Editorial Commentary

Challenges for clinical application of "TRACEBACK" study: testing of historical Tubo-Ovarian cancer patients for hereditary risk genes

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Comment on: Delahunty R, Nguyen L, Craig S, *et al.* TRACEBACK: Testing of Historical Tubo-Ovarian Cancer Patients for Hereditary Risk Genes as a Cancer Prevention Strategy in Family Members. J Clin Oncol 2022;40:2036-47.

Keywords: Ovarian cancer; *BRCA*; genetic testing; TRACEBACK

Submitted Jan 25, 2023. Accepted for publication Feb 06, 2023. Published online Feb 23, 2023.

doi: 10.21037/atm-23-352

View this article at: https://dx.doi.org/10.21037/atm-23-352

Background and significance of the "TRACEBACK" study

Delahunty *et al.* (1) reported a pilot study in which specimens from ovarian cancer patients who had already died were obtained and tested for *BRCA1/2* genes to identify high-risk families for hereditary tumors. For women who carry *BRCA1/2* pathogenic variants, there are established risk-reducing surgery that have demonstrated clinical significance: risk-reducing salpingo-oophorectomy (RRSO) to reduce the risk of ovarian and breast cancer and risk-reducing mastectomy (RRM) to reduce the risk of breast cancer (2,3). Despite the obvious benefits of *BRCA* genetic testing for women who carry *BRCA* pathogenic variants, many women at risk for the pathogenic variants miss the opportunity for *BRCA* genetic testing (4).

Table 1 shows the positive rates for *BRCA* pathogenic variants in epithelial ovarian cancer (5,6). Although there are some regional differences, approximately 15% of epithelial ovarian cancer cases are generally found to harbor *BRCA1/2* pathogenic variants (7). It has also been found that about half of these cases do not have a family history of breast or ovarian cancer (8,9). Against this background, the National Comprehensive Cancer Network (NCCN) and other national guidelines recommend *BRCA* genetic testing for all patients with epithelial ovarian cancer, although some guidelines exclude mucinous ovarian cancer patients (10,11). With the proven efficacy of maintenance therapy with polyadenosine-diphosphate-ribose polymerase (PARP) inhibitors for patients with advanced ovarian cancer (12), the number of cases in which families with *BRCA* pathogenic variants are found to have ovarian cancer patients as probands (PVs) has increased dramatically. However, families of ovarian cancer patients who had already died before *BRCA* genetic testing became widely available have missed the opportunity for the genetic testing, which means they have missed the opportunity to prevent *BRCA*-related cancers.

Attempts to identify such families with *BRCA* pathogenic variants were discussed at a 2016 National Cancer Institute workshop, where a conceptual framework called "TRACEBACK" was developed (13) and a pilot study is now reported.

Summary of the "TRACEBACK" pilot study

The authors designed this study based on an estimated 12,000 ovarian cancer patients in Australia who the authors presumed has not had *BRCA* genetic testing (1). In this study, 10 genes (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*) were tested in ovarian cancer patients who had already died for the clinical application of "TRACEBACK". Obtaining consent for the genetic testing from the patients' families

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Table 1 Prevalence of germline *BRCA* mutation by histological type in ovarian cancer patient (5)

Histological classification	USA (n=1,699)	Australia (n=891)	Germany (n=462)	Japan (n=609)	China (n=1,044)	Korea (n=591)
High-grade serous	16.0% (240/1,498)	16.6%* (118/709)	23.2% (94/406)	28.5% (78/274)	27.2%* (229/843)	22.3% (95/426)
Low-grade serous	5.7% (4/70)	N/A*	5.6% (1/18)	20.0% (1/5)	N/A*	19.4% (6/31)
Endometrioid	10.9% (7/64)	8.4% (10/119)	13.0% (3/23)	6.7% (8/120)	10.8% (7/65)	13.0% (7/54)
Clear cell	6.9% (4/58)	6.3% (4/63)	0.0% (0/6)	2.1% (4/187)	7.6% (6/79)	7.3% (4/55)
Mucinous	0.0% (0/9)	N/A	0.0% (0/9)	0.0% (0/19)	7.0% (4/57)	5.6% (1/18)
Seromucinous	N/A	N/A	N/A	0.0% (0/4)	N/A	0.0% (0/7)

* including either grade. N/A, not applicable.

was not considered a prerequisite for this study.

From the medical records of the PVs or consent forms from previous study cohorts, individuals within the family who would receive the results of genetic testing were identified. Notification of test results was a two-step process: written notification that genetic information was available (data supplement) and telephone contact from a genetic counselor. If a pathological variant was identified in the gene being tested, the family was notified of the results and referred to a local familial cancer clinic for additional genetic testing for the family.

As a result, familial contacts of 39 of 60 (65%) deceased PVs with an identified recipient (60 of 84; 71%) have received a written notification of results, with follow-up verbal contact made in 85% (33 of 39). For many (29 of 33; 88%), the genetic result provided new information and referral to a genetic service was accepted in most cases (66%; 19 of 29). The pilot study concluded that multiple methods of confirmation were feasible for deceased ovarian cancer patients (PVs), demonstrating the effectiveness of "TRACEBACK".

Research issues

There is a report on an international workshop that discussed "TRACEBACK" (13) and an editorial on its contents has also been published (14). The report warns that while "TRACEBACK" has the potential to bring significant benefits in public health, there are legal, ethical, social, clinical, and practical challenges. The most important issues are who should determine consent for testing and how consent should be obtained.

Past reports indicate that more than 90% of participants indicated that genetic test results should be provided to their spouses (15,16), however it is important to note that spouses are not blood relatives. It seems obvious that blood relatives who are directly affected by the benefits and disadvantages related to the results of the genetic test should be notified of the results. Furthermore, it should not be forgotten that blood relatives have the right not to know the results of the genetic test. Although studies similar to "TRACEBACK" have shown that patients' families are highly receptive to receiving genetic test results (15,17), whether these results can be directly applied to "TRACEBACK" remains to be examined.

Because informing the results of little clinical significance to families places an unnecessary burden on them, informing the results only to those families in which a pathogenic variant has been identified seems to be a reasonable approach (18). Even with that policy, however, a great deal of effort is required to notify all families of the results. How to limit the range of family members who receive notification of the results is also an issue, and discussion should continue as to whether, for example, the range of first-degree relatives is sufficient. It has been reported that families who are informed of a positive result are generally less likely to undergo additional genetic testing in males (19,20). If the result is a "Variant of Uncertain Significance (VUS)", whether or not the family should be informed of the result also needs to be discussed.

In selecting PVs for genetic testing, the positive rate of *BRCA* pathogenic variants in ovarian cancer patients with clear cell carcinoma has varied from region to region. Therefore, it may be reasonable to argue that patients with clear cell carcinoma as well as mucinous should be excluded from PVs (*Table 1*).

In formalin-fixed paraffin-embedded (FFPE) specimens obtained from treated facilities or biobanks, it can be difficult to obtain DNA from normal tissue. If DNA analysis of tumor tissue alone reveals a pathological

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Table 2 Prevalence of g*BRCA*m in breast, prostate and pancreatic cancer patients (5,10,23,24)

Cancer type	Prevalence of g*BRCA*m	Risk for malignancy		General population risk
		BRCA1	*BRCA2*	
Female breast	5–10%	>60%	>60%	12%
Triple negative	9.3–15.4%	N/A	N/A	N/A
Male breast	8–18%	1.2%	Up to 8.9%	0.1%
Prostate	6%	8.6% by age 65	15% by age 65	6% through age 69
Pancreatic	4–7%	1–3%	2–7%	0.5%

g*BRCA*m, germline *BRCA* pathogenic variants; N/A, not applicable.

variant (t*BRCA*m), it is controversial whether this result should be informed to the family or not. In the case of t*BRCA*m, approximately 80% of them have germline *BRCA* pathogenic variants (g*BRCA*m), thus it would be highly significant to notify relatives of the t*BRCA*m results (21). If t*BRCA*m is not detected, we can almost assume that g*BRCA*m has been ruled out, however it should be noted that there are exceptions (22).

Future perspectives

The report by Delahunty *et al.* (1) is very important as a major recommendation for the future development of precision medicine. The "TRACEBACK" trial may be beneficial for families with no known risk of hereditary tumors, and the applicability of "TRACEBACK" to other *BRCA*-related cancers should be explored. *Table 2* shows the positive rate and risk for malignancy of *BRCA* pathogenic variants in female breast, male breast, prostate, and pancreatic cancer (5,10,23,24). The positive rate of *BRCA* pathogenic variants and the number of patients who are PVs affect the cost-effectiveness of the "TRACEBACK" study. In breast cancer, triple-negative breast cancer is considered a promising candidate, and multiplex panel testing has begun to be discussed (1). If all breast cancer patients were eligible for genetic testing for PVs, a great deal of effort would be required to notify their families of the results. However, since triple-negative breast cancer accounts for 10–15% of all breast cancers (25), it may be eligible for "TRACEBACK" as well as ovarian cancer.

To discuss the costs of "TRACEBACK" (genetic testing, family search, genetic counseling), a cost-effectiveness study is needed. This pilot study was successful in Australia, a region where biobanking and genetic counseling are widespread. However, the importance and legality of this study is expected to vary from country to country and region to region, and international guidelines need to be established.

Acknowledgments

We would like to thank Mr. Taishin Sekine and Mr. Kenshin Sekine for English editing.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-352/coif). MS received lecture fees from AstraZeneca. KY received lecture fees and a research grant from AstraZeneca. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Sekine M, Isobe M, Nishino K, Adachi S, Suda K, Yoshihara K. Challenges for clinical application of "TRACEBACK" study: testing of historical Tubo-Ovarian cancer patients for hereditary risk genes. Ann Transl Med 2023;11(8):295. doi: 10.21037/atm-23-352

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