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REVIEW ARTICLE

DNA–Based Population Screening for Adults

Katherine W. Saylor, Ph.D.,[1,2] Sonja A. Rasmussen, M.D.,[3,4] and Michael F. Murray, M.D.[5,6]

Abstract

Population screening is a long-established tool for effectively identifying disease risk when existing approaches are inadequate for optimizing care. DNA–based population screening (DNAPS) in adult populations has the power to identify individuals at an increased genetic risk of cancer, heart disease, and other health conditions, thus allowing for evidence-based interventions to reduce associated morbidity and mortality. One example of the type of risk identified in such screening is *BRCA1*- and *BRCA2*-associated cancer risk, where current risk-identification strategies have been shown to miss greater than 70% of at-risk individuals. Since the first DNA–based screening pilot in adults was initiated in 2008, a growing number of other large-scale projects carrying out DNAPS in adults have followed, and, in aggregate, these projects are engaging millions of people around the world. There are features of DNAPS that make this population screening approach distinct from other population health screens, such as the scale of the datasets that will be created and stored for each participant. This review focuses on an examination of DNAPS in the context of other population health screens, the state of the evidence for this screening approach, and gaps to be addressed to optimize implementation of this population screening approach.

C. Corey Hardin, M.D., Ph.D., Editor

Introduction

Population screening, which creates opportunities for preventive health care, sits at the intersection of public health and medical practice. The purpose of population screening is to systematically identify people who have an otherwise undetected problem (i.e., presymptomatic disease or increased disease risk) so that interventions can be offered. In the United States and many other countries, newborns are screened for evidence of more than 30 conditions; women are screened for abnormal cervical cell changes with Pap smears; and adults are screened for adenomatous colorectal polyps, hypertension, and high levels of low-density–lipoprotein cholesterol. These screens are offered through a range of programmatic designs, from public health–initiated screening programs that collaborate with the health system (e.g., newborn screening) to primary care–initiated health screening approaches with implementation of evidence-based guidelines within the health system (e.g., hypertension screening). Once established, a specific population screening approach will typically continue to evolve based on new evidence or technologies (e.g., colonoscopy replaced sigmoidoscopy for colorectal cancer [CRC] screening).[1]

The author affiliations are listed at the end of the article.

Michael F. Murray can be contacted at michael.murray@mssm.edu.

The introduction of novel technologies can bring new screening opportunities to the fore. In the 1990s, the Human Genome Project was tied to the prediction that DNA–based screening would eventually drive patient care,[2] and the introduction of "next-generation sequencing" in 2007 made affordable sequencing feasible for large cohorts.[3] Population-scale DNA-based health risk prediction could then be pursued, given the growing availability of databases linking DNA variants to phenotypes and the establishment of analytic approaches to rapidly identify pathogenic variation. Against this backdrop, a growing number of programs have initiated DNA-based population screening (DNAPS), which, in aggregate, plan to enroll more than 5 million people (Table S1 in the Supplementary Appendix). These programs have shown that they can effectively obtain informed consent from participants, search DNA datasets for disease-associated changes that are indicative of health risks, and return risk results along with plans for the clinical management of those risks to participants. These programs employ varied approaches and return risk information based on different gene–condition lists. Best practices will need to be forged from the evidence that these independent programs gather, and a consensus for programmatic approaches will need to be developed.

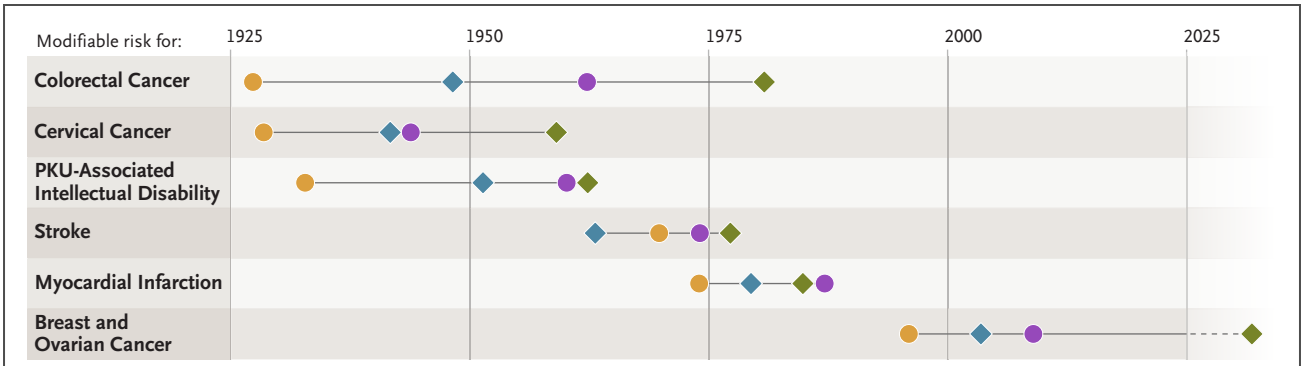
Examination of DNA–Based Screening in the Context of Population Screening

Wilson and Jungner's landmark 1968 monograph, *Principles and Practice of Screening for Disease,* laid out 10 clear, enduring principles for population health screening.[4] The principles include addressing an important health problem, offering evidence-based and accessible treatment, and delivering the program at a reasonable cost. The American College of Medical Genetics and Genomics (ACMG) has published a focused restatement of these principles to guide those offering programmatic DNA-based health screening.[5]

The development of population screening programs consistently follows four steps: (1) identification of a disease-risk biomarker detectable during clinical latency; (2) demonstration of improved health outcomes through interventions offered during clinical latency; (3) pilot testing of steps 1 and 2 combined as a screening strategy; and (4) a population screening recommendation by a governmental body or expert professional organization. Examples of six such programs are detailed in Figure 1.[6-8, 9-22]

DNA-based health screening can assess risk for multiple conditions; however, the available evidence for steps 1 and 2 is at different stages for different gene–condition pairs. Therefore, some clinical applications are currently very well-supported, and others are not yet ready for steps 3 or 4. DNA-based health screening in adults is well into step 3, currently being piloted at many sites, and is increasingly available to individuals who choose to undergo screening; however, it is not currently mandated or endorsed as a standard population screen. In examples of prior population screens, time intervals between initiation of successful screening pilots and recommendations for population implementation varied substantially (Fig. 1). Population screening for CRC was the longest in development.[6] It was built on recognition of the "polyp–cancer sequence," a phenomenon described in the 1920s, along with the recognition that adenomatous polyps are precancerous biomarkers for CRC. Over the ensuing 60 years, that observation was bolstered by long-duration clinical trials and technological advances, which eventually translated into a universal CRC screening program that is now accepted as essential for preventing CRC-associated morbidity and mortality.[23]

Newborn screening is a particularly useful model for DNA-based health screening because it allows for the detection of multiple conditions through a single assay. Newborn screening provides early risk detection and interventions that prevent severe disability, morbidity, or death in nearly 13,000 infants per year in the United States through blood assays, hearing screening, and pulse oximetry.[24] Newborn screening began in 1963 for the detection of phenylketonuria, a condition for which prompt application of an evidence-based intervention in the first weeks of life prevents lifelong morbidity. Its implementation was prompted by the successful piloting of the combination of a novel sample collection approach (a newborn heel stick) with a new technical strategy that allowed rapid identification of high phenylalanine concentrations in a dried blood spot.[12] When screening of a newborn results in the detection of the biomarker, prompt implementation of a specialized diet prevents the devastating form of acquired lifelong intellectual disability associated with untreated phenylketonuria.[13] During the 1960s, newborn screening was expanded to include biochemical screening tests (e.g., for galactosemia and maple syrup urine disease) using the single heel stick sample. In the 1990s, the introduction of tandem mass spectrometry (MS/MS) technology eliminated the need for individual biomarker assays for each condition by allowing for the detection of many blood biomarkers through a single testing procedure. Newborn screening programs were



Modifiable risk for:	FOUR SHARED STEPS IN THE DEVELOPMENT OF POPULATION HEALTH SCREENS			
	1 DISEASE-RISK BIOMARKER Identification of a disease-risk biomarker detectable during clinical latency	2 INTERVENTION Improved health outcome demonstrated with intervention applied during clinical latency	3 PILOT TESTING Pilot testing of health screening strategy	4 SCREENING RECOMMENDATION Initial population screening recommendation
Colorectal Cancer 1927-1980	**Adenomatous polyps** Identified as precursor lesion for colorectal cancer	**Polyp Removal** Rectal polyp removal interrupts the "polyp-cancer sequence"	The prevention of rectal cancer with proctosigmoidoscopy every 5 years	Rec for proctosigmoidoscopy starting age 50 years American Cancer Society 1980
Cervical Cancer 1928-1957	**Abnormal pap smear** Identified as precursor lesion for invasive cervical cancer	**Surgical Intervention** Surgical intervention interrupts development of invasive cancer	Improved outcomes associated with early intervention	Rec for annual pap smear American Cancer Society 1957
PKU-Associated Intellectual Disability 1934-1963	**Elevated phenylalanine** Linked to severe intellectual disability	**Low Phenylalanine Diet** Demonstration of low phenylalanine diet leading to clinical improvement	Pilot of newborn screening for PKU	Universal Newborn Screening for PKU Massachusetts DPH 1963
Stroke 1963-1977	**Elevated blood pressure** Linked to increased risk for stroke	**Control blood pressure** Pharmacologic control of high blood pressure	Evaluation of a mass hypertension screening program	Rec of Joint Natl Committee on Detection, Evaluation, and Treatment of High BP 1977
Myocardial Infarction 1974-1986	**Elevated LDL-C** Linked to increased risk for myocardial infarction	**Cholesterol Control** Lowers MI risk	Pilot of population screening for cholesterol determination	NIH Consensus Development Conference on lowering blood cholesterol 1985
Breast and Ovarian Cancer 1996-20XX	**Pathogenic BRCA1 & BRCA2 variants** Linked to increased risk for breast and ovarian cancer	**Risk reducing surgery** Prophylactic breast and ovarian surgery	The ClinSeq Project and other "large scale pilots"	TBD

Figure 1. Timeline of the Development of Six Major Population Screens.

For each of the six population screening programs, the timeline of four steps (identification of disease-risk biomarker detectable during latency, improved health outcome demonstrated when intervention is applied during clinical latency, pilot testing of health screening strategy, and initial population screening implemented/recommended) is presented. (Data based on the following references: colorectal cancer,[6-8] cervical cancer,[9-11] phenylketonuria (PKU),[12-14] stroke,[15-18] coronary artery disease,[19,20] and *BRCA1/2*.[21,22]) BP denotes blood pressure; DPH, Department of Public Health; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NIH, National Institutes of Health; PKU, phenylketonuria; and TBD, to be determined.

then prompted to decide which risk-associated biomarkers they would choose to interpret and report back to health care delivery teams. There are now 36 conditions recommended for inclusion in newborn screening.[25]

In its ability to detect multiple conditions through a single assay, DNA-based health screening has some important parallels to MS/MS–based newborn screening. When DNA-based health screening programs use exome or genome

sequencing, a single test creates a dataset with information on more than 20,000 genes, of which approximately 5000 currently have known clinical associations. Every gene–condition pair is potentially a distinct population screen. Dramatic differences in clinical context notwithstanding, phenylketonuria and *BRCA1*- and *BRCA2*-associated breast and ovarian cancer (*BRCA* risk) share a role as first exemplars for broader population screens. Just as evidence for the potential to prevent intellectual disability by identifying phenylketonuria made the initial case for newborn screening, *BRCA* risk and other associated cancer risks are among the prominent examples of gene–condition pairs with strong evidence supporting DNA-based health screening where the application of health system based DNAPS has consistently found that greater than 70% of participants found to have *BRCA* risk had never been identified to have this risk via recommended medical history based screening.[21,26-28] The *BRCA* risk case for DNA-based health screening is among a relatively small subset of the 20,000 genes with current evidence demonstrating screening value. Like MS/MS–based newborn screening, DNA-based health screening pilots have started identifying risks from a short list of compelling gene–condition pairs, with an expectation that the list will expand as evidence grows.

DISTINCTIVE FEATURES OF DNA–BASED POPULATION SCREENING

A distinct feature of DNA is the presence of massive amounts of currently uninterpretable variation in the human genome. Each variation in the DNA code is a potential risk-associated biomarker. A five-category classification system for variants exists: benign (B), likely benign (LB), variant of uncertain significance (VUS), likely pathogenic (LP), and pathogenic (P).[29] In the screening setting, only LP and P have an evidentiary basis for conferring risk and, thus, are considered reportable to patients and clinicians. This means that VUSs are set aside pending more evidence that moves them to either B/LB or LP/P, making periodic reanalysis a necessity (and a logistical challenge) for programs seeking to maximize participants' benefit. Although the vast majority of reclassified VUSs are designated as B/LB, about 9% of variant reclassifications after cancer genetic testing have been reclassified as LP/P, thus warranting reporting and intervention.[30] When new gene–condition pairs are added to screening panels, the certainty of the association is expected to increase as more patients are followed over time. Evidence synthesis efforts, such as the ClinVar database of variants, disease, and treatment responses, make it possible to know whether or not a new variant has been seen in other patients and to disseminate new information when variant classifications change.[31]

DNA-based health screening programs need to operate with the understanding that, whereas an individual's DNA dataset is static, the accumulation of two kinds of evidence will potentially increase the number of risks that can be uncovered and used in clinical care for that individual. The categories of new results from the dataset are (1) VUSs that get converted to LP/P as the evidence grows; and (2) newly validated gene–condition pairs with evidence-based interventions that meet the programmatic threshold for screening. Because the amount of clinically useful data expands over time, a suggested best practice is to sequence once and then carry out periodic reanalysis,[5] an approach consistent with Wilson and Jungner's principle that health screening is not a one-and-done process.[4] An optimal frequency of reanalysis has yet to be determined.

There are important limitations to the predictive value of identified genetic risks. Not everyone with a high-risk genetic finding will develop disease. The positive predictive value is limited by the complexity of gene–gene and gene–environment interactions. More research is needed to better understand gene–disease penetrance (i.e., whether and when someone with an identified variant will get the associated disease) and expressivity (i.e., which specific problems associated with the genetic risk will occur).[32] The negative predictive value of a negative DNA-based health screening result is also limited. The lack of a recognized high-risk DNA change does not indicate significantly lower risk than the population risk for cancers, heart diseases, and other complex, common conditions. Therefore, messaging for those with a negative DNA-based health screening result must avoid false reassurance that could be associated with receiving a negative screening result.[33]

THE STATE OF THE EVIDENCE FOR DNA–BASED HEALTH SCREENING

Programmatic Models for Large-Scale DNA–Based Screening Programs

Current pilot programs vary in their approaches to recruitment and sample collection, integration with electronic health records, reporting results to patients and clinicians, and connecting patients with follow-up care.[32]

The launch of large-scale screening programs has been limited by costs and the lack of a standardized funding model. To date, most DNA-based health screening pilots have been supported through either government-funded research,[34-36] health system–business collaborations,[37] or

direct-to-consumer test kits. For example, the ClinSeq project was initiated and funded by the U.S. National Institutes of Health to establish approaches for informed consent and return of genetic information to participants.[35] The program enrolled 1473 participants and successfully returned DNA-based screening results.[22] A research collaboration between Geisinger Health System and Regeneron Pharmaceuticals resulted in the first regional health system–based genomic screening program in 2015.[37] The company Helix has launched a number of regional health system–based collaborations, including the Healthy Nevada Project in 2016 (which also receives state funding).[26] Preceding these collaborations, the direct-to-consumer company 23andMe launched in 2007 and created a commercial DNA-based screening process that is estimated to have engaged 15 million users and returned *BRCA* risk results to more than 20,000 users.[38]

Current DNA-based health screening programs (Table S1), together with direct-to-consumer testing and newborn screening, signal a new landscape for population screening that includes a role for private businesses as an integral element in the workflow (Fig. 2). This new landscape prompts three questions: (1) Will one of the "information workflows" illustrated in Figure 2 emerge as the accepted best practice model for DNA-based health screening?; (2) Who should provide oversight of DNA-based health screening programs?; and (3) What should the ground rules for data use be for those who have access to participant data, including commercial entities and health care institutions?

Gene–Condition Lists for Population Screening

Existing DNA-based health screening programs (Table S1) have generally chosen to use or adapt two established monogenic lists: the U.S. Centers for Disease Control and Prevention (CDC) Tier 1 (T1) list and the ACMG Secondary Findings (ACMG SF) list.

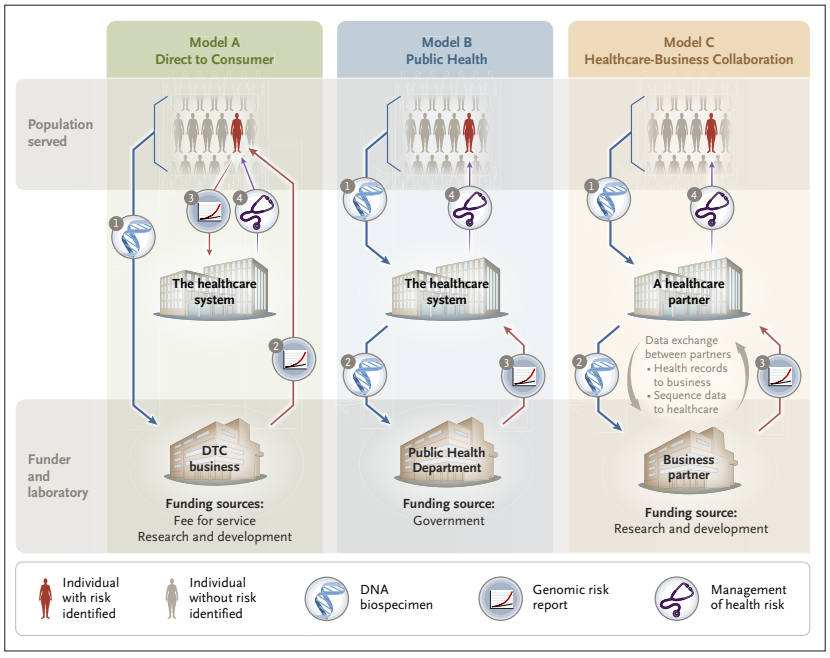


Figure 2. Genomic Screening Models.

Model A is the direct-to-consumer model that currently exists outside of health care as a "fee for service" for consumers. If health benefits are to be realized, the consumers need to bring any positive results to the health care system and engage the appropriate providers. Consumers can opt in to research and development, which allows the company to use their DNA data together with their self-reported health information. Model B, the public health model, currently exists for newborn screening operated in the United States at the state level. The health care system collects the samples, delivers the patient results, and provides the care. Model C, the health care–business collaboration model, is currently used in many of the adult DNA–based population screening programs in Table 1. The health care system collects the samples, delivers the patient's results, and provides the care. The business partner funds the genomic sequencing in exchange for access to deidentified health care data that can be used for research and development (e.g., discovery of new pharmaceutical targets). DNA denotes deoxyribonucleic acid; and R&D, research and development.

In 2014, the CDC used a systematic review process to identify its T1 list, consisting of three conditions that had sufficient evidence to support screening among high-risk patients and their family members: hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia.[39] This initial CDC designation did not suggest support for unselected population screening, but evidence amassed over the past decade of their prevalence and the harms of underdiagnosis of these genetic risks has made a strong case for universal population screening for these conditions. The CDC does not currently have a process for adding to its list.

In 2013, the ACMG developed a process for identifying gene–condition pairs to be included in an ACMG SF list; secondary findings were defined as results obtained through clinical exome or genome sequencing that are unrelated to the diagnostic indication but considered actionable because they are associated with conditions for which interventions are available that could improve patients' outcomes. The ACMG recommends that patients who undergo exome or genome diagnostic testing during routine clinical care be given the option to learn these screening results or to opt out. The ACMG SF list has been updated regularly, with the most recent version published in June 2025 and comprising 84 gene–condition pairs.[40] The CDC T1 genes are included in the ACMG SF list. The ACMG has stated that the ACMG SF list was not designed as a population screening tool. A gene–condition list for population screening from this professional group is anticipated in 2026.[41]

Published reports of DNA-based health screening (Table 1) demonstrate that, among 602,135 individuals screened for CDC T1 monogenic autosomal dominant conditions, risk for one or more conditions was identified in 1 in 75 (1.3%) individuals. The majority of individuals

Table 1. Prevalence of Risk Variants for Centers for Disease Control and Prevention Tier 1 Conditions in 11 DNA–Based Health Screening Cohorts.*

DNAPS and No. of Individuals Included in Analysis	No. of Individuals with Pathogenic and Likely Variants Identified													
	Hereditary Breast and Ovarian Cancer (HBOC)	HBOC Genes		Lynch Syndrome	Lynch Syndrome Genes†				Familial Hypercholesterolemia	Familial Hypercholesterolemia Genes			CDCT1	Refs.
		BRCA1	*BRCA2*		*MLH1*	*MSH2*	*MSH6*	*PMS2*		*APOB*	*LDLR*	*PCSK9*		
ClinSeq N=572	7 (1 in 82)	2 (1 in 286)	5 (1 in 114)	—	—	—	—	—	—	—	—	—	NA	22
Life Pool Cohort N=5908	21 (1 in 281)	6 (1 in 985)	15 (1 in 394)	—	—	—	—	—	—	—	—	—	NA	42
MyCode N=175,500‡	N=50,459 267 (1 in 188)	95 (1 in 531)	172 (1 in 293)	N=175,500 595 (1 in 295)	41 (1 in 4280)	40 (1 in 4389)	276 (1 in 636)	238 (1 in 737)	N=59,729 280 (1 in 213)	64 (1 in 933)	103 (1 in 579)	0	1 in 75	43
eMERGE N=21,915	145 (1 in 151)	64 (1 in 342)	81 (1 in 271)	41 (1 in 535)	3 (1 in 7305)	4 (1 in 5479)	14 (1 in 1565)	20 (1 in 1096)	93 (1 in 236)	12 (1 in 1826)	72 (1 in 304)	9 (1 in 2435)	1 in 79	44
Health Nevada N=26,906	178 (1 in 151)	68 (1 in 396)	110 (1 in 245)	80 (1 in 332)	10 (1 in 2691)	4 (1 in 6727)	28 (1 in 961)	38 (1 in 708)	102 (1 in 260)	21 (1 in 1281)	80 (1 in 336)	1 (1 in 26,906)	1 in 75	26
Estonia Genome Project N=17,679‡	N=17,679 48 (1 in 368)	35 (1 in 505)	13 (1 in 1360)	—	—	—	—	—	N=4776 27 (1 in 177)	11 (1 in 434)	15 (1 in 318)	1 (1 in 4776)	NA	45,46
Alabama Genomic Health Initiative N=5369	20 (1 in 268)	7 (1 in 767)	9 (1 in 597)	9 (1 in 597)	3 (1 in 1790)	1 (1 in 5369)	3 (1 in 1790)	2 (1 in 2685)	9 (1 in 597)	6 (1 in 895)	3 (1 in 1790)	0	1 in 141	47
All of Us N=217,824‡	N=98,590 343 (1 in 287)	119 (1 in 828)	224 (1 in 440)	N=217,824 616 (1 in 354)	63 (1 in 3457)	55 (1 in 3960)	212 (1 in 1027)	286 (1 in 761)	N=98,590 289 (1 in 341)	79 (1 in 1248)	219 (1 in 450)	—	1 in 109	48,49
BioME N=30,223	218 (1 in 139)	86 (1 in 351)	131 (1 in 231)	70 (1 in 432)	12 (1 in 2519)	13 (1 in 2325)	16 (1 in 1889)	29 (1 in 1042)	—	—	—	—	NA	27,50
Tapestry N=98,222	910 (1 in 108)	–	–	404 (1 in 246)	—	—	—	—	516 (1 in 190)	—	—	—	1 in 53	51
Geno4ME N=2017	13 (1 in 155)	7 (1 in 288)	6 (1 in 336)	5 (1 in 403)	1 (1 in 2017)	0	1 (1 in 2017)	3 (1 in 672)	11 (1 in 183)	3 (1 in 672)	7 (1 in 288)	1 (1 in 2017)	1 in 70	52
Total N=602,135	N=357,860 2170 (1 in 165)			N=577,976 1820 (1 in 318)					N=317,524 1327 (1 in 239)				1 in 75	

* CDC denotes Centers for Disease Control and Prevention; DNAPS, DNA–based population screening; HBOC, hereditary breast and ovarian cancer; NA, not available; T1, Tier 1; and Ref, reference.
† *EPCAM* is a fifth Lynch syndrome gene; pathogenic variants in this gene are not identified by DNA sequence analysis.
‡ MyCode, the Estonia Genome Project, and All of Us published analyses of the conditions using subcohorts with different Ns; the "DNAPS N" is the largest subcohort N for each of these three projects.

were not aware of these genetic risks,[28] and 35% of patients had no documented clinical or family history indications for genetic testing.[53] In a recent report on screening 175,500 participant exomes using the ACMG SF 3.2 gene list, 1 in 30 (3.4%) participants had a "positive risk" result, with 87 individuals having more than one risk result.[43]

The routine delivery of information other than monogenic risk results (i.e., pharmacogenomic risk and polygenic risk) is being piloted in a few programs (Table S1) and is beyond the scope of this review. Important pharmacogenomic variants that influence drug efficacy or the risk of adverse drug reactions are powerful tools when available at the time of prescribing medications and are described in a recent *NEJM Evidence* article as part of the update in genetics review series.[54] Polygenic risk scores combine many common low-risk DNA variants to calculate an individual's disease susceptibility. As the predictive accuracy of these scores improves, they are likely to become a routine deliverable for DNA-based genomic screening.[55]

Clinical Utility of Risk Identification

Screening programs must lead to evidence-based clinical management for individuals identified as having elevated risk. It has been pointed out that, "A screening or diagnostic test alone does not have inherent utility; because it is the adoption of therapeutic or preventive interventions that influences health outcomes, the clinical utility of a test depends on effective access to appropriate interventions."[56] There have been important demonstrations of utility in finding presymptomatic disease immediately after identifying an elevated genetic risk.[57] In the near term, evidence that interventions have clinical utility can be extrapolated from the application of these interventions when genetic risk is identified in clinical care. The established evidence-based clinical management strategies for CDC T1 gene–related risk and disease include enhanced clinical surveillance, prevention measures, and targeted treatment, are given in Table 2. Empirical data are accruing on the clinical utility of risk identification for preventing cancer, heart disease, and other major risks within existing large DNA-based health screening pilots. As with newborn screening, long-term follow-up is needed to establish direct evidence for the effect of screening on lifetime population morbidity and mortality.

Preliminary Evidence of Cost-Effectiveness

Wilson and Jungner's principle that "the cost of case-finding (including diagnosis and treatment of patients determined to be at risk) should be economically balanced with possible expenditure on medical care as a whole"[4] remains as important now as it was in 1968. The value or

Table 2. Established Evidence-Based Clinical Management for Centers for Disease Control and Prevention Tier 1 Conditions Risk and Disease.

Syndrome (Genes)	Disease Risk	Enhanced Screening	Preventive Intervention*	Targeted Cancer Management	Refs.
Hereditary breast and ovarian cancer syndrome (*BRCA1*, *BRCA2*)	Breast cancer	Early mammogram Breast MRI	Risk-reducing surgery (prophylactic bilateral mastectomy)	PARP inhibitors	58
	Ovarian cancer	—	Risk-reducing surgery (prophylactic salpingo-oophorectomy)	PARP inhibitors	58
	Prostate cancer	Early prostate-specific antigen and digital rectal exam	—	PARP inhibitors	58
Lynch syndrome (*MLH1*, *MSH2, MSH6, PMS2, EPCAM*)	Colorectal cancer	Early colonoscopy	Polypectomy	Immune checkpoint inhibitors	59
	Endometrial cancer	Transvaginal ultrasound and endometrial biopsy	Risk-reducing surgery	Immune checkpoint inhibitors	59
	Pancreatic cancer	MRI/MRCP and endoscopic ultrasound	—	Immune checkpoint inhibitors	59
Familial hypercholesterolemia (*APOB, LDLR, PCSK9, LDLRAP1*)	Coronary artery disease	LDL-C (primary prevention goal<100 mg/dl)	Statins, PCSK9 inhibitors, others	NA	60

*Risk-reducing surgeries and other enhanced screening and prevention interventions should be offered to individuals as management options to consider. LDL-C denoted low-density lipoprotein cholesterol; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NA, not available; PARP, poly ADP-ribose polymerase; PCSK9, proprotein convertase subtilisin/kexin type 9; and Ref, reference.

cost-effectiveness of DNA-based health screening depends on whether the health benefits of early risk identification outweigh the costs of screening and the costs or harms of risk-reducing interventions. Combined DNA-based health screening for all three CDC T1 conditions at 30 years of age has been shown to be of high value in lifetime cost-effectiveness simulation models.[61] Cost-effectiveness analyses of screening for other individual genetic conditions have not yet shown benefits commensurate with costs. The bulk of the cost of the screening program is related to the genetic sequencing and analysis, so adding genes to a panel or revisiting data over time will increase value by amortizing genetic testing costs.[61] Nevertheless, the cost-effectiveness of additions to a DNA-based health screening panel will depend on the clinical benefits and costs of risk-reducing interventions after screening that may need to be delivered for years or decades. More efficient genetic analysis and advances in risk-reducing interventions hold promise for improved cost-effectiveness for a growing number of conditions.

GAPS TO BE ADDRESSED TO OPTIMIZE DNA–BASED POPULATION SCREENING

Refinement of Age-Based Screening

To date, most DNA-based health screening pilots in adults enroll consenting participants over 18 years of age and deliver risk findings from their gene–disease lists on analysis. This model leads to the receipt of gene–condition risk results, regardless of age. Large-scale projects tend to have a significant age range of participants. For example, the Healthy Nevada Project's cohort reported an age range of 57 years (between 23 and 80 years of age).[26] Evidence is emerging to suggest that management of specific gene–condition risks can be optimized based on age, including recent data suggesting that the value of universal *BRCA* risk screening decreases with screening age and drops precipitously for screening after 60 years of age.[62] As evidence grows, opportunities to develop best practices regarding age-specific screening and age-based intervention for each gene–condition pair are expected.

Support of Cascade Testing

Cascade testing means offering targeted testing to at-risk first-degree relatives following monogenic risk identification. Cascade testing has anticipated value both as an alternative to DNA-based health screening for cancer[63] and as an extension to DNA-based health screening for CDC T1 conditions.[61] Because most monogenic risks currently screened are autosomal dominant, first-degree relatives (i.e., parents, siblings, children) of those identified with these risks have a 50% chance of having the same risk. This creates an opportunity for biological relatives of screening program participants to benefit from positive screening results. In general, cascade testing has not been well-integrated into routine care; however, efforts to improve cascade testing rates within screening programs by providing patients with standardized letters they can share or through direct communication, when possible, within health systems have had some impact.[64] Until entire populations participate in screening, cascade testing provides a low-cost opportunity for screening programs to increase beneficial outcomes.[65]

Avoiding Overdiagnosis

All health screens in asymptomatic patients, including DNA-based health screening, have the potential for overdiagnosis of disease precursors that would never lead to adverse health outcomes. Overdiagnosis can trigger unnecessary clinical tests and interventions. For example, routine mammography in women over 70 years of age has been criticized for driving unnecessary intervention for indolent cancers.[66] The balancing of risks and benefits for specific gene–condition results in the general population will require careful study as data from these programs accumulate. By leveraging impressive participant recruitment and longitudinal clinical data, research biobanks and clinical pilot programs are answering key questions about the penetrance of genetic variants in the unselected population, which will help refine risk predictions and inform clinical management.

Avoiding Unequal Benefits across Populations

DNA-based health screening programs need to optimize benefits for the populations served, which requires attention to at least two issues. First, there is a dearth of genomic data to support accurate interpretation of DNA variant–disease relationships for people with non-European ancestry, which results in higher VUS rates.[67] DNA-based health screening programs should aim to evaluate risk using reference datasets that are optimized for the genomic diversity of their program participants. DNA-based health screening can help improve representation in the available datasets through balanced project recruitment. Balanced recruitment requires attention to the barriers that are known to limit access to routine diagnostic DNA-based testing, including historically marginalized

Table 3. DNA–Based Population Screening Implementation Questions in Need of Consensus Answers.*

Question	Potential Options
What is the optimal consenting process to ensure adequate patient autonomy?	• Capacity to opt out of some results, or to select broad or narrow panels • Capacity to withdraw consent for ongoing variant reinterpretation or additional gene–condition pair findings
What is the optimal way to deliver timely education and clinical decision support to clinicians and patients?	• Electronic health record optimization to manage genetic results and automate age-based or variant-based management alerts • Commercial platforms (e.g., bots) to integrate evolving evidence into clinical decision-making • In-person, remote, or electronic informed consent processes for patients, delivered by primary care or genetic counselors • Ongoing clinician and patient communication triggered by new evidence or changing guidelines • Genetics training for all primary care specialties and just-in-time resources to address evolving gene–condition panels
What is the optimal funding model?	• Insurance coverage (similar to most guideline-directed adult screening programs) • Public funding (similar to newborn screening) • Self-pay • Commercial entities (with careful consideration of commercial reuse of genetic data)
What is the best data storage approach that takes into account costs, security, and privacy?	• Health care institution–based (similar to most adult screening tests) • Department of Public Health storage (similar to newborn screening) • Cloud storage, encryption, and consent documentation
What is the optimal approach to the reanalysis of DNA datasets?	• Periodic review at standard intervals (e.g., annual) • Real-time updates triggered when relevant evidence is added to databases (i.e., ClinVar)
What process should be used for adding (or removing) gene–condition pairs to the screening panel?	• National government-funded group that reviews and makes recommendations (similar to the Recommended Uniform Screening Panel developed by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children for newborn screening) • ACMG recommendations
Are new regulatory and oversight rules needed?	• Reinforcement and expansion of the Genetic Information Nondiscrimination Act or ACA protections to cover life insurance, disability insurance, and long-term care insurance • Potential FDA regulation of laboratory-developed tests as medical devices (FDA final rule vacated by federal court in 2025)
What measures should be in place to manage patients after positive genetic screening results?	• Guideline development for medical management of asymptomatic or presymptomatic patients • Automated referral strategies to relevant specialty care • Insurance coverage of guideline-directed medical management for government or ACA-compliant health plans

*ACA denotes Affordable Care Act; ACMG, American College of Medical Genetics and Genomics; DNA, deoxyribonucleic acid; and FDA, U.S. Food and Drug Administration.

background race, poor insurance coverage, lower educational attainment, and geographic deprivation.[68]

Second, people with poor access to health care face barriers to DNA-based health screening and follow-up care. Unless these barriers are proactively addressed, implementation of DNA-based health screening could exacerbate disparities. On the other hand, universal DNA-based health screening has great potential to overcome current inequalities in genetic diagnosis due to incomplete personal and family history records, patients' and clinicians' awareness of genetic conditions, and other informational barriers.

Achieving Operational Consensus

Many of the operational decisions that are required to launch a DNA-based health screening pilot are being made in the absence of established best practices. This creates opportunities to gather evidence from projects, insurers, and others to support operational choices that can inform ongoing best practices. Table 3 lists questions that await evidence-driven best practice answers.

Conclusions

Many patients and clinicians currently have or will soon have opportunities to participate in DNA-based health screening. However, the establishment of universal and uniform approaches to DNAPS for adults will require more evidence, investment, and infrastructure.

Existing projects (Table S1) represent opportunities to deliver benefit while innovating and building evidence that advances the field. Anticipated advances include the definition of a common list of returnable monogenic risks with sufficient evidence for population screening and inclusion of validated polygenic risk scores and high-value pharmacogenomic gene–drug pairs.

The optimal programmatic design to support national strategies for DNA-based health screening is unclear. Included in the range of possibilities are centrally driven government-led programs and a multifocal federation of regional health systems that applies a shared set of evidence-based guidelines. Newborn screening in the United States developed in a manner that was responsive to available financing and evidence. Adult DNA-based health screening will likely follow a similar trajectory, with design driven by the financing, programmatic structure, and developing evidence.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

Author Affiliations

[1] Department of Bioethics and Decision Sciences, Geisinger College of Health Sciences, Danville, PA, USA

[2] Department of Genomic Health, Geisinger College of Health Sciences, Danville, PA, USA

[3] Department of Genetic Medicine, Johns Hopkins University School of Medicine, Johns Hopkins University, Baltimore, MD, USA

[4] Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Johns Hopkins University, Baltimore, MD, USA

[5] Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[6] Institute for Genomic Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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