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SPECIAL ARTICLE

Traceback: A Proposed Framework to Increase Identification and Genetic Counseling of *BRCA1* and *BRCA2* Mutation Carriers Through Family-Based Outreach

Goli Samimi, Marcus Q. Bernardini, Lawrence C. Brody, Charlisse F. Caga-anan, Ian G. Campbell, Georgia Chenevix-Trench, Fergus J. Couch, Michael Dean, Joanne A. de Hullu, Susan M. Domchek, Ronny Drapkin, Heather Spencer Feigelson, Michael Friedlander, Mia M. Gaudet, Marline G. Harmsen, Karen Hurley, Paul A. James, Janice S. Kwon, Felicitas Lacbawan, Stephanie Lheureux, Phuong L. Mai, Leah E. Mechanic, Lori M. Minasian, Evan R. Myers, Mark E. Robson, Susan J. Ramus, Lisa F. Rezende, Patricia A. Shaw, Thomas P. Slavin, Elizabeth M. Swisher, Masataka Takenaka, David D. Bowtell, and Mark E. Sherman

Author affiliations and support information (if applicable) appear at the end of this article.

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D.D.B. and M.E.S. are joint senior authors.

This report reflects a summary of the discussion from the workshop and is not intended to represent an opinion or recommendation from the National Institutes of Health.

Corresponding author: Goli Samimi, PhD, MPH, Division of Cancer Prevention, National Cancer Institute, 9609 Medical Center Dr, MSC 9783, Bethesda, MD 20892; e-mail: goli.samimi@nih.gov.

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ABSTRACT

In May 2016, the Division of Cancer Prevention and the Division of Cancer Control and Population Sciences, National Cancer Institute, convened a workshop to discuss a conceptual framework for identifying and genetically testing previously diagnosed but unreferred patients with ovarian cancer and other unrecognized *BRCA1* or *BRCA2* mutation carriers to improve the detection of families at risk for breast or ovarian cancer. The concept, designated Traceback, was prompted by the recognition that although *BRCA1* and *BRCA2* mutations are frequent in women with ovarian cancer, many such women have not been tested, especially if their diagnosis predated changes in testing guidelines. The failure to identify mutation carriers among probands represents a lost opportunity to prevent cancer in unsuspecting relatives through risk-reduction intervention in mutation carriers and to provide appropriate reassurances to noncarriers. The Traceback program could provide an important opportunity to reach families from racial, ethnic, and socioeconomic groups who historically have not sought or been offered genetic counseling and testing and thereby contribute to a reduction in health disparities in women with germline *BRCA* mutations. To achieve an interdisciplinary perspective, the workshop assembled international experts in genetics, medical and gynecologic oncology, clinical psychology, epidemiology, genomics, cost-effectiveness modeling, pathology, bioethics, and patient advocacy to identify factors to consider when undertaking a Traceback program. This report highlights the workshop deliberations with the goal of stimulating research and providing a framework for pilot studies to assess the feasibility and ethical and logistical considerations related to the development of best practices for implementation of Traceback studies.

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CHALLENGES AND OPPORTUNITIES

Since 2007, the National Comprehensive Cancer Network guidelines have recommended the offering of genetic counseling for *BRCA1* and *BRCA2* mutation testing to women with ovarian cancer.[1] This guideline offers a critical opportunity to identify *BRCA1/2* mutation carriers who lack a family history of breast or ovarian cancer and would not have been offered genetic testing previously. The potential impact of this approach is demonstrated by data that show that 44% of 141 women with nonmucinous ovarian cancer positive for *BRCA1/2* mutations did not report a family history of breast or ovarian cancer.[2] Anecdotally, clinicians describe newly diagnosed *BRCA1/2*-related cancers in families in which relatives with breast and/or ovarian cancer were never tested for mutations. These findings highlight missed opportunities for cancer prevention and risk management through breast cancer screening, prophylactic mastectomy, and risk-reducing salpingo-oophorectomy.[3-6]

Women unselected for family history of breast or ovarian cancer with pathogenic *BRCA1/2* mutations have a 45% to 65% risk for breast cancer and an 11% to 59% risk for ovarian cancer by age 70 years.[7-9] High-grade ovarian, fallopian tube, and peritoneal cancers are important sentinel cancers for *BRCA1/2* carriers, with germline mutations found in 15% of unselected women.[10] Less information exists about the prevalence of *BRCA1/2* mutations in nonwhite populations; in

ASSOCIATED CONTENT

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a study of the data repository of Myriad Genetics, *BRCA1/2* pathogenic mutations were found in 14.8%, 15.6%, 12.7%, and 13.2% of tested Latin American, African, Asian, and Native American women, respectively.[11] However, opportunities to counsel and test individuals at high risk of carrying *BRCA1/2* mutations often are missed, especially among minority groups.[12] On average, only approximately 20% to 30% of patients with cancer at high risk for *BRCA1/2* mutations undergo genetic testing, with lower percentages among women with ovarian cancer (Table 1). This modest uptake of testing likely reflects a lack of referral, access, and follow-through by patients. Although referral rates for genetic testing have increased in the United States since 2004,[18,19,24] it is estimated that only 48,700 of > 348,000 women who are *BRCA1/2* mutation carriers have been identified.[26] Approximately 220,000 of these *BRCA1/2* carriers have not been given a diagnosis of cancer, which indicates challenges with regard to awareness of genetic risk and cascade testing of unaffected relatives. Given that reliance on self-referral, physician referral, and communication within families is not sufficient, a more active approach is needed to identify at-risk individuals.[27]

Genetic counseling and testing for *BRCA1/2* mutation carriers have emerged as a health disparity issue.[28] Genetic testing varies across generations, ethnic groups, socioeconomic classes, and geographic regions with varying access to health

Table 1. Genetic Counseling and Testing Uptake in Eligible Women

First Author	Population	Frequency of Referral or Testing for *BRCA1/2* Mutations
Armstrong[13]	Retrospective study of women without cancer who had been offered breast cancer risk assessment, genetic counseling, and *BRCA1/2* testing at the University of Pennsylvania BCREP3 Program from 1996 to 1998	125 (49.8%) of 251 underwent *BRCA1/2* testing
Lee[14]	Retrospective study of high-risk patients (estimated chance of carrying *BRCA1/2* mutation ≥ 10%) at Johns Hopkins Breast and Ovarian Surveillance Service from 1996 to 1999	68 (26.4%) of 258 eligible women underwent *BRCA1/2* testing
Schwartz[15]	Patients with newly diagnosed breast cancer and a family history at Lombardi Comprehensive Cancer Center offered genetic counseling and *BRCA1/2* testing	177 (76.6%) of 231 underwent *BRCA1/2* testing
Armstrong[16]	Case-control study of women within the University of Pennsylvania Health System with a family history of breast or ovarian cancer from 1999 to 2003	Of women who underwent genetic counseling (cases), 7.4% were African American and 84.8% were white Of women who did not undergo genetic counseling (control subjects), 28.8% were African American and 65.8% were white
Metcalfe[17]	Ontario Cancer Registry review of patients who had been given a diagnosis of epithelial ovarian cancer from 2002 to 2004	80 (19.2%) of 416 underwent *BRCA1/2* testing, with differences in testing frequencies by race: white, 20.6%; Asian, 3.5%; black, 0%
Meyer[18]	Retrospective review of women with ovarian cancer at the University of Texas MD Anderson Cancer Center from 1999 to 2007	896 (23.8%) of 3,765 met eligibility for *BRCA1/2* testing (> 20%-25% chance of having a mutation) of whom 242 were counseled and 208 tested African American women less likely to be referred than white women (OR, 0.25; 95% CI, 0.09 to 0.70)
Levy[19]	National review of insured women ages 20 to 40 years with breast cancer from 2004 to 2007	446 (30%) of 1,474 underwent *BRCA1/2* testing, with differences in testing frequencies by race: white, 34%; Asian, 27%; black, 12%; Hispanic, 18%
Powell[20]	Retrospective chart review of patients with breast cancer age ≤ 40 years or with ovarian, peritoneal, or tubal cancer age ≤ 60 years at Kaiser Permanente Northern California from January to June 2008	47 (44.8%) of 105 eligible patients were referred for genetic testing of whom 27 attended counseling and 17 were tested Breast cancer: 32 (59.3%) of 54 referred for genetic testing Ovarian cancer: 7 (21.2%) of 33 referred for genetic testing
Petzel[21]	Retrospective chart review of women with epithelial ovarian cancer at the Women's Cancer Center, University of Minnesota, from 2004 to 2006	72 (19.1%) of 376 women referred for genetic testing of whom 42 were counseled and 34 tested
Demsky[22]	Retrospective cancer registry review of women with invasive serous ovarian cancer (including fallopian tube and primary peritoneal carcinoma) at Princess Margaret Hospital from 2002 to 2009	144 (23.1%) of 623 women received genetic counseling of whom 142 were tested
Stuckey[23]	Retrospective review of women who met NCCN guidelines for genetic referrals (breast cancer diagnosis at age ≤ 50 years) from a tumor registry in the Program in Women's Oncology, Brown University, from 2004 to 2010	107 (34.1%) of 314 were referred for genetic counseling of whom 77.6% received genetic counseling, with 95.2% of counseled women tested
Febbraro[24]	Retrospective chart review of women with epithelial ovarian cancer, breast cancer at age ≤ 50 years, or uterine cancer at age < 50 years at the Program in Women's Oncology, Brown University, from 2004 to 2010	178 (21.7%) of 820 referred for genetic testing Ovarian cancer: 42 (14.5%) of 290 referred for genetic testing of whom 25 were tested. Breast cancer: 107 (34.1%) of 314 referred for genetic testing of whom 79 were tested Uterine cancer: 29 (13.4%) of 216 referred for genetic testing of whom 16 were tested
Rosenberg[25]	Cross-sectional analysis of data collected from women with breast cancer age ≤ 40 years as part of the Young Women's Breast Cancer Study from 2006 to 2014	780 (87.0%) of 897 underwent *BRCA1/2* testing

Abbreviations: BCREP3, Breast and Ovarian Cancer Risk Evaluation Program 3; NCCN, National Comprehensive Cancer Network; OR, odds ratio.

services.[29,30] This disparity is partly driven by lack of awareness of the value of testing, poor understanding of risk in relation to family history, lack of referral, and lack of capacity for genetic counseling and testing.[31] Reaching out to disadvantaged populations to offer *BRCA1/2* mutation testing represents an important goal particularly because these women have worse outcomes.[30]

A Traceback approach of retrospective identification of mutation carriers provides an opportunity to offer informative genetic counseling, testing, and cancer risk assessments to probands and their family members (Appendix Table A1, online only). Furthermore, the approaches developed for retrospective identification of *BRCA1/2* mutations among patients with ovarian cancer could be applied to other actionable high-penetrance mutations. However, substantial logistical, ethical, legal, social, and clinical challenges are associated with genetic testing of previously diagnosed and unreferred patients and communicating results to family members (Appendix Table A2, online only). Accordingly, the Traceback workshop and this report were organized around three interconnected themes that are summarized in Figure 1: (1) strategies to ascertain probands who carry pathogenic *BRCA1/2* mutations; (2) approaches for molecular testing, including the scope of genetic testing and reporting; and (3) ethical considerations related to obtaining permission to perform genetic testing and communication of risk information to relatives.

Identification of Probands to Reach Untested Individuals and Their Families

Germline *BRCA1/2* mutations are particularly prevalent in epithelial ovarian cancers, which are efficient sentinel cancers to detect carriers among family members. Once identified, a carrier provides an entry point for reaching other family members who could potentially benefit from genetic counseling, genetic testing and interpretation of results, and appropriate risk-management strategies.

Several factors influence the feasibility, acceptability, and potential utility of genetic testing a proband's blood or pathology specimen to determine *BRCA1/2* mutation status: the value of identifying or ruling out a pathogenic mutation; access to genetic testing, counseling services, and future risk-reduction strategies, particularly for underserved populations; the ability to obtain consent for genetic testing; and the ability and willingness of probands to facilitate contact with relatives. Although a Traceback approach could be applicable to a number of *BRCA1/2*-associated cancers, workshop participants suggested the piloting of approaches with women with previous high-grade ovarian, fallopian tube, or peritoneal cancer because 15% of cases carry *BRCA1/2* mutations in unselected populations.[10] With feasibility and best-practice data derived from such a study, the approach could be extended to other predisposition genes and tumor types.

Approaches for identifying these probands include a search of pathology records or tumor registry databases, community engagement campaigns, and self-referral on the basis of family

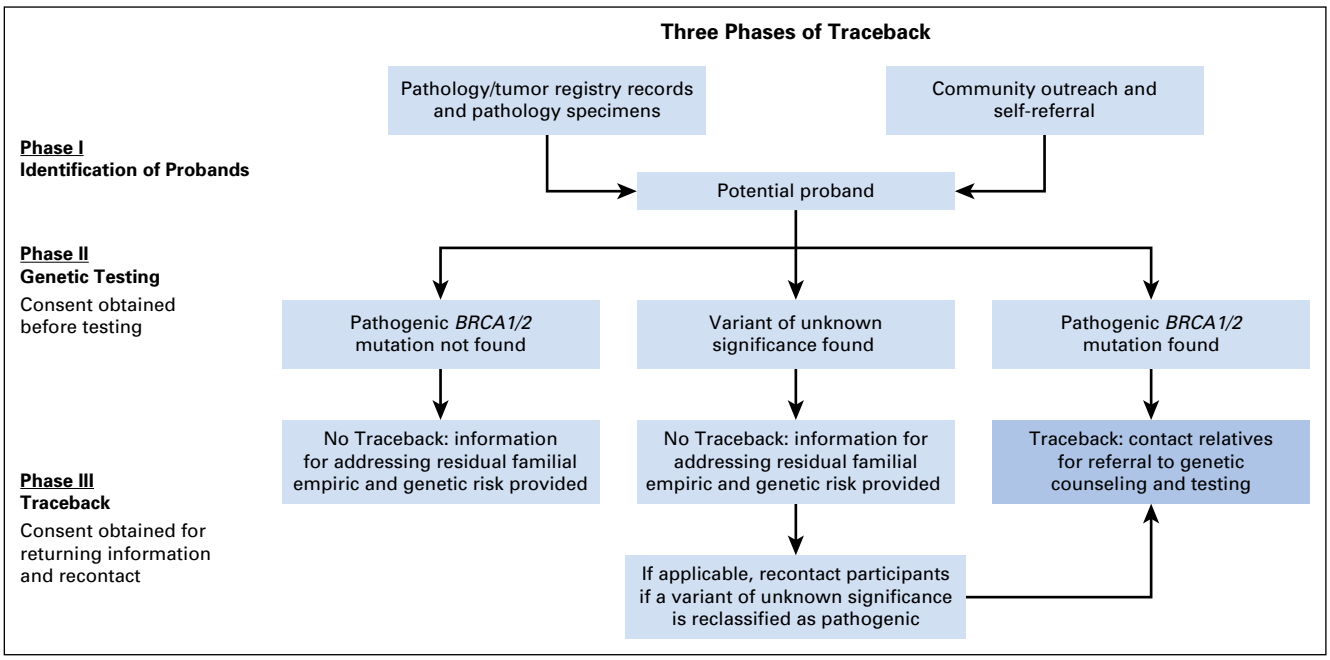

Fig 1. Three phases of Traceback. Phase I: potential previously diagnosed, unreferred probands are identified through searches of pathology or tumor registry records or through self-referral. Phase II: consent is obtained for *BRCA1/2* genetic testing according to method used to identify potential probands. If proband is living and contactable, direct consent is obtained, and blood is tested in a clinically and molecularly certified laboratory. If archived pathology specimen is used to test potential proband because individual is deceased or cannot be contacted, consent is sought from next of kin (which also allows investigators to determine whether family members have already been tested). Phase III: variants of unknown significance are by definition not clinically actionable and, thus, should not be considered with respect to decision making. As such, a Traceback approach to genetic testing should only return pathogenic or likely pathogenic variants.[32] If the potential proband is confirmed to have a *BRCA1/2* pathogenic mutation, cooperation of the proband or next of kin is enlisted to reach relatives to offer education, counseling, and testing. If potential proband is not found to carry a *BRCA1/2* pathogenic mutation or is found to have a variant of unknown significance, participants are informed about residual familial empirical and genetic risk. If a variant of unknown significance is later reclassified as a pathogenic mutation, relatives are contacted to offer education, counseling, and testing.

(and/or personal) cancer history. Each approach poses specific ethical, legal, and logistical issues, including whether the individual is already a candidate for genetic testing according to current guidelines, procedures needed to obtain consent to perform genetic testing, and the proband's vital status and availability for contact (as described in the section on Ethics and Privacy Considerations).

Identification of probands by using pathology records and tumor registry data. Record searches may identify patients with cancer who have not undergone genetic testing and are unlikely to seek genetic counseling. For patients who can be contacted, informed consent and blood for germline genetic testing may be possible to obtain, or they could be directed to a high-risk clinic for genetic counseling. However, high-grade ovarian, fallopian tube, and peritoneal cancer have a high fatality rate, and many individuals may be deceased. DNA derived from normal tissues in archived pathology specimens should be suitable for assessing germline *BRCA1/2* mutation status, although the sensitivity and specificity of this approach relative to more-conventional testing remain unclear.[33,34]

Evidence suggests that many women with high-grade ovarian, fallopian tube, or peritoneal cancers should be viewed as a single disease.[35,36] Thus, patients with these cancers are appropriate candidates for genetic testing. In addition, this consideration may extend to individuals with serous tubal intraepithelial carcinoma, the presumptive precursor of ovarian, tubal, and peritoneal carcinomas.[37,38] Histopathologic subtyping of these cancers is not entirely reproducible, and diagnostic practices have changed over time and differ among institutions[39]; in particular, cancers classified as endometrioid, serous, mixed, and undifferentiated have been inconsistently distinguished. Accordingly, consideration of inclusion of all nonmucinous high-grade ovarian, tubal, and peritoneal carcinomas would be appropriate. By contrast, genetic testing of nonepithelial ovarian cancers, low-grade carcinomas, or borderline (low malignant potential) neoplasms is unlikely to identify additional probands.

Diagnostic formalin-fixed paraffin-embedded surgical pathology blocks stored under adequate conditions and linked to medical records are the most appropriate biospecimens for genetic testing of tissues from previously diagnosed cases, with uninvolved lymph node or uterine tissues being the best source of normal DNA. Where normal tissue is not accessible, consideration could be given to the use of DNA from tumor material. Although the distinguishing of germline from somatic mutations would be difficult, a null result would be useful, and if pathogenic mutations are found, especially for established founder mutations, ascertainment of germline status among family members may be warranted. Consideration should also be given to the development of central repositories to store culled pathology specimens (and the associated issues around ownership, consent, cost, etc).

Community engagement and self-referral. Traceback that is based on community engagement campaigns and that seeks to raise awareness about the genetic risk of breast or ovarian cancer provides a parallel strategy to recruit either affected individuals or relatives of women with ovarian cancer. Self-referral offers ease of consent and optimal collection of blood samples and may reflect an inclination to assist in identifying family members for referral. However, self-referral may not reach underserved groups unless appropriate media campaigns and community engagement are specifically tailored. Furthermore, in contrast to pathology-based proband identification in which a cancer diagnosis is relatively certain, self-referral could be based on incorrect recollections of cancer diagnoses among relatives, potentially leading to unnecessary genetic testing.

The Prevent Ovarian Cancer Program developed in Ontario, Canada, provides a model for a community Web-based campaign in which self-referred relatives of women with high-grade ovarian cancer participate in an online evaluation for genetic testing referral, if indicated. Media outreach has encompassed primary care practitioners, social media, and television and print news media. Since its launch in September 2015, the Prevent Ovarian Cancer Program has enrolled $>$ 500 of the planned total recruitment of 1,000 women.

Scope of Molecular Testing and Reporting

Currently, detection of individuals with pathogenic mutations in *BRCA1/2* provides the strongest argument for developing Traceback; however, numerous new variants in genes associated with *BRCA*-mediated DNA repair have been identified. Most of these variants are low risk, but some, such as *RAD51C*, *RAD51D*, and *BRIP1*, are associated with at least a moderate risk of ovarian cancer,[10,40,41] and National Comprehensive Cancer Network guidelines recommend consideration of risk-reduction gynecologic surgery for women with pathogenic mutations in these genes.[42] Multigene testing for mutations in many cancer susceptibility genes in parallel is increasingly being used as it becomes cost-effective, technically feasible, and increasingly accessible.

A prospective study of 1,046 individuals who were at risk for or given a diagnosis of breast or ovarian cancer and were not known *BRCA1/2* mutation carriers found that 3.8% had positive test results for putative pathogenic mutations in moderate- or high-penetrance genes other than *BRCA1/2*.[43] On the basis of existing guidelines, detection of these mutations was estimated to influence clinical management of approximately 52% of carriers and prompt genetic testing of additional first-degree family members in 72% of cases.[43] These findings indicate that multigene testing for hereditary breast and ovarian cancer could provide clinical benefit beyond testing for *BRCA1/2* alone; however, challenges persist related to the translation of a currently incomplete knowledge of risks and benefits into optimal clinical management.[44,45]

Multigene testing of DNA derived from fixed pathology samples has been demonstrated through either targeted capture– or multiplexed amplicon–based approaches followed by next-generation sequencing. Methodological limitations in using tissue blocks for genetic testing include variable quantity and preservation of tissue and DNA. Technical advances in sequencing methodology may enable more-affordable molecular testing and expand the ability to handle small or suboptimally preserved tissues with increasing specificity.[33,34] Even under stringent conditions, some false-positive and -negative results that lead to misclassification of proband status may be unavoidable. False-positive results would likely raise concern and could result in harm if communicated to family members but may be resolved through further genetic testing. To minimize false-negative results in the proband, the offer of full gene sequencing for *BRCA1/2* and/or

a multigene germline hereditary cancer risk panel may be preferred. When a specific mutation is identified, targeted testing of relatives offers advantages. Full gene testing could be recommended for patients with breast cancer who have a relative with ovarian cancer to determine phenocopy or mutation carrier status. Participating individuals or communities in Traceback should be informed about the residual familial empirical and genetic risk caveats that apply when a mutation is not identified (uninformative testing). Conveying the scope of the mutation testing that was performed on the proband's sample is critical to provide a clear future understanding of which genes were or were not evaluated. Informing family members that a relative has negative test results for pathogenic *BRCA1/2* mutations may avoid unnecessary testing.

The development of multigene testing raises the important issue of genetic counseling and what findings to report. Some providers favor only the disclosure of pathogenic or likely pathogenic variants, whereas others may report variants of uncertain significance or likely benign or benign variants,[46] and interpretations of variants can differ among clinical laboratories.[47] Furthermore, risk estimates for many genes are imprecise[48] and may be influenced by the presence or absence of other low-risk variants,[49] which means that knowledge is likely to evolve over time. The complex nuances of interpreting and communicating risk related to the detection of wild-type *BRCA1/2* or variants of unknown significance in the context of a family history of cancer must be considered, but the limiting of testing to specific mutations found in relatives with cancer can lessen the problem.

Research to clarify the implications of variants of unknown significance in a variety of clinical contexts is ongoing,[50] and research associated with Traceback may enable the construction of research pedigrees that clarify the biologic importance of these findings. The responsibilities for recontacting Traceback participants when the pathogenicity of a variant of uncertain significance is reclassified should be defined at the outset and communicated to participants.

Ethics and Privacy Considerations

A Traceback protocol to identify and test previously diagnosed cases engenders ethical and legal concerns related to consent to perform genetic testing and to return results to probands and/or their relatives. These considerations may vary with the design of the protocol and in accordance with local, state, national, and institutional mandates and applicable laws.[51]

The most straightforward situation is proband self-referral because these patients have opted in for genetic testing. However, if probands are identified through medical records, ethical considerations may vary by vital status and ability to be contacted. If the patient is living and locatable, she can be approached to provide informed consent to undergo testing. Although a *BRCA1/2* pathogenic mutation itself does not pose an imminent threat, the strong association between these mutations and potentially lethal, yet preventable cancers[52] provides a strong justification for unsolicited contact or recontact.

If the potential proband cannot be reached, the ethical, legal, and social challenges of genetic testing of pathology blocks without antecedent consent from a representative of the family and returning results to family members are complex. One option is to test diagnostic blocks without consent and then contact next of kin if a pathogenic mutation is found; this approach was used for hereditary colorectal cancer in a health services research study in Australia. After approval by three human research ethics committees, the investigators successfully contacted 18 at-risk individuals or their next of kin, 17 of whom agreed to attend genetic counseling. The majority of the at-risk individuals were happy with the follow-up and considered it a valuable extension of their health care.[53] The authors provided a detailed commentary on the reasons for and against proceeding without prior consent, which favored the opportunity to limit concern about a possible genetic risk to a minority of families, and advantages of cost, logistics, and speed of progress.[53]

Whether a nonconsented evaluation of ovarian cancer diagnostic specimens could be allowed will be dictated by local factors, including laws related to consent/authorization for testing, the receptivity of the community to genetic testing, laws related to genetic discrimination, and ability to access health and life insurance if a mutation is found. Accordingly, Traceback protocols should define ethical and legal requirements of the program, including the resolution of state and national privacy restrictions.

In the United States, the Health Insurance Portability and Accountability Act (HIPAA) speaks to obtaining consent before testing; returning genetic results to family members; and the logistics related to contacting family members, such as time frame, number of attempted contacts, and geographic limitations.[51] In Australia, the National Health and Medical Research Council Guidelines for research that involves human subjects makes provisions for nonconsented access to diagnostic blocks under certain circumstances, although these are typically for research rather than for the clinical intent of Traceback.[54] Similar guidelines exist in Japan concerning access to previously collected tissues. In Ontario, Canada, according to the Public Hospitals Act, all diagnostic tissue remains property of the hospital.[55] Similar to Australia, this tissue could be used secondarily for research without informed consent but only if the risk of identification of the individual is considered low.[56]

Significant cultural differences exist about the trust and willingness of communities with regard to genetic research and clinical genetic testing,[57-60] and genetic discrimination is a global concern.[61,62] In some instances, the discovery of a high-risk gene can have an impact on the ability of unaffected carriers to obtain health or life insurance. In the United States, the Genetic Information Nondiscrimination Act and Affordable Care Act legally prohibit various forms of discrimination (including employment and health insurance) but still leave gaps in protection (eg, life insurance).[63] In Canada, Bill S-201 (Genetic Non-Discrimination Act) was passed unanimously by the Senate in April 2016 and currently is being debated in the House of Commons. This bill would protect individuals from having to disclose genetic testing results to employers or insurance companies. Currently, Canada is the only Group of Seven country without such legislation to prevent genetic discrimination.

Once testing of a proband has occurred and a mutation is found, important issues related to disclosure remain. Studies have demonstrated that barriers to cascade testing within a family include the burden on a proband to inform, emotional and developental readiness, family culture, and genetic risk

misinformation/misunderstanding.[3] In addition, a shortage of adequately trained genetic specialists among health care providers and challenges with respect to reimbursement and insurance policies exist.[64] Efforts to improve cascade testing are actively being pursued. Some investigators are examining improved technologies for sharing genetic results, including secure Web sites or the development of educational videos to send to relatives. Some specialists advocate for greater direct involvement of the clinician or genetic counselor to relieve probands of the pressure of communicating the results themselves.[27] Greater involvement of a genetic specialist also streamlines testing by identifying the most appropriate family member to test first.[64] Changes in health policy, such as the offer of tests at reduced costs or remote counseling, could also improve the uptake of cascade genetic testing.[64]

Under HIPAA, a designated personal representative may authorize disclosure of the genetic results of a deceased person under certain circumstances.[65,66] If a deceased patient has not designated a personal representative, the law in most US states grants the responsibility to a default personal representative, such as a close relative, which potentially provides access to genetic test results by biologically related family members.[67] HIPAA also permits disclosure of genetic information to health care providers who request it (for purposes of risk assessment and treatment of family members) provided that the individual has not previously restricted disclosure.

An ethical, legal, and social implications working group within a National Institutes of Health–funded program published a consensus paper that provides recommendations for the ethical and legal framework for returning a research participant's genomic results to relatives, including communication after the participant's death.[51] Although a distinction exists between genomic results obtained for research versus clinical contexts, many of the recommendations and analyses may be applicable to Traceback. The consensus document stated that when research participants are found to bear pathogenic actionable genetic variants, the sharing of these results with relatives may be ethical if provision of this information can lead to a reduction in harm.[51]

A survey of institutional review board chair and vice chair perspectives on returning genetic research results to family members found that a majority of respondents favored disclosure of clinically actionable research results to family members if the proband is deceased and prior consent was given; only a minority agreed, however, to disclosure when consent was not expressly given.[68] By contrast, a survey conducted by FORCE: Facing Our Risk of Cancer Empowered, an advocacy organization for patients with hereditary breast and ovarian cancer, to determine which factors influence decisions about communicating cancer risk to family members found that most respondents shared their genetic results with family members and were satisfied with the outcome, although decision making can be influenced by personal privacy, ease of contact, or the influence of other family members.[69] Similarly, in a survey of individuals with pancreatic cancer and their family members, most respondents believed that genetic research results obtained after a patient's death should be offered to his or her spouse and adult biologic children irrespective of whether the spouse wanted to know the information and even if the deceased's wishes were unknown.[70]

Data from the aforementioned surveys and the experience in the Prevent Ovarian Cancer Program in Ontario suggest that Traceback might receive public acceptance; however, potential concerns exist related to risks and fear of genetic discrimination and costs for the individual as well as about important local community issues that should be recognized. As such, the workshop participants suggested a population-based survey to assess attitudes about seeking and testing potential probands and returning test results to relatives.

MARKERS OF SUCCESS

Important metrics for the success and cost-effectiveness of a Traceback program include the proportion of potentially eligible probands and relatives identified and tested, rates of mutation detection, and effectiveness of cascade testing. A recent study of the economic impact of screening in Singapore suggested that government subsidies for the testing of first-degree relatives are cost saving if $\geq$ 36% of relatives were tested, although these results were sensitive to assumptions about adherence to post-testing surveillance.[71] Although formal cost-effectiveness analyses in the United States are needed, these results suggest that a target of 40% to 50% uptake would be reasonable for a pilot feasibility project. Other important parameters are related to the acceptability of the program to probands and relatives; the ability to reach underserved communities; and the impact on cancer incidence, mortality and overall quality of life. Information on program-specific resource utilization and downstream health interventions, such as testing facilities and genetic counseling services, also should be captured.

Pilot programs are warranted for a variety of reasons, including the opportunity to provide estimates of program-specific resource utilization and specific outcomes, which could be applied to the development of a large-scale Traceback program. Although a single approach may not prove equally effective in all communities, pilot studies will help to determine the relative weaknesses and strengths of different strategies as well as identify critical aspects germane to all designs.

CONCLUSION

Given that most *BRCA1/2*-related cancers can be potentially prevented by risk-reducing surgery or detected at early stages with screening (breast cancer), an increase in the identification of *BRCA1/2* mutation carriers offers an important opportunity for cancer control. Efforts to increase physician referral of patients with ovarian cancer are under way,[28] and population *BRCA1/2* mutation testing has been proposed.[72,73] Traceback seeks to leverage limited resources by using medical records and pathology specimens as well as community and individual education to identify probands and engage families with limited awareness of genetic risk. This approach is potentially cost-effective, more acceptable than population testing, and applicable to other hereditary cancers such as Lynch syndrome. In fact, the Cancer Moonshot Blue Ribbon Panel Report 2016 recommended a demonstration project to identify families who carry Lynch syndrome predisposition genetic mutations by initially germline sequencing patients diagnosed with a Lynch syndrome–related cancer and offering testing and counseling to relatives.[74]

Although considerable value is anticipated to arise from Traceback, the ethical, legal, and social implications of obtaining consent for genetic testing of a previously diagnosed case and communicating results to family members are complicated, are incompletely understood, and should not be underestimated. Although significant ethical and logistical challenges exist, the workshop participants formulated considerations related to the Traceback concept to stimulate interest and informative studies to evaluate the value of such programs in reaching the many untested individuals at elevated risk of carrying pathogenic mutations. The identification of such individuals would represent a major step toward providing genetic counseling, testing, and effective preventive interventions to lower cancer risk in mutation carriers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Goli Samimi, Lawrence C. Brody, Charlisse F. Caga-anan, Georgia Chenevix-Trench, Fergus J. Couch, Ronny Drapkin, Michael Friedlander, Karen Hurley, Susan J. Ramus, Thomas P. Slavin, David D. Bowtell, Mark E. Sherman
Collection and assembly of data: Goli Samimi, Marcus Q. Bernardini, Lawrence C. Brody, Charlisse F. Caga-anan, Ian G. Campbell, Michael Dean, Joanne A. de Hullu, Heather Spencer Feigelson, Michael Friedlander, Mia M. Gaudet, Marline G. Harmsen, Paul A. James, Janice S. Kwon, Felicitas Lacbawan, Phuong L. Mai, Evan R. Myers, Mark E. Robson, Lisa F. Rezende, Patricia A. Shaw, Thomas P. Slavin, Elizabeth M. Swisher, Masataka Takenaka, David D. Bowtell, Mark E. Sherman
Data analysis and interpretation: Goli Samimi, Marcus Q. Bernardini, Charlisse F. Caga-anan, Ian G. Campbell, Michael Dean, Joanne A. de Hullu, Susan M. Domchek, Ronny Drapkin, Heather Spencer Feigelson, Michael Friedlander, Mia M. Gaudet, Marline G. Harmsen, Paul A. James, Janice S. Kwon, Felicitas Lacbawan, Stephanie Lheureux, Leah E. Mechanic, Lori M. Minasian, Evan R. Myers, Mark E. Robson, Lisa F. Rezende, Patricia A. Shaw, Elizabeth M. Swisher, David D. Bowtell, Mark E. Sherman
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Goli Samimi, **Charlisse F. Caga-anan**, **Michael Dean**, **Leah E. Mechanic**, **Lori M. Minasian**, and **Mark E. Sherman**, National Cancer Institute; **Lawrence C. Brody**, National Human Genome Research Institute, Bethesda, MD; **Marcus Q. Bernardini**, **Stephanie Lheureux**, **Patricia A. Shaw**, Princess Margaret Cancer Centre, Toronto, Ontario; **Janice S. Kwon**, University of British Columbia; British Columbia Cancer Agency, Vancouver, British Columbia, Canada; **Ian G. Campbell**, **Paul A. James**, **Masataka Takenaka**, and **David D. Bowtell**, Peter MacCallum Cancer Centre; **David D. Bowtell**, University of Melbourne, Melbourne, Victoria; **Georgia Chenevix-Trench**, QIMR Berghofer Medical Research Institute, Brisbane, Queensland; **Michael Friedlander**, The Prince of Wales Hospital; **Susan J. Ramus**, University of New South Wales; **Susan J. Ramus** and **David D. Bowtell**, Garvan Institute of Medical Research, Sydney, New South Wales, Australia; **Fergus J. Couch**, Mayo Clinic, Rochester, MN; **Joanne A. de Hullu** and **Marline G. Harmsen**, Radboud University Medical

Center, Nijmegen, the Netherlands; **Susan M. Domchek** and **Ronny Drapkin**, University of Pennsylvania, Philadelphia; **Phuong L. Mai**, Magee-Women's Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA; **Heather Spencer Feigelson**, Kaiser Permanente Institute for Health Research, Denver, CO; **Mia M. Gaudet**, American Cancer Society, Atlanta, GA; **Karen Hurley** and **Mark E. Robson**, Memorial Sloan Kettering Cancer Center; **Mark E. Robson**, Weill Cornell Medical College, New York, NY; **Felicitas Lacbawan**, Quest Diagnostics Nichols Institute, San Juan Capistrano; **Thomas P. Slavin**, City of Hope, Duarte, CA; **Evan R. Myers**, Duke University Medical Center, Durham, NC; **Lisa F. Rezende**, FORCE: Facing Our Risk of Cancer Empowered, Tampa; **Mark E. Sherman**, Mayo Clinic, Jacksonville, FL; and **Elizabeth M. Swisher**, University of Washington Medical Center, Seattle, WA.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Traceback: A Proposed Framework to Increase Identification and Genetic Counseling of *BRCA1* and *BRCA2* Mutation Carriers Through Family-Based Outreach

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Goli Samimi
No relationship to disclose

Marcus Q. Bernardini
Consulting or Advisory Role: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

Lawrence C. Brody
Consulting or Advisory Role: Boehringer Ingelheim (I), Roche (I), Global Blood Therapeutics (I)
Research Funding: Roche (I)
Travel, Accommodations, Expenses: Roche (I), Boehringer Ingelheim (I), Global Blood Therapeutics (I)

Charlisse F. Caga-anan
No relationship to disclose

Ian G. Campbell
No relationship to disclose

Georgia Chenevix-Trench
No relationship to disclose

Fergus J. Couch
Travel, Accommodations, Expenses: Ambry Genetics

Michael Dean
No relationship to disclose

Joanne A. de Hullu
No relationship to disclose

Susan M. Domchek
Research Funding: AstraZeneca (Inst), Clovis Oncology (Inst), AbbVie (Inst), Pharmar (Inst)

Ronny Drapkin
No relationship to disclose

Heather Spencer Feigelson
No relationship to disclose

Michael Friedlander
Honoraria: Pfizer, AstraZeneca
Consulting or Advisory Role: AstraZeneca, Pfizer
Research Funding: AstraZeneca (Inst)

Mia M. Gaudet
No relationship to disclose

Marline G. Harmsen
No relationship to disclose

Karen Hurley
Honoraria: Sanofi, Genzyme, GeneDx, BioReference
Speakers' Bureau: Sanofi, Genzyme, GeneDx

Paul A. James
No relationship to disclose

Janice S. Kwon
No relationship to disclose

Felicitas Lacbawan
Employment: Quest Diagnostics, Nichols Institute
Stock or Other Ownership: Quest Diagnostics

Stephanie Lheureux
Consulting or Advisory Role: AstraZeneca

Phuong L. Mai
No relationship to disclose

Leah E. Mechanic
No relationship to disclose

Lori M. Minasian
No relationship to disclose

Evan R. Myers
Consulting or Advisory Role: Merck, Ernst & Young

Mark E. Robson
Honoraria: AstraZeneca
Consulting or Advisory Role: McKesson, AstraZeneca
Research Funding: AstraZeneca (Inst), AbbVie (Inst), Myriad Genetics (Inst), Medivation (Inst)

Susan J. Ramus
No relationship to disclose

Lisa F. Rezende
Employment: Ventana Medical Systems (I)

Patricia A. Shaw
Honoraria: AstraZeneca

Thomas P. Slavin
No relationship to disclose

Elizabeth M. Swisher
No relationship to disclose

Masataka Takenaka
No relationship to disclose

David D. Bowtell
Research Funding: Roche (Inst), Genentech (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: Genentech

Mark E. Sherman
No relationship to disclose

Appendix

Table A1. Elements of a Best-Practice Traceback Program

Element	Approach
Ensure broad representation	Organize an advisory panel that includes patient advocates Target underserved populations
Use multiple approaches to identify probands	Obtain permission to access state, national, and institutional registries Engage with clinician specialists Engage with patient advocacy groups for input and awareness campaigns
Provide appropriately comprehensive genetic testing to a high standard	Option 1: only test for *BRCA1* and *BRCA2* Option 2: panel test for multiple genes associated with ovarian cancer risk Perform testing in accredited testing facilities Know false-negative rate of testing, especially for newer methods
Report findings	Option 1: report only findings where the mutation is clearly pathogenic and reliable risk estimates are available Option 2: provide all findings, even genes/mutations of unknown significance Apply stringent safeguards to ensure confidentiality Establish approaches for remote genetic counseling
Use strategies to maximize cascade testing when a pathogenic mutation is detected	Use study coordinators with knowledge of genetic testing Use approaches that are sensitive to various family situations and interactions
Monitor outcomes and measure cost benefit	Define metrics of success at the outset and include instruments to objectively measure relevant outcomes

Table A2. Ethical, Legal, and Social Issues Associated With the Testing of Potential Probands

Scenario	Issues
Proband alive	What was consent for tissue use at time of tissue collection (surgery)? Was there discussion of recontact in the event of advances in genetic knowledge? Can proband be contacted? Will proband consent to genetic testing and contacting of family members? If not, do local laws permit waiver of consent to perform genetic testing on tissue blocks?
Proband deceased	Can a family member/personal representative be identified/contacted? Is it logistically feasible and is funding available to consent next of kin? If not, do local laws permit waiver of consent to perform genetic testing on tissue blocks?
Considerations for all approaches	Is it justifiable to raise concern about a potentially serious genetic condition in a majority when only a minority of individuals are at risk? To what standards and where will the work be performed? Who will interpret the findings, particularly those that involve genes other than *BRCA1* and *BRCA2* for which less information is available about pathogenic variants and risk estimates? What genetic findings will be communicated to next of kin and how will this be done (eg, letter, e-mail, phone call)? Which family members will be contacted (eg, first degree only, beyond)? How will data be recorded (eg, research folders, medical records)? Does local legislation exist to protect the individual against genetic discrimination (eg, employment, health or life insurance)? How receptive is the target community to genetic testing when cultural differences are taken into account? Who are the stakeholders who should be involved in implementing this program in a particular setting?