismatch repair genes, the VAF supports clinicians in recognizing the variants as PGPVs, because the VAF of heterozygous germline variants generally ranges from 30% to 70% in tissue-based tests [2]. However, the VAF in the tissue-based tests depends on tumor purity, DNA ploidy, and local copy number, and is not

always within this range [10]. In contrast, the VAFs of germline variants in liquid-based tests would be approximately 50%, which are more distinguishable from somatic mutations [11]. Indeed, the VAF of Guardant360 in our 3 patients with germline-positive tumors was 45.8-50.4%. Although the liquid-based tests are more informative compared to the tissue-based tests in terms of the detection of PGPVs, their utility for the screening of germline variants remains unclear due to a discrepancy in interpretation between somatic and germline sequence variants and technical limitations in tumor DNA sequencing to detect a broad spectrum of pathogenic variants that cause predisposition to inherited diseases. There are still concerns to be solved in the liquid-based tests [1].

In Japan, CGP tests have been reimbursed by the Japanese National Health Insurance System for cancer patients with unknown primary sites, rare tumors, or solid tumors refractory to standard treatment since June 2019 [Ministry of Health, Labour and Welfare:] <https://www.mhlw.go.jp/stf/newpage_06821.html>. A previous report on CGP findings in 11 core hospitals in Japan demonstrated that 2.3% of patients were referred for GC, based on the CGP results [12]. Increased recognition of patients with PGPVs requires increased collaboration with GC providers. Another recent Japanese study revealed that 13.7% of patients had PGPVs, but only 42% of these patients received GC [13]. One of the reasons for not undergoing germline genetic testing was reported to be patient death shortly after disclosure [13]. These findings were similar to those of our study, in which 7 of 16 patients (44%) with PGPVs received GC, whereas 6 patients (38%) could not receive GC due to poor health or death. This indicates the need to ensure appropriate timing of CGP, shorten its turnaround time, and quickly refer patients to genetic specialists.

A recent Canadian study suggested that most patients who underwent CGP were interested in knowing their germline status [14]. However, in our study, a quarter of the G group (3/13) and one-third of the F group (3/8) refused GC because they were "not interested", even though all patients provided their consent to be informed of the germline results before their CGP. A randomized study of genetic education versus usual care in CGP-tested patients demonstrated that web-based genetic education, before CGP, increased understanding of the process in patients and reduced distress, especially in women [15]. Online genetic education is one of the solutions to this problem, and some initiatives in this direction are being carried out in Japan. In the present study, we attempted a new approach to disclosing genomic findings to patients. Once the germline board recommends GC to a patient, a medical geneticist accompanies the physician in charge at the time of initial disclosure of CGP results and explains the possibility of hereditary cancer to the patient in plain language, as an introduction. A formal visit to a genetics specialist is scheduled if the patient agrees to GC. Neither GC nor confirmatory genetic testing is covered by the national health insurance system in Japan, and the high cost of germline genetic testing may be one of the barriers for the patients who respond that they are not interested in testing. Easier access to genetic medical services, including financial support, is also needed.

In this study, a patient with ovarian cancer harboring germline pathogenic variants of *BRCA2* was treated with Niraparib after CGP testing. Nonetheless, her tumor rapidly progressed. She experienced the progression during the prior platinum-based chemotherapy and might have some acquired resistance to PARP inhibitors [16], although no reversion mutation in *BRCA2* was detected in the results of her Gurdant360 test.

The limitations of this study include that it was a single-center, retrospective investigation. Furthermore, given the small cohort of patients, we could not assess the impact of the presence of PGPVs on the GC-referral rate by comparing between the patients with personal and familial history and those with no history. A larger nationwide study should be conducted in the future.

In conclusion, CGP contributes to the identification of germline variants in patients with no history of hereditary cancer. However, the proportion of patients who undergo GC and confirmatory genetic testing should be improved.

Acknowledgments. The authors are grateful to all members of the Molecular Tumor Board at the NHO Shikoku Cancer Center and Department of Clinical Genomic Medicine, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences.

This work was supported by a Grant-in-Aid for Early-Career Scientists (JSPS KAKENHI Grant Number JP21K17854).

References

1. Li MM, Chao E, Esplin ED, Miller DT, Nathanson KL, Plon SE, Scheuner MT and Stewart DR; ACMG Professional Practice and Guidelines Committee: Points to consider for reporting of germline variation in patients undergoing tumor testing: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med (2020)22: 1142–1148.
2. Mandelker D, Donoghue M, Talukdar S, Bandlamudi C, Srinivasan P, Vivek M, Jezdic S, Hanson H, Snape K, Kulkarni A, Hawkes L, Douillard JY, Wallace SE, Rial-Sebbag E, Meric-Bersntam F, George A, Chubb D, Loveday C, Ladanyi M, Berger MF, Taylor BS and Turnbull C: Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group. Ann Oncol (2019) 30: 1221–1231.
3. Miller DT, Lee K, Chung WK, Gordon AS, Herman GE, Klein TE, Stewart DR, Amendola LM, Adelman K, Bale SJ, Gollob MH, Harrison SM, Hershberger RE, McKelvey K, Richards CS, Vlangos CN, Watson MS, Martin CL and ACMG Secondary Findings Working Group: ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med (2021) 23: 1381–1390.
4. Blair VR, McLeod M, Carneiro F, Coit DG, D'Addario JL, van Dieren JM, Harris KL, Hoogerbrugge N, Oliveira C, van der Post RS, Arnold J, Benusiglio PR, Bisseling TM, Boussioutas A, Cats A, Charlton A, Schreiber KEC, Davis JL, Pietro MD, Fitzgerald RC, Ford JM, Gamet K, Gullo I, Hardwick RH, Huntsman DG, Kaurah P, Kupfer SS, Latchford A, Mansfield PF, Nakajima T, Parry S, Rossaak J, Sugimura H, Svrcek M, Tischkowitz M, Ushijima T, Yamada H, Yang HK, Claydon A, Figueiredo J, Paringatai K, Seruca R, Bougen-Zhukov N, Brew T, Busija S, Carneiro P, DeGregorio L, Fisher H, Gardner E, Godwin TD, Holm KN, Humar B, Lintott CJ, Monroe EC, Muller MD, Norero E, Nouri Y, Paredes J, Sanches JM, Schulpen E, Ribeiro AS, Sporle A, Whitworth J, Zhang L, Reeve AE and Guilford P: Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol (2020) 21: e386–e397.
5. Mandelker D, Zhang L, Kemel Y, Stadler ZK, Joseph V, Zehir A, Pradhan N, Arnold A, Walsh MF, Li Y, Balakrishnan AR, Syed A, Prasad M, Nafa K, Carlo MI, Cadoo KA, Sheehan M, Fleischut MH, Salo-Mullen E, Trottier M, Lipkin SM, Lincoln A, Mukherjee S, Ravichandran V, Cambria R, Galle J, Abida W, Arcila ME, Benayed R, Shah R, Yu K, Bajorin DF, Coleman JA, Leach SD, Lowery MA, Garcia-Aguilar J, Kantoff PW, Sawyers CL, Dickler MN, Saltz L, Motzer RJ, O'Reilly EM, Scher HI, Baselga J, Klimstra DS, Solit DB, Hyman DM, Berger MF, Ladanyi M, Robson ME and Offit K: Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing. JAMA (2017) 318: 825–835.
6. Meric-Bernstam F, Brusco L, Daniels M, Wathoo C, Bailey AM, Strong L, Shaw K, Lu K, Qi Y, Zhao H, Lara-Guerra H, Litton J, Arun B, Eterovic AK, Aytac U, Routbort M, Subbiah V, Janku F, Davies MA, Kopetz S, Mendelsohn J, Mills GB and Chen K: Incidental germline variants in 1000 advanced cancers on a prospective somatic genomic profiling protocol. Ann Oncol (2016) 27: 795–800.
7. Schrader KA, Cheng DT, Joseph V, Prasad M, Walsh M, Zehir A, Ni A, Thomas T, Benayed R, Ashraf A, Lincoln A, Arcila M, Stadler Z, Solit D, Hyman DM, Zhang L, Klimstra D, Ladanyi M, Offit K, Berger M and Robson M: Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA. JAMA Oncol (2016) 2: 104–111.
8. Seifert BA, O'Daniel JM, Amin K, Marchuk DS, Patel NM, Parker JS, Hoyle AP, Mose LE, Marron A, Hayward MC, Bizon C, Wilhelmsen KC, Evans JP, Earp HS, 3rd, Sharpless NE, Hayes DN and Berg JS: Germline Analysis from Tumor-Germline Sequencing Dyads to Identify Clinically Actionable Secondary Findings. Clin Cancer Res (2016) 22: 4087–4094.
9. Terraf P, Pareja F, Brown DN, Ceyhan-Birsoy O, Misyura M, Rana S, O'Reilly E, Carlo MI, Aghajanian C, Liu Y, Derakhshan F, Jayakumaran G, Weigelt B, Walsh M, Stadler Z, Offit K, Ladanyi M, Robson M, Zehir A, Reis-Filho JS and Mandelker D: Comprehensive assessment of germline pathogenic variant detection in tumor-only sequencing. Ann Oncol (2022) S0923-7534(22)00015-1.
10. Sun JX, He Y, Sanford E, Montesion M, Frampton GM, Vignot S, Soria JC, Ross JS, Miller VA, Stephens PJ, Lipson D and Yelensky R: A computational approach to distinguish somatic vs. germline origin of genomic alterations from deep sequencing of cancer specimens without a matched normal. PLoS Comput Biol (2018) 14: e1005965.
11. Slavin TP, Banks KC, Chudova D, Oxnard GR, Odegaard JI, Nagy RJ, Tsang KWK, Neuhausen SL, Gray SW, Cristofanilli M, Rodriguez AA, Bardia A, Leyland-Jones B, Janicek MF, Lilly M, Sonpavde G, Lee CE, Lanman RB, Meric-Bernstam F, Kurzrock R and Weitzel JN: Identification of Incidental Germline Mutations in Patients With Advanced Solid Tumors Who Underwent Cell-Free Circulating Tumor DNA Sequencing. J Clin Oncol (2018) 36: JCO1800328.
12. Sunami K, Naito Y, Aimono E, Amano T, Ennishi D, Kage H, Kanai M, Komine K, Koyama T, Maeda T, Morita S, Sakai D, Kohsaka S, Tsuchihara K and Yoshino T: The initial assessment of expert panel performance in core hospitals for cancer genomic medicine in Japan. Int J Clin Oncol (2021) 26: 443–449.
13. Kikuchi J, Ohhara Y, Takada K, Tanabe H, Hatanaka K, Amano T, K CH, Hatanaka Y, Mitamura T, Kato M, Shibata Y, Yabe I, Endoh A, Komatsu Y, Matsuno Y, Sugiyama M, Manabe A, Sakurai A, Takahashi M, Naruse H, Torimoto Y, Dosaka-Akita H and Kinoshita I: Clinical significance of comprehensive genomic profiling tests covered by public insurance in patients with advanced solid cancers in Hokkaido, Japan. Jpn J Clin Oncol (2021) 51: 753–761.
14. Stjepanovic N, Stockley TL, Bedard PL, McCuaig JM, Aronson M, Holter S, Semotiuk K, Leighl NB, Jang R, Krzyzanowska MK, Oza AM, Gupta A, Elser C, Ahmed L, Wang L, Kamel-Reid S, Siu LL and Kim RH: Additional germline findings from a tumor profiling program. BMC Med Genomics (2018) 11: 65.
15. Bradbury AR, Lee JW, Gaieski JB, Li S, Gareen IF, Flaherty KT, Herman BA, Domchek SM, DeMichele AM, Maxwell KN, Onitilo AA, Virani S, Park S, Faller BA, Grant SC, Ramaekers RC, Behrens RJ, Nambudiri GS, Carlos RC and Wagner LI: A randomized study of genetic education versus usual care in tumor profiling for advanced cancer in the ECOG-ACRIN Cancer Research Group (EAQ152). Cancer (2021) 128: 1381–1391.
16. Norquist B, Wurz KA, Pennil CC, Garcia R, Gross J, Sakai W, Karlan BY, Taniguchi T and Swisher EM: Secondary Somatic Mutations Restoring BRCA1/2 Predict Chemotherapy Resistance in Hereditary Ovarian Carcinomas. J Clin Oncol (2011) 29: 3008–3015.