Cascading After Peridiagnostic Cancer Genetic Testing: An Alternative to Population-Based Screening

Kenneth Offit, MD, MPH[1,4]; Kaitlyn A. Tkachuk, BS[1]; Zsofia K. Stadler, MD[1,4]; Michael F. Walsh, MD [1]; Hector Diaz-Zabala, PhD[1]; Jeffrey D. Levin, BS[1]; Zoe Steinsnyder, BS[1]; Vignesh Ravichandran, MS[1]; Ravi N. Sharaf, MD, MS[4]; Melissa K. Frey, MD[4]; Steven M. Lipkin, MD, PhD[4]; Mark E. Robson, MD[1,3,4]; Jada G. Hamilton, PhD, MPH[1,2,4]; Joseph Vijai, PhD[1,4]; and Semanti Mukherjee, PhD[1]

PURPOSE Despite advances in DNA sequencing technology and expanded medical guidelines, the vast majority of individuals carrying pathogenic variants of common cancer susceptibility genes have yet to be identified. An alternative to population-wide genetic screening of healthy individuals would exploit the trend for genetic testing at the time of cancer diagnosis to guide therapy and prevention, combined with augmented familial diffusion or "cascade" of genomic risk information.

METHODS Using a multiple linear regression model, we derived the time interval to detect an estimated 3.9 million individuals in the United States with a pathogenic variant in 1 of 18 cancer susceptibility genes. We analyzed the impact of the proportion of incident patients sequenced, varying observed frequencies of pathogenic germline variants in patients with cancer, differential rates of diffusion of genetic information in families, and family size.

RESULTS The time to detect inherited cancer predisposing variants in the population is affected by the extent of cascade to first-, second-, and third-degree relatives (FDR, SDR, TDR, respectively), family size, prevalence of mutations in patients with cancer, and the proportion of patients with cancer sequenced. In a representative scenario, assuming a 7% prevalence of pathogenic variants across cancer types, an average family size of 3 per generation, and 15% of incident patients with cancer in the United States undergoing germline testing, the time to detect all 3.9 million individuals with pathogenic variants in 18 cancer susceptibility genes would be 46.2, 22.3, 13.6, and 9.9 years if 10%, 25%, 50%, and 70%, respectively, of all FDR, SDR, and TDR were tested for familial mutations.

CONCLUSION Peridiagnostic and cascade cancer genetic testing offers an alternative strategy to achieve population-wide identification of cancer susceptibility mutations.

J Clin Oncol 38:1398-1408. © 2020 by American Society of Clinical Oncology

INTRODUCTION

More than 2 decades after the discovery of genetic variants conferring substantial risks for breast, ovarian, prostate, colon, and other malignancies, and despite advances in DNA sequencing technologies, it has become increasingly clear that the promise of genomics as a tool for cancer prevention has yet to be realized.[1] Fewer than 1 in 5 individuals with a family history of breast or ovarian cancer who meet established criteria for genetic testing have received it, and most have never discussed their hereditary cancer risk with a health care provider.[2] For Lynch syndrome, the most common colon cancer predisposition syndrome, only 1 in 4 individuals who met criteria were screened in the Cancer Research Network,[3] and 64%-85% of Community Hospital Cancer Programs do not screen for this syndrome.[4]

The scale of these shortcomings is measured in lives lost because for Lynch syndrome, as for hereditary breast and ovarian cancer, medical or surgical interventions have been shown to decrease mortality.[1,5] To address these challenges more broadly, there have been renewed calls for population-wide testing for *BRCA* and other genes,[6,7] and in the United States and abroad, efforts have begun to sequence the DNA of large cohorts to screen for a broad spectrum of inherited risks.[8,9] At the same time, for-profit companies have sought to market genomic testing outside of the traditional medical context, despite public and professional diminished trust in the accuracy and privacy of direct-to-consumer genetic testing.[10-14]

Because population-based approaches to genomic screening remain costly and involve challenges in high through-put sequencing, obtaining informed consent, and interpretation of genomic variants,[15,16] alternative strategies have been proposed, including testing isolated populations at higher risk for cancer,[17,18] as well

as testing family members of those found to harbor pathogenic variants (mutations) in disease predisposition genes (Data Supplement). An emerging strategy, emphasized in this article, takes its origin from the increasing use of genetic testing at the time of a diagnosis of cancer, affecting both preventive and therapeutic management.[19,20] Rapidly expanding peridiagnostic analysis of patients with cancer has the potential to allow physician-facilitated family outreach to disseminate risk information and promote cancer prevention. We seek to model various parameters that would affect the time needed to identify *all* individuals heterozygous for pathogenic variants of clinically actionable cancer susceptibility genes in the United States through a strategy of peridiagnostic cancer genetic testing and family diffusion.

METHODS

To model the time course of familial transmission of testing for a pathogenic variant after peridiagnostic tumor-normal or germline panel testing, we assumed various rates of detection of pathogenic variants in probands and diffusion of this information in families, starting with 1.7 million patients with cancer diagnosed per year in the United States,[21] assuming these to be among unrelated individuals, with a fraction of these patients offered tumor-normal or germline sequencing for a panel of cancer predisposition genes. For this analysis, a subset of 18 "clinically actionable" genes (Table 1) was chosen from a larger group of genes used in a prior analysis.[20] Clinical actionability of pathogenic variants was defined by

evidence for their utility in cancer prevention and/or potential utility as therapeutic targets.[20] For this analysis, *CHEK2, MUTYH, CDKN2A,* and *NBN* were not included because of low penetrance of some common variants (*CHEK2*) or uncertain clinical actionability. However, all "high penetrance" genes proposed in a recent population-screening proposal[7] were included.

We assumed the prevalence of germline mutations in patients sequenced ranged from 5% to 15%.[20-22] We next considered extended families across 3 generations with 2 to 4 offspring per generation[23] (Data Supplement), with communication progressing from proband to first-, second-, and third-degree relatives (FDR, SDR, TDR, respectively) and then in successive years to FDR, SDR, and TDR of those contacted the prior year (Data Supplement). We projected that from 0% to 75% of relatives potentially heterozygous for an inherited mutation would be tested. We estimated the number of individuals carrying pathogenic variants already identified (Data Supplement). Driven by "cascade" testing of incident patients with cancer, we measured the time to pass a calculated threshold of 3.9 million individuals older than 25 years of age in the United States, representing the number heterozygous for pathogenic variants in this panel of 18 genes, as directly estimated by frequencies in the ExAC resource (Data Supplement). We assumed a steady state of mutation carriers with countervailing influences of compromised fitness, death due to hereditary cancer, and preimplantation genetic diagnosis, balanced by the birth and immigration of new carriers of pathogenic variants.

We performed a sensitivity analysis on time (in years) to reach a threshold of detection of 3.9 million heterozygotes for these pathogenic variants by varying parameters, including the proportion of patients with cancer in the United States tested (range, 7.5%-75%), the proportion of patients with cancer with germline mutations (5%-15%), and the proportion of FDR, SDR, and TDR tested for familial pathogenic variants (0% to 75%). Multiple linear regression was performed in RStudio version 1.0.143[24] on log-transformed response variables to define significant determinants/parameters and the magnitude of their effects (Data Supplement). A tornado plot was generated for the graphic representation of the degree to which the number of years (the result) was sensitive to the specific parameters, thus depicting the univariate sensitivity analysis (Fig 1).

RESULTS

Figure 2 and the Data Supplement show the time to detect all cancer predisposing pathogenic variants of 18 cancer susceptibility genes in the US population, assuming a 5%-15% prevalence of germline variants in cohorts with cancer, varying proportions of family sizes, varying proportions of incident patients with cancer germline sequenced each year, and 0% to 75% rates of cascade of

TABLE 1. Selected Cancer Susceptibility Genes Used in Model

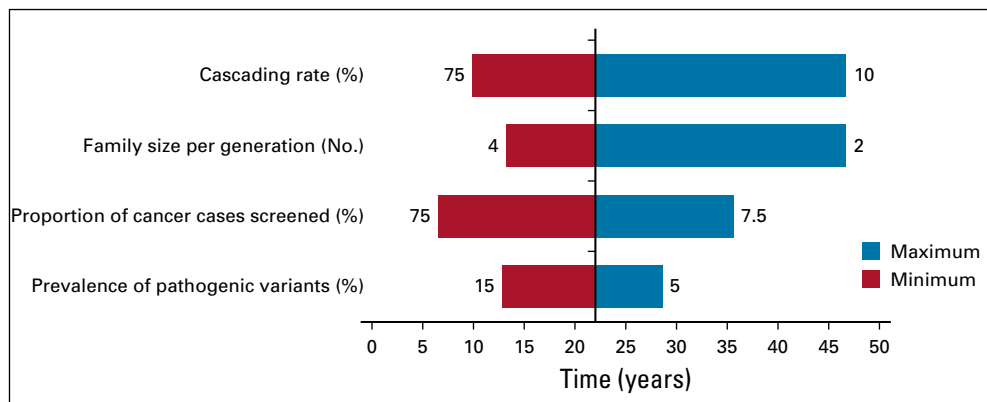| Gene	Predominant Tumor Susceptibility
APC	Colon
ATM	Breast, pancreas, prostate
BRCA1	Breast, ovary
BRCA2	Breast, ovary, prostate, pancreas
CDH1	Gastric
FLCN	Renal
MLH1	Colon, uterine
MSH2	Colon, uterine
MSH6	Colon, uterine
NF1	Sarcoma
PALB2	Breast
PMS2	Colon
PTEN	Breast
RET	Thyroid
SDHB	Paraganglioma
STK11	Breast, pancreas
TP53	Breast, leukemia, other
VHL	Renal

FIG 1. Tornado plot depicting univariate sensitivity analysis performed using baseline model: 7% prevalence of pathogenic variants across cancer types, an average family size of 3 per generation, 15% of incident patients with cancer undergoing germline testing, and 25% first-degree relatives, 25% second-degree relatives, and 25% third-degree relatives cascading, the time to detect 3.9 million individuals with a germline cancer susceptibility mutation was 22.2 years. The plot shows the effect on the output (number of years) of varying each input variable at a time, keeping all the other input variables at their baseline value. The cascading rate here is defined by the proportion of first-degree, second-degree, and third-degree relatives transmitting information, ranging from 10% to 75%; family size per generation refers to the number of siblings per generation, ranging from 2 to 4; proportion of patients with cancer screened refers to the proportion of incident patients with cancer subjected to germline sequencing of 18 selected genes, ranging from 7.5% to 75%; prevalence of pathogenic mutations refers to the prevalence of pathogenic variants of 18 cancer susceptibility genes in patients with cancer sequenced, ranging from 5% to 15%. The upper and lower bounds for each variable are labeled in the tornado plot.

mutation detection to FDR, SDR, and TDR. Sensitivity analysis using a multiple regression model demonstrates that the time to detect pathogenic variants in the population is significantly affected by rates of FDR, SDR, and TDR tested by cascade, family size, and prevalence of mutations in patients with cancer, followed by the proportion of patients with cancer tested; Table 2 and Figure 1 demonstrate model fit metrics for the simulated data. As a base case, assuming a 7% frequency of clinically actionable germline pathogenic variants in 18 cancer susceptibility genes across all cancer types, based on a SEER weighted adjustment of data derived from patients tested at our Center (Data Supplement), and assuming 15% of incident cancers (the proportion of patients treated at US Comprehensive Cancer Centers) receiving tumor-normal or germline panel testing, for an average family size of 3 offspring per generation (as measured empirically; Data Supplement), the time to detect 3.9 million individuals with germline cancer susceptibility mutations would be 46.2, 22.3, 13.6, and 9.9 years, if 10%, 25%, 50%, and 70%, respectively, of FDR, SDR and TDR were tested for the familial mutation. In such a scenario (Fig 3), the 9.9-year interval to detect all mutations in the population compares with 59.5 years if there is no cascade testing of relatives (Data Supplement). The time to detect all mutations in the population decreased from more than 30 years if only 70% of FDR relatives are tested, to 15 years if 70%, 70%, and 25% of FDR, SDR, and TDR, respectively, are tested and 9.9 years if the proportion of TDRs tested increases from 25% to 70% (Fig 4).

DISCUSSION

Although referral rates for genetic testing have increased in the United States since 2004,[25-28] only a modest proportion of individuals carrying pathogenic variants of common cancer susceptibility genes have been identified.[29] Of 1.4 million breast cancer survivors eligible for genetic testing and at risk for subsequent cancers, 1.2 million have yet to be tested. An additional 10.7 million women who are cancer free but at risk for a primary cancer have not yet received genetic testing.[2] For the most common form of hereditary colorectal cancer,[30] it has been estimated that 98% of those carrying genetic variants predictive of Lynch syndrome have yet to be diagnosed,[31,32] and DNA testing for other cancer syndromes is also less than optimal.[33,34] These shortfalls are because of varying clinical guidelines as well as disparities in access to cancer prevention services.[35-41] Even if universally accessible, it is now evident that 26%-56% of individuals with inherited pathogenic variants in cancer susceptibility genes will not be detected by clinical guidelines based on family history; this has been shown for "panel" genetic testing,[20] as well as family history–targeted testing for *BRCA1/2, RET, FH, BAP1, VHL, MET, SDHA*, and *SDHB* germline mutations.[17,18,42-49]

Despite calls for population screening for common cancer predisposition genes such as *BRCA1/2*,[6] and other high penetrance genes,[7] there remain concerns about accessibility to diverse populations, including needs for intensive counseling and evaluation after detection of variants of unknown significance (VUS)[15,16] and adverse
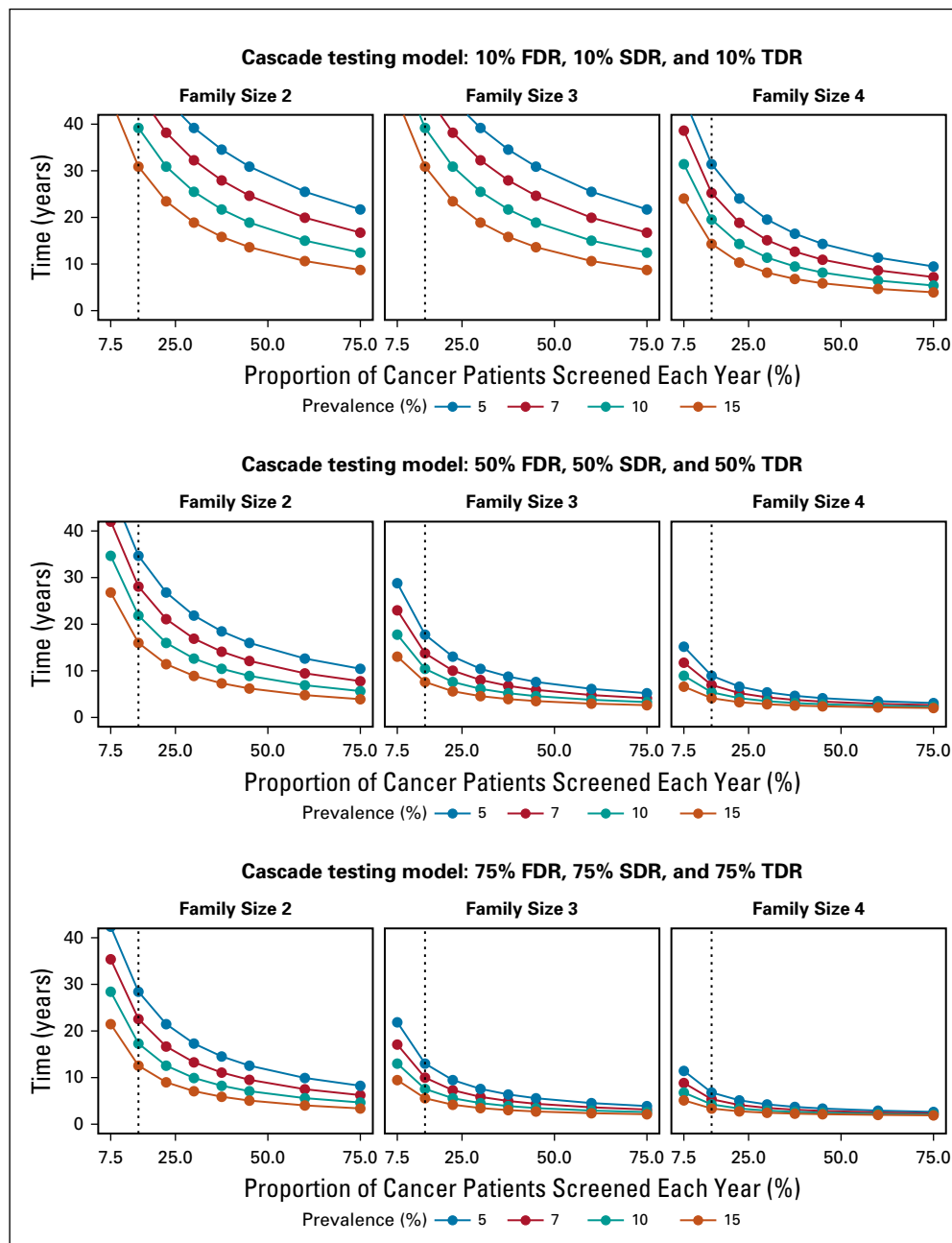
FIG 2. Sensitivity analysis; Prevalence (%), patients with mutations of 18 cancer susceptibility genes; Proportion, of 1.7 million incident cancers sequenced; Years to detect 3.9 million mutation carriers. FDR, first-degree relatives; SDR, second-degree relatives; TDR, third-degree relatives.

psychological sequelae.[50] For these and other reasons, the US Preventive Services Task Force in February 2019 reinforced recommendations against population-based genetic screening for *BRCA* mutations.[51,52] The cost effectiveness of population sequencing depends on assumptions of the models[53,54] reflecting varying costs of systems for monitoring and reclassifying VUS, raising public/health professional awareness, education, cost of medical interventions, delivery logistics, quality control, call-recall mechanisms, and fail-safe checks/processes for quality assurance.[54] To provide *BRCA1/2* tests for all women older than 30 years of age in the United States would cost more than $14 billion,[55] mostly as a

nonreimbursable charge within the current US medical system.[56] The model proposed here combines 2 elements as an alternative to population-based testing: peridiagnostic cancer genetic testing and familial cascade of results.

Genetic testing at the time of diagnosis of cancer (referred to by some as "mainstreaming"[57]) has several advantages.[20] It identifies those who may benefit from poly (ADP-ribose) polymerase inhibitors for treatment of breast, ovarian, prostate, and other cancers[58-61]; checkpoint blockade immunotherapy for those with mismatch repair deficiency[62]; or targeted treatment of those with inherited mutations in *MTOR*,[63,64] *RET*,[65] *Hedgehog*,[66] or other pathways. We have reported that the prevalence of

TABLE 2. Multiple Linear Regression Model to Predict Outcome as No. of Years to Detect All Pathogenic Variants of Selected Cancer Predisposition Genes in the At-Risk Population

Parameters	Coefficient	SE	95% CI	Pr(>ltl)
Proportion of patients with cancer tested	−0.02	0.0003	−0.022 to −0.021	< .0001
Prevalence of germline mutation	−0.07	0.002	−0.08 to −0.072	< .0001
Family size (2, 3, or 4)	−0.31	0.008	−0.33 to −0.30	< .0001
Proportion of FDR tested	−0.003	0.0003	−0.004 to −0.002	< .0001
Proportion of SDR tested	−0.006	0.0003	−0.007 to −0.005	< .0001
Proportion of TDR tested	−0.009	0.0004	−0.01 to 0.009	< .0001

NOTE. No. of years is log transformed in this analysis to allow readout of No. of years to achieve alternative strategies (Data Supplement). Aggregate statistics: residual SE: 0.25 on 1,369 df; multiple R-squared: 0.908; adjusted R-squared: 0.908; F-statistic: 2,266 on 6 and 1,369 df; $P = < 2.2^{e-16}$.

Abbreviations: FDR, first-degree relatives; SDR, second-degree relatives; TDR, third-degree relatives.

pathogenic variants in cancer predisposition genes is higher in patients with metastatic prostate and other malignancies, compared with those with localized forms of these diseases.[20,61] Germline testing of those with advanced malignancies regardless of family history also offers potential cost advantages, shown in the Data Supplement.

A limitation of the peridiagnostic testing model proposed is that it assumes sequencing of incident patients with cancer only. In 2016, there were 15.5 million individuals with a previous diagnosis of cancer (prevalent patients), including 429,000 survivors of childhood cancer in the United States.[21] Although such individuals would eventually be tested by cascade, active ascertainment, and testing, even a fraction of these prevalent patients will decrease the time to achieve population-wide detection of cancer-predisposing mutations. Oversampling of early-onset or pediatric cancers will increase germline mutation detection and also lead to cascade testing of parents. Pediatric cancers demonstrate 8%-12% pathogenic germline variants,[22,67-70] and there was a 2-fold increase in germline mutations in those older than 40 years of age compared with those younger than 60 years in 12,823 patients we have analyzed (MSK IMPACT[20] and unpublished data). The model also assumes a low proportion of "de novo" mutations, observed for common syndromes[71]; however, when such de novo events occur, they will transmit to offspring, offering subsequent opportunity for cascade. Another limitation of the model is that it did not include polygenic effects of common, but lower-risk, single-nucleotide polymorphisms, which may offer the promise of passing thresholds of clinical actionability.[72] The model was sensitive to the proportion of patients with cancer carrying germline pathogenic variants, which we have shown to be affected by founder mutations as well as case mix[20]; such correlations can be used to prioritize peridiagnostic genetic testing toward those in genetic isolates or with hereditary forms of cancer.

First described for cystic fibrosis and hypercholesterolemia[73-75], cascade testing is a process of diffusion of genetic information from an affected family member (proband or index patient) to family members, involving iterative rounds of testing of both close and more distant relatives.[75] Although 75%-82% of index patients may share familial cancer information with relatives,[76-78] only 35%-64% of these at-risk adult relatives actually undergo genetic testing,[79-88] with one study finding that 47.5% of FDR agreed to be tested after contact by a commercial laboratory offering them Internet access to self-pay sequencing for their familial mutation.[89] Other investigators have increased familial testing to 46%-92% by contacting the proband's relatives by mail or phone,[90-93] achieving 57%-94% cascade to relatives in breast and colon cancer syndromes, respectively, with genetics professionals playing a role in the family outreach.[94-96] Family dissemination of genomic risk information appears to be lower among minority populations,[97-99] with patients of African American and Asian/Pacific ancestry less likely to share results with relatives.[81] Because a focus on cascade testing could actually widen existing disparities in cancer genetic testing, a multifaceted approach will be required. Tailored and culturally sensitive interventions, including community-based outreach, partnering to decrease distrust and improve genetic literacy, navigators to assist genetic counselors and families, and an emphasis on telegenetics and phone counseling to decrease barriers, have been suggested.[100] Our recent study in the United States by Frey et al[101] (in this issue of *J Clin Oncol.*), a prior study in the United Kingdom,[96] and a recent study in Trinidad and Tobago[102] all achieved 60%-70% levels of cascade testing among at-risk relatives using a strategy of outreach by health care providers, indicating the cross-cultural feasibility of this approach. At the time of counseling, outreach to distant family members, such as first cousins, is vital; our analysis shows that expanding cascade from FDR to include SDR and TDR decreased *by half* the time to detect all carriers of pathogenic variants in the population. The model used was sensitive to family size; the estimates for family size were derived from empiric measures in a cancer clinic (Data Supplement).
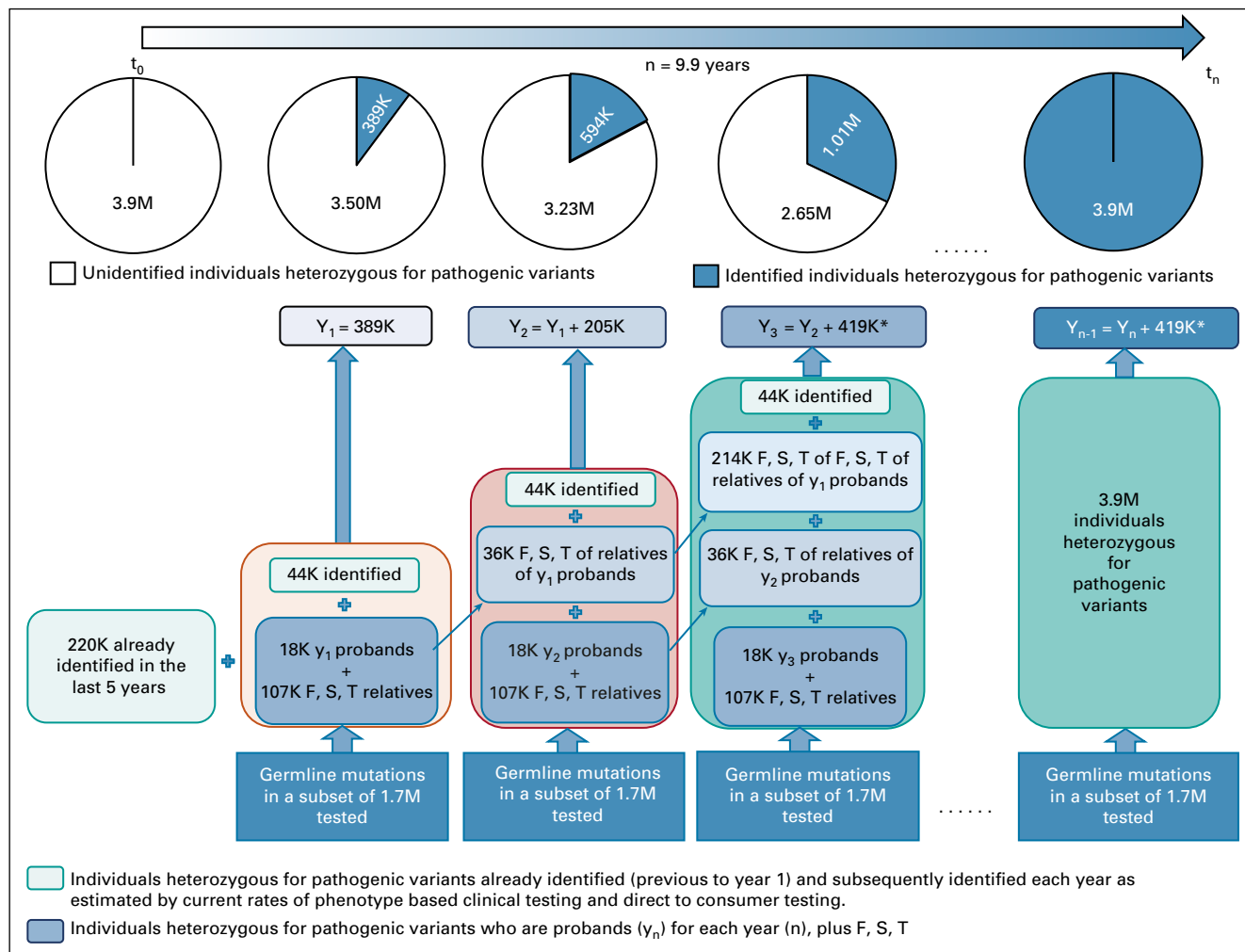
FIG 3. Diagram of peridiagnostic genetic testing and familial diffusion of information under the assumptions of a family size of 3 siblings per generation, 15% of patients with cancer receiving germline genetic testing at the time of diagnosis, a 7% frequency of pathogenic mutations found at the time of testing, and 70% diffusion of familial genetic information to first-degree relatives (F), second-degree relatives (S), and third-degree relatives (T). In this example, it is assumed that 220,000 carriers of pathogenic variants have been identified in the United States, with 44,000 additional individuals identified each year by virtue of expanded commercial clinical and direct-to-consumer testing. Y_n represents the cumulative number of individuals with pathogenic variants identified each year. Under these assumptions, the time to detect all 3.9 million individuals with pathogenic variants in the United States is 9.9 years. (*) 419K heterozygous for pathogenic variants identified each year after Y_3 (Data Supplement).

Population-based estimates of biologic family size are not included in household composition measures in census data; a recent population-based study found a mean of 19.7 FDR, SDR, and TDR per family sampled, with only modest variation by income strata.[23] Finally, a substantial advantage of cascade-based approaches is decreased detection of VUS compared with population-wide sequencing. Cascade testing includes only established pathogenic variants that segregate in families, diminishing the complexities of counseling and interpretation of VUS.

Peridiagnostic and cascade testing has been shown to be cost effective for hypercholesterolemia[103] and Lynch syndrome,[30] where it is strongly influenced by the number of FDR tested.[104] Importantly, the success of such strategies has been limited by the relative shortage of genetic

counselors. As one means to address this need, digital media interventions to facilitate outreach of familial risk information have been piloted for colon cancer[99] and pancreas cancer,[103] and offer promise for implementing this proposed strategy. We have piloted digital learning tools in the context of a Web-based founder mutation testing program (www.bforstudy.com) that includes the option of follow-up with one's primary health care provider.[105] Integrating such tools in the peridiagnostic setting would offer at-home convenience and pretest education,[106,107] and also avoid the logistic, privacy, and ethical barriers of "traceback" testing of DNA from paraffin archives of deceased patients.[108-111] In contrast to population-screening approaches, patients with cancer can be offered germline genetic testing in a medical setting. The majority will want to know these results, emphasizing the potential advantages
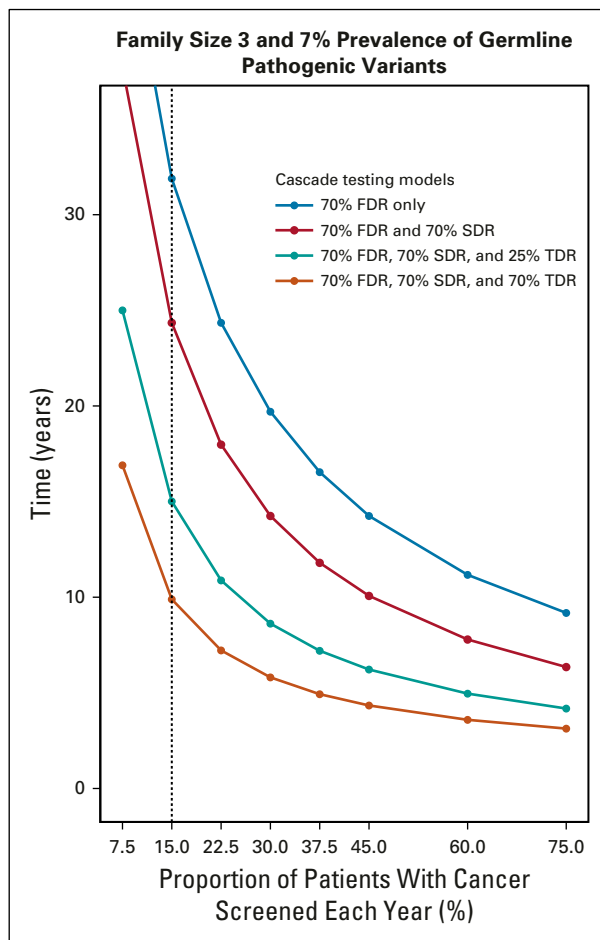
FIG 4. Sensitivity analysis of the example of a family structure of 3 siblings per generation and a 7% prevalence of pathogenic variants in 1 of 18 clinically actionable cancer susceptibility genes; Proportion, of 1.7 million incident cancers sequenced; Years to detect 3.9 million mutation carriers. FDR, first-degree relatives; SDR, second-degree relatives; TDR, third-degree relatives.

as well as the emotional and psychosocial components in a process that involves caregivers and family members.[112]

Testing for known inherited cancer susceptibility alleles in families is professionally endorsed,[113] increasingly reimbursed by third-party carriers, and responsive to the legal and ethical "duty to warn" about familial disease risks.[114] Although tumor genetic testing is now an Advanced Diagnostic Laboratory Test,[115] Centers for Medicare & Medicaid Services is currently reevaluating including inherited germline testing in its coverage guidelines.[116] These factors will help to mitigate disparities in access to genetic services, which constitute a barrier to peridiagnostic testing as well as cascade models.[113,117] In the United States, peridiagnostic DNA sequencing has been initiated at many of the 71 National Cancer Institute (NCI)-designated cancer centers, which currently care for 15% of patients with cancer, and this effort could involve the more than 1,100 community cancer programs and oncology networks conducting clinical trials and approximately 250 academic and NCI-designated cancer research centers,[118,119] with peridiagnostic genetic testing for prostate cancer to be offered through the US Veterans Administration.[120] The Food and Drug Administration has approved targeting immunotherapy to a genetic defect in mismatch DNA repair,[121] and a professional society recently provided a rationale for genetic testing of all patients with breast cancer.[116]

If adopted by clinicians, patients, and families, widespread peridiagnostic genetic testing and cascade to family members could identify all of the cancer predisposing mutations in the United States in a decade or less, diminishing the need for a costly effort to test and identify genetic variants in all healthy individuals in the population. As shown in recent studies (eg, Evans et al,[96] Donenberg et al,[102] and Frey et al[101] [in this issue of *J Clin Oncol*.]), high rates of cascade of familial genetic information can be achieved by health care providers facilitating outreach and assisting patients and their families to communicate genetic risk information. Augmented by additional development, including Web-based applications, peridiagnostic cancer genetic testing, and familial transmission of genomic risk information can substantially decrease the burden of hereditary cancer.

AFFILIATIONS

[1]Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center; and Program in Cancer Biology and Genetics, Sloan Kettering Institute, New York, NY

[2]Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY

[3]Breast Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[4]Weill Cornell College of Medicine, Cornell University, New York, NY

CORRESPONDING AUTHOR

Kenneth Offit, MD, MPH, Chief, Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Box 295, New York, NY, 10065; e-mail: Offitk@mskcc.org.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

AUTHOR CONTRIBUTIONS

Conception and design: Kenneth Offit, Kaitlyn A. Tkachuk, Melissa K. Frey, Steven M. Lipkin, Mark E. Robson, Semanti Mukherjee
Financial support: Kenneth Offit, Semanti Mukherjee
Administrative support: Kenneth Offit, Jeffrey D. Levin
Provision of study materials or patients: Kenneth Offit
Collection and assembly of data: Kenneth Offit, Kaitlyn A. Tkachuk, Hector Diaz-Zabala, Vignesh Ravichandran, Semanti Mukherjee

Data analysis and interpretation: Kenneth Offit, Kaitlyn A. Tkachuk, Zsofia K. Stadler, Michael F. Walsh, Hector Diaz-Zabala, Jeffrey D. Levin, Zoe Steinsnyder, Vignesh Ravichandran, Ravi N. Sharaf, Melissa K. Frey, Steven M. Lipkin, Jada G. Hamilton, Joseph Vijai, Semanti Mukherjee
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Offit K: The future of clinical cancer genomics. Semin Oncol 43:615-622, 2016

2. Childers CP, Childers KK, Maggard-Gibbons M, et al: National estimates of genetic testing in women with a history of breast or ovarian cancer. J Clin Oncol 35: 3800-3806, 2017

3. Cross DS, Rahm AK, Kauffman TL, et al: Underutilization of Lynch syndrome screening in a multisite study of patients with colorectal cancer. Genet Med 15: 933-940, 2013

4. Mange S, Bellcross C, Cragun D, et al: Creation of a network to promote universal screening for Lynch syndrome: The Lynch Syndrome Screening Network. J Genet Couns 24:421-427, 2015

5. Finch AP, Lubinski J, Møller P, et al: Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 32: 1547-1553, 2014

6. King MC, Levy-Lahad E, Lahad A: Population-based screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA 312:1091-1092, 2014

7. Turnbull C, Sud A, Houlston RS: Cancer genetics, precision prevention and a call to action. Nat Genet 50:1212-1218, 2018 [Erratum: Nat Genet 51:196, 2019]

8. Sankar PL, Parker LS: The Precision Medicine Initiative's All of Us Research Program: An agenda for research on its ethical, legal, and social issues. Genet Med 19:743-750, 2017

9. Turnbull C, Scott RH, Thomas E, et al: The 100 000 Genomes Project: Bringing whole genome sequencing to the NHS. BMJ 361:k1687, 2018 [Erratum: BMJ 361:k1952, 2018]

10. Burke W, Trinidad SB: The deceptive appeal of direct-to-consumer genetics. Ann Intern Med 164:564-565, 2016

11. van der Wouden CH, Carere DA, Maitland-van der Zee AH, et al: Consumer perceptions of interactions with primary care providers after direct-to-consumer personal genomic testing. Ann Intern Med 164:513-522, 2016

12. Roberts JS, Gornick MC, Carere DA, et al: Direct-to-consumer genetic testing: User motivations, decision making, and perceived utility of results. Public Health Genomics 20:36-45, 2017

13. Gray SW, Gollust SE, Carere DA, et al: Personal genomic testing for cancer risk: Results from the impact of personal genomics study. J Clin Oncol 35:636-644, 2017

14. Carere DA, VanderWeele T, Moreno TA, et al: The impact of direct-to-consumer personal genomic testing on perceived risk of breast, prostate, colorectal, and lung cancer: Findings from the PGen study. BMC Med Genomics 8:63, 2015

15. Yurgelun MB, Hiller E, Garber JE: Population-wide screening for germline BRCA1 and BRCA2 mutations: Too much of a good thing? J Clin Oncol 33: 3092-3095, 2015

16. Murray ML, Cerrato F, Bennett RL, et al: Follow-up of carriers of BRCA1 and BRCA2 variants of unknown significance: Variant reclassification and surgical decisions. Genet Med 13:998-1005, 2011

17. Metcalfe KA, Poll A, Royer R, et al: Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. J Clin Oncol 28:387-391, 2010

18. Manchanda R, Loggenberg K, Sanderson S, et al: Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: A randomized controlled trial. J Natl Cancer Inst 107:379, 2014

19. Zehir A, Benayed R, Shah RH, et al: Erratum: Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 23:1004, 2017

20. Mandelker D, Zhang L, Kemel Y, et al: 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 318:825-835, 2017

21. National Cancer Institute: Cancer statistics. https://www.cancer.gov/about-cancer/understanding/statistics

22. Zhang J, Walsh MF, Wu G, et al: Germline mutations in predisposition genes in pediatric cancer. N Engl J Med 373:2336-2346, 2015

23. Garceau A, Wideroff L, McNeel T, et al: Population estimates of extended family structure and size. Community Genet 11:331-342, 2008

24. RStudio: Integrated Development for R. Boston, MA, RStudio, 2017

25. Meyer LA, Anderson ME, Lacour RA, et al: Evaluating women with ovarian cancer for BRCA1 and BRCA2 mutations: Missed opportunities. Obstet Gynecol 115:945-952, 2010

26. Levy DE, Byfield SD, Comstock CB, et al: Underutilization of BRCA1/2 testing to guide breast cancer treatment: Black and Hispanic women particularly at risk. Genet Med 13:349-355, 2011

27. Powell CB, Littell R, Hoodfar E, et al: Does the diagnosis of breast or ovarian cancer trigger referral to genetic counseling? Int J Gynecol Cancer 23:431-436, 2013

28. Febbraro T, Robison K, Wilbur JS, et al: Adherence patterns to National Comprehensive Cancer Network (NCCN) guidelines for referral to cancer genetic professionals. Gynecol Oncol 138:109-114, 2015

29. Drohan B, Roche CA, Cusack JC Jr, et al: Hereditary breast and ovarian cancer and other hereditary syndromes: Using technology to identify carriers. Ann Surg Oncol 19:1732-1737, 2012

30. Hampel H: Genetic counseling and cascade genetic testing in Lynch syndrome. Fam Cancer 15:423-427, 2016

31. Centers for Disease Control and Prevention: EGAPP: Informing the effective integration of genomics into health practice—Lynch syndrome. https://www.cdc.gov/genomics/gtesting/egapp/lynch_study.htm

32. Hampel H, de la Chapelle A: The search for unaffected individuals with Lynch syndrome: Do the ends justify the means? Cancer Prev Res (Phila) 4:1-5, 2011

33. Schultz KAP, Rednam SP, Kamihara J, et al: *PTEN, DICER1, FH*, and their associated tumor susceptibility syndromes: Clinical features, genetics, and surveillance recommendations in childhood. Clin Cancer Res 23:e76-e82, 2017

34. Williams MD: Paragangliomas of the head and neck: An overview from diagnosis to genetics. Head Neck Pathol 11:278-287, 2017

35. Canedo JR, Miller ST, Myers HF, et al: Racial and ethnic differences in knowledge and attitudes about genetic testing in the US: Systematic review. J Genet Couns 28:587-601, 2019

36. Hann KEJ, Freeman M, Fraser L, et al: Awareness, knowledge, perceptions, and attitudes towards genetic testing for cancer risk among ethnic minority groups: A systematic review. BMC Public Health 17:503, 2017

37. Peters N, Rose A, Armstrong K: The association between race and attitudes about predictive genetic testing. Cancer Epidemiol Biomarkers Prev 13:361-365, 2004

38. Suther S, Kiros GE: Barriers to the use of genetic testing: A study of racial and ethnic disparities. Genet Med 11:655-662, 2009

39. Hall MJ, Olopade OI: Disparities in genetic testing: Thinking outside the BRCA box. J Clin Oncol 24:2197-2203, 2006

40. Butrick M, Kelly S, Peshkin BN, et al: Disparities in uptake of BRCA1/2 genetic testing in a randomized trial of telephone counseling. Genet Med 17:467-475, 2015

41. Willis AM, Smith SK, Meiser B, et al: Sociodemographic, psychosocial and clinical factors associated with uptake of genetic counselling for hereditary cancer: A systematic review. Clin Genet 92:121-133, 2017

42. Struewing JP, Hartge P, Wacholder S, et al: The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 336:1401-1408, 1997

43. Moslehi R, Chu W, Karlan B, et al: BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet 66: 1259-1272, 2000

44. King MC, Marks JH, Mandell JB: Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 302:643-646, 2003

45. Warner E, Foulkes W, Goodwin P, et al: Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst 91:1241-1247, 1999

46. Risch HA, McLaughlin JR, Cole DE, et al: Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 68:700-710, 2001

47. Hartman AR, Kaldate RR, Sailer LM, et al: Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer 118: 2787-2795, 2012

48. Parkhurst E, Calonico E, Abboy S: Utilization of genetic testing for RET mutations in patients with medullary thyroid carcinoma: A single-center experience. J Genet Couns 27:1411-1416, 2018

49. Carlo MI, Mukherjee S, Mandelker D, et al: Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma. JAMA Oncol 4:1228-1235, 2018

50. Metcalfe KA, Poll A, Llacuachaqui M, et al: Patient satisfaction and cancer-related distress among unselected Jewish women undergoing genetic testing for BRCA1 and BRCA2. Clin Genet 78:411-417, 2010

51. Moyer VA: Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 160:271-281, 2014

52. US Preventive Services Task Force: Draft recommendation statement: BRCA-related cancer: Risk assessment, genetic counseling, and genetic testing. https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing1

53. Long EF, Ganz PA: Cost-effectiveness of universal BRCA1/2 screening: Evidence-based decision making. JAMA Oncol 1:1217-1218, 2015

54. Manchanda R, Patel S, Gordeev VS, et al: Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women. J Natl Cancer Inst 110:714-725, 2018

55. Foulkes WD, Knoppers BM, Turnbull C: Population genetic testing for cancer susceptibility: Founder mutations to genomes. Nat Rev Clin Oncol 13:41-54, 2016

56. Best AF, Tucker MA, Frone MN, et al: A pragmatic testing-eligibility framework for population mutation screening: The example of *BRCA1/2*. Cancer Epidemiol Biomarkers Prev 28:293-302, 2019

57. Slade I, Riddell D, Turnbull C, et al: Development of cancer genetic services in the UK: A national consultation. Genome Med 7:18, 2015

58. Lord CJ, Ashworth A: PARP inhibitors: Synthetic lethality in the clinic. Science 355:1152-1158, 2017

59. Ashworth A, Lord CJ: Synthetic lethal therapies for cancer: What's next after PARP inhibitors? Nat Rev Clin Oncol 15:564-576, 2018

60. Lord CJ, Ashworth A: BRCAness revisited. Nat Rev Cancer 16:110-120, 2016

61. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016

62. Le DT, Durham JN, Smith KN, et al: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357:409-413, 2017

63. Sampson JR: Therapeutic targeting of mTOR in tuberous sclerosis. Biochem Soc Trans 37:259-264, 2009

64. Bissler JJ, Kingswood JC, Radzikowska E, et al: Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): A multicentre, randomised, double-blind, placebo-controlled trial. Lancet 381:817-824, 2013

65. Wells SA Jr, Gosnell JE, Gagel RF, et al: Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol 28:767-772, 2010

66. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al: Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med 366: 2180-2188, 2012

67. Walsh M, Wu G, Edmonson M, et al: Incidence of germline mutations in cancer-predisposition genes in children with hematologic malignancies: A report from the Pediatric Cancer Genome Project. Blood 124:127, 2014

68. Parsons DW, Roy A, Yang Y, et al: Diagnostic yield of clinical tumor and germline whole-exome sequencing for children with solid tumors. JAMA Oncol 2: 616-624, 2016

69. Mody RJ, Wu YM, Longiro RJ, et al: Integrative clinical sequencing in the management of refractory or relapsed cancer in youth. JAMA 314:913-925, 2015

70. Walsh MF, Kennedy J, Harlan M, et al: Germline *BRCA2* mutations detected in pediatric sequencing studies impact parents' evaluation and care. Cold Spring Harb Mol Case Stud 3:a001925, 2017

71. Robson M, Scheuer L, Nafa K, et al: Unique de novo mutation of BRCA2 in a woman with early onset breast cancer. J Med Genet 39:126-128, 2002

72. Chatterjee N, Shi J, García-Closas M: Developing and evaluating polygenic risk prediction models for stratified disease prevention. Nat Rev Genet 17:392-406, 2016

73. Super M, Schwarz MJ, Malone G: Screening for cystic fibrosis carriers. Lancet 340:490-491, 1992

74. Holloway S, Brock DJ: Cascade testing for the identification of carriers of cystic fibrosis. J Med Screen 1:159-164, 1994

75. Knowles JW, Rader DJ, Khoury MJ: Cascade screening for familial hypercholesterolemia and the use of genetic testing. JAMA 318:381-382, 2017

76. Taber JM, Chang CQ, Lam TK, et al: Prevalence and correlates of receiving and sharing high-penetrance cancer genetic test results: Findings from the Health Information National Trends Survey. Public Health Genomics 18:67-77, 2015

77. Montgomery SV, Barsevick AM, Egleston BL, et al: Preparing individuals to communicate genetic test results to their relatives: Report of a randomized control trial. Fam Cancer 12:537-546, 2013

78. Stoffel EM, Ford B, Mercado RC, et al: Sharing genetic test results in Lynch syndrome: Communication with close and distant relatives. Clin Gastroenterol Hepatol 6:333-338, 2008

79. Dilzell K, Kingham K, Ormond K, et al: Evaluating the utilization of educational materials in communicating about Lynch syndrome to at-risk relatives. Fam Cancer 13:381-389, 2014

80. Cheung EL, Olson AD, Yu TM, et al: Communication of BRCA results and family testing in 1,103 high-risk women. Cancer Epidemiol Biomarkers Prev 19:2211-2219, 2010

81. Fehniger J, Lin F, Beattie MS, et al: Family communication of BRCA1/2 results and family uptake of BRCA1/2 testing in a diverse population of BRCA1/2 carriers. J Genet Couns 22:603-612, 2013

82. McGivern B, Everett J, Yager GG, et al: Family communication about positive BRCA1 and BRCA2 genetic test results. Genet Med 6:503-509, 2004

83. Daly MB, Montgomery S, Bingler R, et al: Communicating genetic test results within the family: Is it lost in translation? A survey of relatives in the randomized six-step study. Fam Cancer 15:697-706, 2016

84. Landsbergen K, Verhaak C, Kraaimaat F, et al: Genetic uptake in BRCA-mutation families is related to emotional and behavioral communication characteristics of index patients. Fam Cancer 4:115-119, 2005

85. Sharaf RN, Myer P, Stave CD, et al: Uptake of genetic testing by relatives of Lynch syndrome probands: A systematic review. Clin Gastroenterol Hepatol 11:1093-1100, 2013

86. Barrow P, Green K, Clancy T, et al: Improving the uptake of predictive testing and colorectal screening in Lynch syndrome: A regional primary care survey. Clin Genet 87:517-524, 2015

87. Lerman C, Hughes C, Trock BJ, et al: Genetic testing in families with hereditary nonpolyposis colon cancer. JAMA 281:1618-1622, 1999

88. Hadley DW, Jenkins J, Dimond E, et al: Genetic counseling and testing in families with hereditary nonpolyposis colorectal cancer. Arch Intern Med 163:573-582, 2003

89. Caswell-Jin JL, Zimmer AD, Stedden W, et al: Cascade genetic testing of relatives for hereditary cancer risk: Results of an online initiative. J Natl Cancer Inst 111:95-98, 2019

90. Suthers GK, Armstrong J, McCormack J, et al: Letting the family know: Balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. J Med Genet 43:665-670, 2006

91. Kerzin-Storrar L, Wright C, Williamson PR, et al: Comparison of genetic services with and without genetic registers: Access and attitudes to genetic counselling services among relatives of genetic clinic patients. J Med Genet 39:e85, 2002

92. Sermijn E, Delesie L, Deschepper E, et al: The impact of an interventional counselling procedure in families with a BRCA1/2 gene mutation: Efficacy and safety. Fam Cancer 15:155-162, 2016

93. Forrest LE, Burke J, Bacic S, et al: Increased genetic counseling support improves communication of genetic information in families. Genet Med 10:167-172, 2008

94. Chivers Seymour K, Addington-Hall J, Lucassen AM, et al: What facilitates or impedes family communication following genetic testing for cancer risk? A systematic review and meta-synthesis of primary qualitative research. J Genet Couns 19:330-342, 2010

95. Menko FH, Ter Stege JA, van der Kolk LE, et al: The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: A systematic review of the literature and implications for clinical practice. Fam Cancer 18:127-135, 2019

96. Evans DG, Binchy A, Shenton A, et al: Comparison of proactive and usual approaches to offering predictive testing for BRCA1/2 mutations in unaffected relatives. Clin Genet 75:124-132, 2009

97. Kinney AY, Gammon A, Coxworth J, et al: Exploring attitudes, beliefs, and communication preferences of Latino community members regarding BRCA1/2 mutation testing and preventive strategies. Genet Med 12:105-115, 2010

98. Etchegary H, Potter B, Perrier C, et al: Cultural differences in family communication about inherited cancer: Implications for cancer genetics research. J Cult Divers 20:195-201, 2013

99. Trottier M, Lunn J, Butler R, et al: Prevalence of founder mutations in the BRCA1 and BRCA2 genes among unaffected women from the Bahamas. Clin Genet 89:328-331, 2016

100. Hinchcliff EM, Bednar EM, Lu KH, et al: Disparities in gynecologic cancer genetics evaluation. Gynecol Oncol 153:184-191, 2019

101. Frey KM, Kahn R, Chapman-Davis E, et al: Prospective feasibility trial of a novel strategy of facilitated cascade genetic testing using telephone counseling. J Clin Oncol 38:1389-1397, 2020

102. Donenberg T, George S, Ali J, et al: A clinically structured and partnered approach to genetic testing in Trinidadian women with breast cancer and their families. Breast Cancer Res Treat 174:469-477, 2019

103. Hadfield SG, Humphries SE: Implementation of cascade testing for the detection of familial hypercholesterolaemia. Curr Opin Lipidol 16:428-433, 2005

104. Grosse SD: When is genomic testing cost-effective? Testing for Lynch syndrome in patients with newly-diagnosed colorectal cancer and their relatives. Healthcare (Basel) 3:860-878, 2015

105. Morgan K, Gabriel C, Synmecko H, et al: Early results from the BRCA Founder Outreach (BFOR) study: Population genetic screening using a medical model. Presented at the ASCO Annual Meeting, Chicago, IL, May 31-June 4, 2019

106. Singleton A, Erby LH, Foisie KV, et al: Informed choice in direct-to-consumer genetic testing (DTCGT) websites: A content analysis of benefits, risks, and limitations. J Genet Couns 21:433-439, 2012

107. Lachance CR, Erby LA, Ford BM, et al: Informational content, literacy demands, and usability of websites offering health-related genetic tests directly to consumers. Genet Med 12:304-312, 2010

108. Samimi G, Bernardini MQ, Brody LC, et al: Traceback: A proposed framework to increase identification and genetic counseling of BRCA1 and BRCA2 mutation carriers through family-based outreach. J Clin Oncol 35:2329-2337, 2017

109. National Institutes of Health: Traceback testing: Increasing Identification and Genetic Counseling of Mutation Carriers Through Family-based Outreach (U01 Clinical Trial Optional). https://grants.nih.gov/grants/guide/pa-files/par-18-616.html

110. Schwartz MD: Identification of BRCA1 and BRCA2 mutation carriers through a traceback framework: Consent, privacy, and autonomy. J Clin Oncol 35: 2226-2228, 2017

111. Moss HA, Samimi G, Havrilesky LJ, et al: Estimating the number of potential family members eligible for BRCA1 and BRCA2 mutation testing in a "traceback" approach. Genet Epidemiol 42:117-122, 2018

112. Hamilton JG, Shuk E, Genoff MC, et al: Interest and attitudes of patients with advanced cancer with regard to secondary germline findings from tumor genomic profiling. J Oncol Pract 13:e590-e601, 2017

113. Roberts MC, Dotson WD, DeVore CS, et al: Delivery of cascade screening for hereditary conditions: A scoping review of the literature. Health Aff (Millwood) 37: 801-808, 2018

114. Bombard Y, Offit K, Robson ME: Risks to relatives in genomic research: A duty to warn? Am J Bioeth 12:12-14, 2012

115. Centers for Medicare & Medicaid Services: Decision memo for next generation sequencing (NGS) for Medicare beneficiaries with advanced cancer: (CAG-00450N). https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290

116. Manahan ER, Kuerer HM, Sebastian M, et al: Consensus guidelines on genetic' testing for hereditary breast cancer from The American Society of Breast Surgeons. Ann Surg Oncol 26:3025-3031, 2019

117. Nikolaidis C, Ming C, Pedrazzani C, et al: Challenges and opportunities for cancer predisposition cascade screening for hereditary breast and ovarian cancer and Lynch syndrome in Switzerland: Findings from an international workshop. Public Health Genomics 21:121-132, 2018

118. National Cancer Institute: Cancer Centers. https://cancercenters.cancer.gov/Center/CancerCenters

119. Pavia L: Cancer clinical trials in the community: Hospitals & health networks: 2013: https://www.hhnmag.com/articles/5748-cancer-clinical-trials-in-the-community

120. Prostate Cancer Foundation: PCF & the VA: Shepherding extraordinary care. https://www.pcf.org/va-partnership/

121. Boyiadzis MM, Kirkwood JM, Marshall JL, et al: Significance and implications of FDA approval of pembrolizumab for biomarker-defined disease. J Immunother Cancer 6:35, 2018