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Cascade Genetic Testing of Relatives for Hereditary Cancer Risk: Results of an Online Initiative

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Abstract

In cascade testing, genetic testing for an identified familial pathogenic variant extends to disease-free relatives to allow genetically targeted disease prevention. We evaluated the results of an online initiative in which carriers of 1 of 30 cancer-associated genes, or their first-degree relatives, could offer low-cost testing to at-risk first-degree relatives. In the first year, 1101 applicants invited 2280 first-degree relatives to undergo genetic testing. Of invited relatives, 47.5% (95% confidence interval [CI] = 45.5 to 49.6%) underwent genetic testing, and 12.0% (95% CI = 9.2 to 14.8%) who tested positive continued the cascade by inviting additional relatives to test. Of tested relatives, 4.9% (95% CI = 3.8 to 6.1%) had a pathogenic variant in a different gene from the known familial one, and 16.8% (95% CI = 14.7 to 18.8%) had a variant of uncertain significance. These results suggest that an online, low-cost program is an effective approach to implementing cascade testing, and that up to 5% of the general population may carry a pathogenic variant in 1 of 30 cancer-associated genes.

Testing those diagnosed with a disease is the most efficient way to identify carriers of predisposing germline genetic variants, and is consistent with clinical practice guidelines (1). To achieve the goal of genetically targeted primary disease prevention, testing for an identified familial pathogenic variant must then extend to disease-free relatives in a process known as "cascade testing" (2–4). Cascade testing has been designated by the Centers for Disease Control and Prevention as a Tier 1 genomic application for Lynch Syndrome and Hereditary Breast and Ovarian Cancer Syndrome (5). However, there are major barriers to cascade testing, including cost, insurance constraints (6), and confidentiality laws that prohibit direct contact of a patient's relatives by her/his physician or genetic counselor. The burden of informing relatives about test results and their implications falls primarily on the patient, who may simultaneously be struggling with a new diagnosis (7). In the cancer genetics field, technologic advances have reduced testing costs and enabled

new care delivery models (8,9). We evaluated the first year of an online, low-cost family testing initiative offered by a testing laboratory.

People with a previously identified pathogenic variant ("carriers") detected by any Clinical Laboratory Improvements Amendment (CLIA)-certified laboratory in one of 30 cancer-associated genes (Supplementary Table 1, available online), or their first-degree relatives (FDRs), could apply to the family testing program (Figure 1A). People with a qualifying pathogenic result from the testing laboratory received an email introducing the family testing program; information about the program was also distributed to potential participants with the results from other laboratories through online advertisements, at clinics, and at events for families with hereditary cancer. After initial application, the testing laboratory sent emails to FDRs identified by the applicant, inviting them to undergo CLIA-certified multiplex sequencing of these 30 genes at an out-of-pocket cost of US
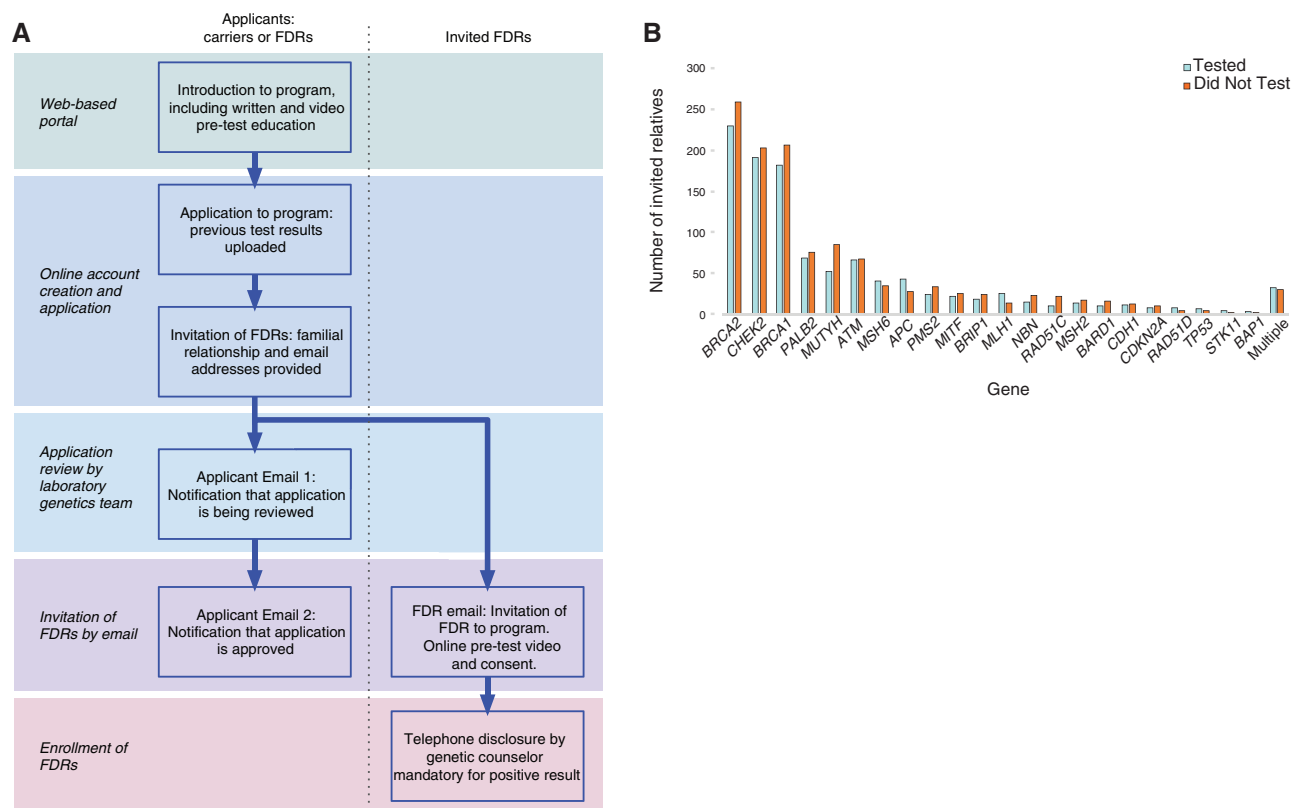
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Figure 1. The family testing program. **A)** Flowchart of the application process. Positive results were available only after telephone-based genetic counseling, and posttest genetic counseling was also optionally available if the results were variant of uncertain significance or negative. **B)** Affected genes and uptake of testing. FDR = first-degree relative.

$50. Sequencing and variant classification followed standard practice guidelines (Supplementary Methods, available online). FDRs with pathogenic results were required to speak by telephone with a genetic counselor to obtain their test results and counseling about cancer risk (10,11). All participants signed informed consent approved by the Western Institutional Review Board, Inc. All P-values are two-sided, and a P-value of less than .05 was considered statistically significant.

In the program's first year (September 27, 2016 to September 27, 2017), 1101 applicants (741 carriers and 360 FDRs) invited 2280 FDRs. Applicants were more often women (78.1% of carrier applicants, binomial $P < .001$; 63.9% of FDR applicants, binomial $P < .001$); demographic details are in Supplementary Table 2 (available online). During the follow-up period (median = 216 days), 47.5% (95% CI = 45.5 to 49.6%) of invited FDRs underwent testing. Invited female relatives were more likely to test than males (52.6% vs 42.0%, $\chi 2\, P < .001$). There were no differences in testing by gene (Figure 1B): relatives who were invited because of a pathogenic variant associated with a well-characterized syndrome (BRCA1/2, MLH1, MSH2, MSH6, PMS2, CDH1, CDKN2A, STK11, and TP53) were tested as often as those who were invited because of a pathogenic variant in a less well-characterized gene (48.1% vs 45.9%, $\chi 2\, P = .31$) (Supplementary Table 2, available online). Among all invited FDRs who tested positive, 12.0% (95% CI = 9.2 to 14.8%) continued the cascade by inviting additional FDRs.

Of FDRs who tested (Figure 2A), 48.1% (95% CI = 45.4 to 50.8%) carried the identified familial pathogenic variant (consistent with their stated first-degree genetic relationship to carriers)

and 4.9% (95% CI = 3.8 to 6.1%) a different pathogenic variant. Of these unexpected pathogenic variants, 42.4% (95% CI = 30.5 to 54.3%) were in low-penetrance alleles (specifically APC I1307K, CHEK2 I157T, and MUTYH heterozygotes), 37.9% (95% CI = 26.2 to 49.6%) in less well-characterized cancer risk genes (specifically ATM, BARD1, BRIP1, CHEK2, MITF, NBN, RAD51C, and RAD51D), and 19.7% (95% CI = 10.1 to 29.3%) in syndromic genes (specifically BRCA1/2, MLH1, MSH2, MSH6, and PMS2) (Figure 2B). Of tested FDRs, 16.8% (95% CI = 14.7 to 18.8%) had a variant of uncertain significance, and 54.5% (95% CI = 48.0 to 61.1%) of these also had a pathogenic variant.

Cascade testing for cancer susceptibility gene mutations faces substantial challenges. Despite recent cost declines, testing often costs $500 or more and may lack insurance coverage: Medicare does not cover preventive genetic testing of cancer-free relatives. In the US, privacy regulations prohibit direct contact of relatives by patients' clinicians, which concentrates the burden of informing relatives on carriers themselves. Cascade testing rates in specialized genetics clinics are low, at approximately 30% of eligible FDRs (12–14). Alternative care models that allow direct contact of relatives by patients' clinicians can improve testing rates to 50 to 60% (12,14), but have not been explored in the US. In the model described here, patients empowered the laboratory to initiate testing by providing FDRs' email addresses for direct contact. At 47.5%, FDRs' testing uptake equaled that of the Lynch Syndrome cascade protocols at expert centers (15). However, continued cascade testing beyond one FDR was low (12.0%). Cascade rates beyond the first degree are not described in the existing literature, which has relied on
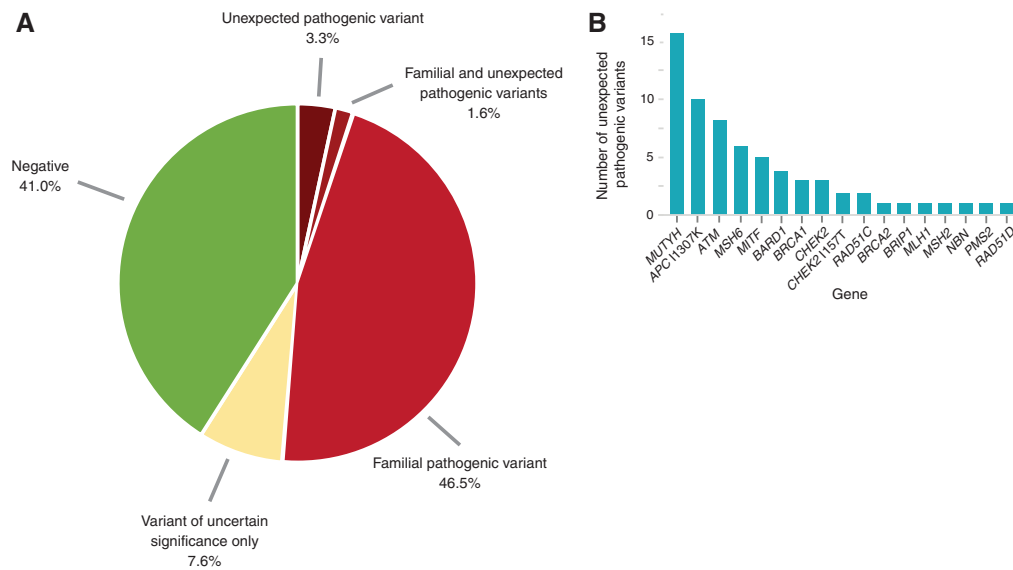
Figure 2. Panel testing results of first-degree relatives of carriers. **A)** Overall results. **B)** Unexpected pathogenic variants.

patient report, and the rate documented here should serve as a benchmark for future studies. While the cascade rate might be expected to decrease with each successive invitation of relatives, the observed drop-off to 12.0% is likely suboptimal. This drop-off could reflect limited understanding of test results, which is the major potential weakness of an online approach without in-person counseling. While FDRs with pathogenic results received posttest genetic counseling by telephone (10,11), pretest counseling was provided only as a video, and informed decision-making outcomes were not measured.

Interestingly, 4.9% of FDRs carried an unexpected pathogenic variant that the carrier applicant did not share. Previous studies estimated that 10 to 20% of patients with breast, colon, or ovarian cancer carry germline cancer suspectibility genes (16–19). Because the FDRs tested here were selected based on their relationship to a carrier of a different pathogenic variant, and not for family or personal history of cancer suggesting the pathogenic variant they were found to carry, their results (outside of the familial pathogenic variant) may approximate those of the general population. Even excluding unexpected mutations in genes with higher prevalence in the Ashkenazi Jewish population (*BRCA1*, *BRCA2*, *APC I1307K*), we estimate that 3.9% (2.9 to 5.0%) of people may carry a pathogenic variant in a cancer susceptibility gene; this estimate may inform discussion about population-wide genetic testing.

Study limitations include selection bias (eg, computer literacy) and missing information on the number of relatives eligible for testing and whether relatives were tested previously. Most important, this study addresses the first step in cascade testing—enhancing identification and testing of at-risk FDRs—but not the essential next steps of engaging FDRs in informed decision-making about options to manage their risk, such as screening or preventive surgery. Future research must explore strategies to extend affordable testing more broadly; to integrate clinician expertise both pre- and posttesting with online approaches like the one described here; and to enable those testing positive to understand their cancer risks and access appropriate risk-reducing interventions.

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