

RESEARCH LETTER

Implementing Primary Care Mediated Population Genetic Screening Within an Integrated Health System

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Introduction: Genetic screenings can have a large impact on enabling personalized preventive care. However, this can be limited by the primary use of medical history-based screenings in determining care. The purpose of this study was to understand the impact of DNA10K, a population-based genetic screening program mediated by primary care physicians within an integrated health system to emphasize its contribution to preventive healthcare.

Methods: Construction of the patient experience as part of DNA10K shaped the context for PCP engagement within the program. A cross-sectional analysis of patient consents, orders, tests, and results of nearly 10,000 patients within the primary care specialties of family medicine, internal medicine or obstetrics/gynecology between April 1, 2019 and January 22, 2020 was conducted.

Results: Across all specialties, a median number of 7.5 cancer and cardiovascular disease variants per PCP was found. The average age of the study population was 49.6 years. Over 8% of these patients had at least one actionable genetic risk variant and almost 2% of patients had at least one CDC Tier 1 variant. The median numbers of patients per PCP with either hereditary breast and ovarian cancer, Lynch Syndrome, or Familial Hypercholesterolemia was 1 (Interquartile Range 0-2).

Discussion: The analysis of test results and the engagement of an integrated healthcare system in the implementation of a genetic screening program suggests that it can have a large impact on population health outcomes and minimal referral burden to PCPs if identified risks can lead to preventive care. (J Am Board Fam Med 2021;34:861–865.)

Keywords: Chronic Disease, Cross-Sectional, Studies, Genetic Testing, Genomics, Integrated Health Care Systems, Primary Care Physicians, Primary Health Care

Introduction

Genetic testing for pathogenic variants that confer susceptibility for cancer and heart disease—the 2

most common causes of death in the United States (US)—has the potential to guide individualized disease prevention, treatment, and risk identification. Primary care physicians (PCPs) play a pivotal role in preventive services, such as applying family histories in identifying high genetic risk for disease. However, medical history-based screening can under-detect pathogenic cancer syndromes, such as hereditary breast and ovarian cancer (HBOC), Lynch

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syndrome, and familial hypercholesterolemia (FH),¹⁻³ 3 conditions present in at least 1% of the US population considered by the Centers for Disease Control and Prevention (CDC) to be of high public health importance (CDC Tier 1 applications). The purpose of this study was to characterize the impact of PCP engagement in a population genetic screening program (DNA10K) by analyzing patient participation and test results.

Methods

DNA10K was conducted within an integrated health care system to provide genomics-guided care to more than 10,000 patients by their PCPs ($n = 116$) in family medicine (FM), internal medicine (IM), and obstetrics/gynecology (OBGYN) across 14 clinical practice locations in northern Cook and

Lake Counties, Illinois. The context of the DNA10K implementation is described in Figure 1.

A cross-sectional analysis of consents, orders, tests, results, and actionable genetic variants of patients who were genotyped between April 1, 2019, and January 22, 2020, was conducted. Medians and interquartile (IQR) ranges of genetic test result frequencies per PCP are reported at the overall and specialty levels for cancer and cardiovascular pathogenic variants, Tier 1 pathogenic variants,¹ non-Tier 1 pathogenic variants, and the percentage of actionable pharmacogenomic variants.⁴ Group differences for demographics and test results were examined using Kruskal-Wallis, ANOVA with posthoc Tukey's honestly significant difference (HSD) test, and Wilcoxon Rank Sum tests in Statistical Analysis System (SAS) version 9.4 (Cary, NC) with $P < .05$ being considered significant.

Figure 1. Context for Supporting PCP Engagement in Population Genetic Screening. Figure Legend: The NorthShore Center for Personalized Medicine DNA10K program consisted of multiple components. (a) patient educational video and consent via the NorthShore Connect (NSC) patient portal, (b) PCP electronic clinical decision support and electronic health record (EHR) order, (c) access to a NorthShore lab for phlebotomy, (d) Color Genomics, Inc. genetic testing using a 74 gene next-generation sequencing panel, (e) discrete reporting of results available in the EHR, (f) coordination of results with PCP health maintenance visits, (g) automated patient messaging about next steps, (h) access to genetic counseling, (i) return of results on the patient portal, and (j) clinical follow-up with PCP and specialists. The NorthShore Institutional Review Board approved this study as an exempt quality improvement evaluation. Abbreviations: PCP, primary care physician; EHR, electronic health record.

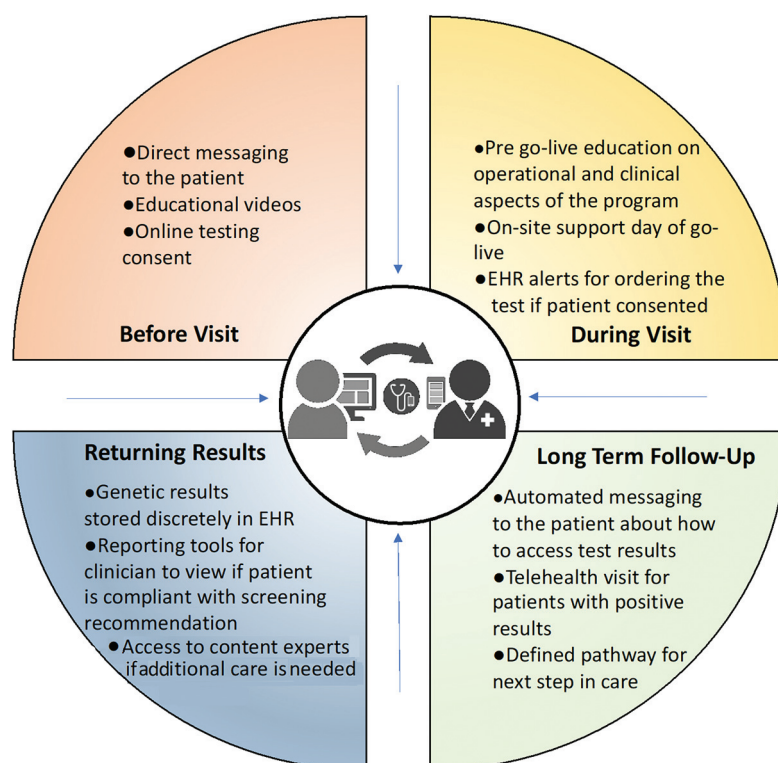


Table 1. DNA10K Primary Care Physician-Mediated Genetic Screening Results*

Variable	Overall No./Total (%) or Mean \pm SD or Median (IQR)	FM No./Total (%) or Median (IQR)	IM No./Total (%) or Median (IQR)	OBGYN No./Total (%) or Median (IQR)	P value [†]
Clinical Demographics					
PCPs	116	28	72	16	...
Patients contacted	49413	10640	32220	6553	...
Tests consented	14063/49419 (28.5%)	3143/10640 (29.5%)	8956/32220 (27.8%)	1964/6553 (30.0%)	.13
Orders placed	10933/14063 (77.7%)	2416/3143 (76.9%)	6920/8956 (77.3%)	1597/1964 (81.3%)	.60
Test completed	9797/10933 (89.6%)	2190/2416 (90.6%)	6255/6920 (90.4%)	1352/1597 (84.7%)	.24
Patient Demographics					
Age	49.6 \pm 6.4	46.5 \pm 4.9	52.3 \pm 4.9	40.5 \pm 3.3	<.0001 ^{†,§, ,¶}
Female	6464/9797 (66.0%)	1270/2190 (58.0%)	3844/6255 (61.5%)	1350/1352 (99.9%)	.80**
African American	272/9797 (2.8%)	100/2190 (4.6%)	108/6255 (1.7%)	64/1352 (4.7%)	.02 [‡]
American Indian/Alaskan Native	22/9797 (0.22%)	6/2190 (0.27%)	14/6255 (0.22%)	2/1352 (0.15%)	.86
Asian	679/9797 (6.9%)	234/2190 (10.7%)	368/6255 (5.8%)	77/1352 (5.7%)	.04
White	6528/9797 (66.6%)	1229/2190 (56.1%)	4424/6255 (70.7%)	875/1352 (64.7%)	.04 [§]
Hispanic/Latino	461/9797 (4.7%)	145/2190 (6.6%)	218/6255 (3.5%)	98/1352 (7.2%)	.01 [¶]
Pacific Islander/Hawaiian Native	6/9797 (0.06%)	0/2190 (0%)	6/6255 (0.1%)	0/1352 (0%)	.20
Declined/Other	1829/9797 (18.7%)	476/2190 (21.7%)	1117/6255 (17.9%)	236/1352 (17.5%)	.69
Test Results					
Cancer and cardiovascular disease variants ^{††}	813/9797 (8.3%)	177/2190 (8.1%)	537/6255 (8.6%)	99/1352 (7.3%)	...
Tier 1 pathogenic variants (HBOC, Lynch syndrome, and FH) ^{‡‡}	182/9797 (1.9%)	42/2190 (1.9%)	114/6255 (1.8%)	26/1352 (1.9%)	...
HBOC	116/9797 (1.2%)	27/2190 (1.2%)	73/6255 (1.2%)	16/1352 (1.2%)	...
Lynch Syndrome	38/9797 (0.39%)	3/2190 (0.14%)	28/6255 (0.45%)	7/1352 (0.52%)	...
FH	29/9797 (0.30%)	12/2190 (0.55%)	13/6255 (0.21%)	4/1352 (0.30%)	...
Non-Tier 1 pathogenic variants	631/9797 (6.4%)	135/2190 (6.2%)	423/6255 (6.8%)	73/1352 (5.4%)	...
Pharmacogenomic variants ^{§§}	9607/9797 (98.1%)	2154/2190 (98.4%)	6128/6255 (98.0%)	1325/1352 (98.0%)	...
Actionable pharmacogenomic variants	9599/9607 (99.9%)	2150/2154 (99.8%)	6124/6128 (99.9%)	1325/1325 (100%)	...
Test Results per PCP					
Patients who completed test per PCP	89	62.5 (33 to 120)	69	75 (40 to 118.2)	...
Cancer and cardiovascular disease variants per PCP	7.5 (4.9 to 10.2)	6.8 (3.7 to 9.1)	7.8 (5.6 to 10.8)	7.4 (5.5 to 8.8)	.40
Tier 1 pathogenic variants per PCP (HBOC, Lynch syndrome, & FH) ^{††}	1.4 (0 to 2.5)	1.5 (0 to 2.8)	1.4 (0 to 2.5)	1.3 (0 to 2.4)	.97
HBOC per PCP	0.8 (0 to 1.5)	0.7 (0 to 1.5)	0.7 (0 to 1.5)	1.0 (0 to 1.8)	.95

Continued

Table 1. Continued

Variable	Overall No./Total (%) or Mean \pm SD or Median (IQR)	FM No./Total (%) or Median (IQR)	IM No./Total (%) or Median (IQR)	OBGYN No./Total (%) or Median (IQR)	P value [†]
Lynch syndrome per PCP	0 (0 to 0.4)	0 (0)	0 (0)	0 (0 to 1)	.12
FH per PCP	0 (0)	0 (0)	0 (0)	0 (0-0.2)	.08
Non-Tier 1 pathogenic variants per PCP	5.8 (3.5 to 7.5)	5.0 (2.1 to 7.0)	6.1 (3.8 to 8.6)	5.8 (3.7-6.8)	.28
Actionable pharmacogenomic variants per PCP ^{††}	98.3(97.2 to 100)	98.6(97.5 to 100)	98.2(96.7 to 99.6)	97.9(97.3 to 100)	.39

Abbreviations: FH, familial hypercholesterolemia; FM, family medicine; HBOC, hereditary breast and ovarian cancer; IM, internal medicine; IQR, interquartile range; OBGYN, obstetrics/gynecology; PCP, primary care physician; SD, standard deviation.

*Results refer to patients who were contacted, agreed to consent to testing or did not agree to testing, and who had orders placed by PCPs before a scheduled annual physical and genetic tests performed and resulted between April 1, 2019, and January 22, 2020.

[†]P values are for the Kruskal-Wallis test unless otherwise indicated; $P < .05$.

[‡]ANOVA with posthoc Tukey HSD Test.

[§]FM versus IM, $P < .05$.

^{||}IM versus OBGYN; $P < .05$.

¹OBGYN versus FM, $P < .05$.

^{**}Wilcoxon Rank Sum Test comparing females across FM and IM only.

^{††}The Color Genomics, Inc. next generation sequencing panel includes the following genes:

Cancer risk (30 genes): *APC*, *ATM*, *BAP1*, *BARD1*, *BMPRI1A*, *BRC1A*, *BRC2*, *BRIPI*, *CDHI*, *CDK4*, *CDKN2A* (p14ARF, p16INK4a), *CHEK2*, *EPCAM*, *GREM1*, *MITF*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, *TP53*.

Cardiovascular disease risk (30 genes): *ACTA2*, *ACTC1*, *APOB*, *COL3A1*, *DSC2*, *DSG2*, *DSP*, *FBN1*, *GLA*, *KCNH2*, *KCNQ1*, *LDLR*, *LMNA*, *MYBPC3*, *MYH7*, *MYH11*, *MYL2*, *MYL3*, *PCSK9*, *PKP2*, *PRKAG2*, *RYR2*, *SCN5A*, *SMAD3*, *TGFBR1*, *TGFBR2*, *TNNT2*, *TPM1*.

^{‡‡}HBOC variants: *BRC1A*, *BRC2*; Lynch syndrome variants: *MLH1*, *MSH2*, *MSH6*, *PMS2*; FH variants: *LDLR*, *APOB*, *PCSK9*.

^{§§}Pharmacogenomic (14 genes): *CYP1A2*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *DPYD*, *F5*, *IFNL3*, *NUDT15*, *SLCO1B1*, *TPMT*, *VKORC1*.

Results

Overall, 49,413 patients were contacted. Of those who consented ($n = 14,063$), 77.7% ($n = 10,933$) had an order placed by a PCP and 89.6% ($n = 9,797$) of these patients completed testing. Mean age of the participants was 49.6 years. An additional 442 patients completed testing ordered by medical geneticists and other specialists (DNA10K total $n = 10,239$). Table 1 presents stratified results by primary care specialty for DNA10K participants. A total of 813 (8.3%) patients had at least 1 actionable genetic risk variant (excluding pharmacogenomics), and 182 (1.9%) patients had at least 1 CDC Tier 1 variant. HBOC variants were present in 116 patients (1.2%), Lynch syndrome in 38 (0.39%) patients, and FH in 29 (0.3%) patients. More than 99% of patients (9599 of 9607) had at least 1 actionable pharmacogenomic variant. The median number of participants per PCP ranged from 62.5 (IQR, 33 to 120) for FM, 66 (IQR, 22.5 to 138) for IM, and 75 (IQR, 40 to 118.2) for OBGYN. Median numbers of patients per PCP with at least 1 CDC Tier 1 variant or at least 1 actionable cancer or cardiovascular disease variant is 1 (IQR, 0 to 2) and 5 (IQR, 1 to 10), respectively. No statistically significant differences were observed per specialty PCP for analyzed test results.

Discussion

In this study, the engagement and implementation of a genetic screening program in an integrated health system enabled PCPs to identify cancer and cardiovascular disease variants in more than 8% of patients and at least 1 CDC Tier 1 variant in nearly 2% of patients. Limitations included the lack of

detailed patient family histories, which restricted an evaluation of its sensitivity. In addition, there was not sufficient follow-up time to assess the effects of testing on downstream screenings (eg, mammography, colonoscopy, lipid testing, genetics referrals, and medical outcomes). However, results suggest PCP-guided population-based genetic screenings could complement routine family histories to identify high genetic risks for cancer and cardiovascular disease.

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To see this article online, please go to: <http://jabfm.org/content/34/4/861.full>.

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