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ACMG STATEMENT

DNA-based screening and population health: a points to consider statement for programs and sponsoring organizations from the American College of Medical Genetics and Genomics (ACMG)

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Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this statement. Clinicians also are advised to take notice of the date this statement was adopted, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

INTRODUCTION

Screening is an organized application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from either further evaluation or direct preventive action.[1] DNA-based screening, that is, the identification of DNA variants in unselected individuals to predict latent disease risk, constitutes a new approach for health screening. The use of DNA-based health screening to guide preventive care in the screened individual has long been discussed, but until recently has had limited applications.[2] Screening is distinct from indication-driven DNA testing, referred to as diagnostic testing. DNA technologies now make primary screening applications possible in a wide range of settings. Beyond institutional review board (IRB)-approved research, any screening application for DNA-based risk detection should be evidence-based and adherent to the health screening criteria established by Wilson and Jungner more than 50 years ago.[3]

The American College of Medical Genetics and Genomics (ACMG) has generated this document with seven points to consider (Table 1) to guide programs and sponsoring organizations that are considering DNA-based health screening. Individuals who are undergoing DNA-based screening and their health-care providers are encouraged to review the ACMG statement on DNA-based screening and personal health for additional points to consider.[4] In aggregate, DNA-based screening efforts have the potential to improve population health, but only if risk identification is effectively combined with evidence-based risk-reducing clinical care.

This document will focus on issues related to implementation strategies for DNA-based screening, which requires distinguishing "screening" from the use of DNA-based "diagnostic testing" that has been applied within health care for decades. When DNA-based testing is pursued as part of a diagnostic effort, the individual who is undergoing the testing has already been identified as having an increased pretest probability of a positive genetic test based on signs, symptoms, physical exam, other diagnostic tests or family history (Fig. 1a). ACMG secondary findings recommendations are limited to the review of existing exome or genome sequencing data that was generated as part of the diagnostic process.[5–7] In contrast, the goal of DNA-based screening is to introduce testing within an unselected population to identify persons without prior suspicion of genetic risk for disease development (Fig. 1b, c).

There are longstanding principles that guide health screening. Ten enduring criteria were outlined by Wilson and Jungner in their 1968 treatise.[3] For the purposes of this document, these original criteria are displayed alongside a version of the criteria tailored for a DNA-based screening and population health context (Table 2).

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Table 1. Seven points to consider from the American College of Medical Genetics and Genomics (ACMG).

	DNA-based screening and population health points to consider
1	The ACMG secondary findings recommendations do not constitute a primary health screening recommendation or strategy.
2	DNA-based screening should not replace a standard-of-care evaluation for individuals with a clinical indication for diagnostic assessment.
3	Disease risks identified through screening should not include DNA variants of uncertain significance (VUS).
4	DNA-based screening should be linked to opportunities for evidence-based risk-reducing clinical care.
5	Risk-reducing clinical follow-up for DNA-based screening should be consistent with best practices outlined by professional societies with appropriate expertise.
6	Organizations involved in DNA-based screening are expected to participate in sharing of outcomes-related data.
7	DNA-based screening applications with proven beneficial clinical outcomes should be made available to entire populations to promote health-care equity and limit health disparities.

To date, evidence of fulfillment of these ten criteria have not been unambiguously demonstrated for any DNA-based health screening application for adults.

The genes associated with "tier 1 genomic applications" are widely considered a core list for consideration in the context of screening.[8] These applications are defined by the Centers for Disease Control and Prevention (CDC)'s Office of Public Health Genomics (OPHG) as those having significant potential for positive impact on public health based on available evidence-based guidelines and recommendations.[8] The genomic conditions are hereditary breast and ovarian cancer (HBOC), Lynch syndrome (LS), and familial hypercholesterolemia (FH). The three tier 1 genomic conditions are specifically associated with risk for breast, ovarian, colon, and endometrial cancers, coronary artery disease, and stroke and are therefore consistent with Wilson and Jungner's guidance to focus health screening on "important health problems" (Table 3).[3,8] The three genomic conditions on this consensus list are associated with nine genes that are also included in the list of ACMG secondary finding recommendations.[5,6]

A key data gap in our efforts to demonstrate the fulfillment of the health screening criteria for DNA-based screening is our incomplete understanding of what Wilson and Jungner referred to as the "natural history of the condition." Natural history in this context involves penetrance; the proportion of individuals with a given genomic risk who show evidence of the associated clinical problems; expressivity, the range of clinical manifestations associated with a specific genomic risk; and age of onset. While we have a detailed understanding of the tier 1 conditions in the context of cohorts identified through diagnostic testing, the natural history data are far more limited for cohorts identified through DNA-based screening approaches (Table 3). Estimates of population penetrance for *BRCA1/2* have been published, and these were developed using four interdependent epidemiologic parameters: (1) the probability of developing breast cancer, (2) the proportion of breast cancer cases with a *BRCA1* or *BRCA2* pathogenic variant, (3) the proportion of women that carries a pathogenic variant, and (4) the proportion of women with a pathogenic variant that develops cancer.[9] This approach will prove useful for organizations who desire to make estimates for *BRCA1/2* or other monogenic risks.

Penetrance and DNA-based screening

It is important to emphasize that a positive result in DNA-based screening is not equivalent to a diagnosis of the "health problem" of interest.[10,11] DNA-based risk identification in the absence of relevant medical history places individuals in a category for which we do not have sufficient consensus on clinical classification and management (Table 2). For example, a patient with a pathogenic *MLH1* variant but without relevant family history or clinical evidence of colon or other associated cancers has nonpenetrant "disease risk" but not LS. Health-care systems, insurers, providers, and patients need better language to describe someone who has a DNA-based risk identified and needs ongoing surveillance (Fig. 1c), but does not have, and may never develop, penetrant disease. Simply listing the positive genetic test result in the problem list of the electronic health record to prompt appropriate ongoing follow-up without labeling a patient as having a "diagnosis" has been proposed.[12] Further study is needed to develop a best practice solution.

Expressivity and DNA-based screening

Our understanding of the range of clinical problems associated with any genetic risk is mostly based on our understanding from cases ascertained through diagnostic testing. As screening becomes more routine, an appreciation of an extended range of clinical problems, particularly on the mild end of the spectrum, is likely to be elucidated. An example of this improved understanding of expressivity has occurred with cystic fibrosis where proactive screening for disease has helped to clarify the association of bilateral absence of the vas deferens and CFTR-related metabolic syndrome.[13]

Age of onset and DNA-based screening

The natural history of a condition includes an age of onset for the relevant diseases in question. More research will be required to understand both the median age and the age range for diseases attributed to the risks ascertained through this type of DNA-based screening. Clearer understanding of age of onset will allow for more strategic decision making about the optimal age for the initial DNA screen and the optimal ages for the follow-up preventive measures.

BACKGROUND AND DISCUSSION OF THE INDIVIDUAL POINTS TO CONSIDER

The ACMG secondary findings recommendations do not constitute a primary health screening recommendation or strategy[7]

The ACMG published recommendations for reporting of secondary findings in clinical exome and genome sequencing in 2013 and updated those recommendations in 2016.[5,6] In these efforts the ACMG has produced a list of 59 genes and 30 conditions to help guide secondary analysis of genomic data generated as part of diagnostic care.[6] This list emphasizes the medical actionability of existing data as the motivation for uncovering secondary findings. The ACMG Secondary Finding Maintenance Working Group's 2016 statement summarized their approach as including five major criteria for medical actionability: (1) severity of disease/nature of the health threat, (2) likelihood of the disease/health threat materializing (i.e., penetrance), (3) efficacy of specific

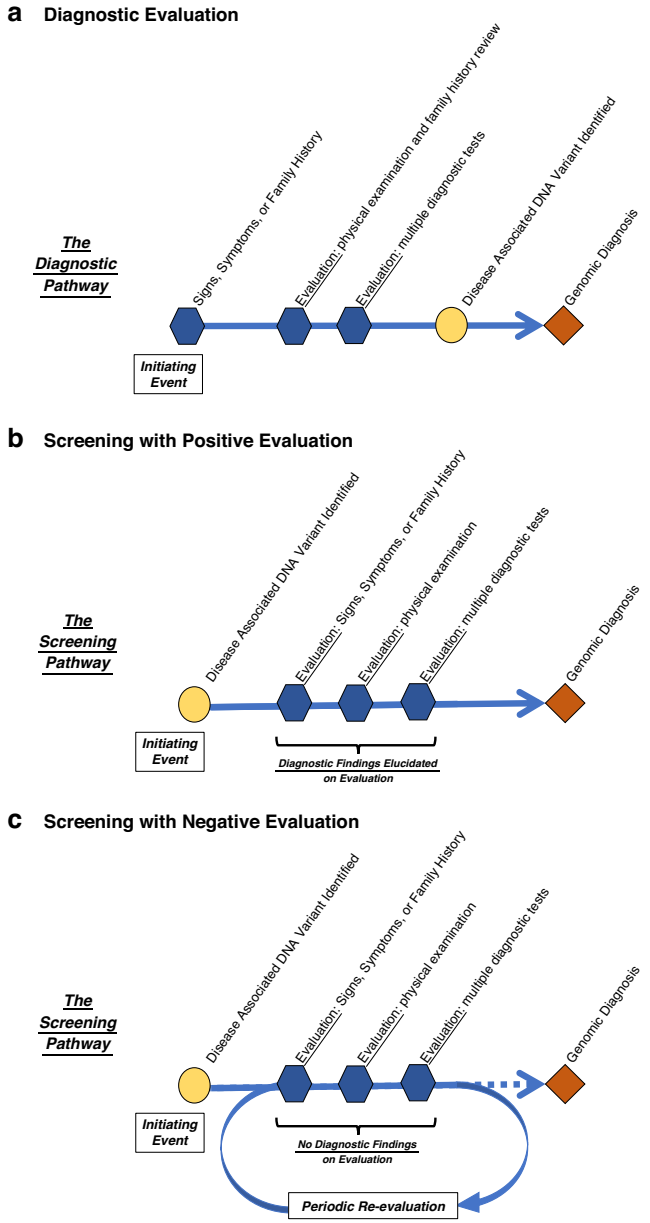

Fig. 1 Comparison of two distinct testing pathways: diagnostic and screening. The diagnostic pathway (**a**) is prompted by clinical signs, symptoms, or a positive family history. The screening pathway (**b**, **c**) is prompted by a pathogenic or likely pathogenic variant reported on the DNA-based test aimed at identifying those individuals with sufficient risk of a specific disorder to warrant further investigation or direct preventive action. While many of the elements of the two pathways are the same, they are in a different order in the diagnostic versus screening pathways. In (**c**) it is the absence of diagnostic findings signifying a "nonpenetrant risk" that prompts condition-specific periodic re-evaluation.

intervention(s), (4) overall strength of the current knowledge base about the gene/condition, and (5) acceptability of the proposed intervention based on its risks and benefits. They also noted that the last criterion was highly personal and subjective. Efforts to formalize a more quantitative approach to clinical actionability have been furthered within the ClinGen project, and we have incorporated output from that standardized ClinGen Actionability Scale 0–12 into this document (Table 3).[14]

Actionability is a key concept used in the selection of gene–condition pairs for both secondary findings (identified within existing data generated in a diagnostic effort) as well as new data generated proactively through screening. An overlap of genes and conditions for these different applications is to be expected, and as the evidence base is built to effectively prevent disease, there may be a more complete overlap. Currently, however, proactive efforts to screen for disease risk through DNA analysis is distinct from secondary findings and should be grounded in the same long-established principles as other health screening. This grounding includes extending attention beyond individual risk identification and risk-reducing clinical care to include broader societal concepts, such as health services delivery and economics. The health service delivery options for DNA-based health screening are currently in flux.[4,15] The economic concept articulated by Wilson and Jungner (Table 2) is "the cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole."[3] Much of the health services and economic research needed to address the DNA-based screening issues are yet to be done.

DNA-based screening should not replace a standard-of-care evaluation for individuals with a clinical indication for diagnostic assessment

Individuals with signs, symptoms, or family history should be assessed for the potential need for DNA-based diagnostic testing (Fig. 1a), and such individuals would be ill-served by a limited DNA-based screening approach. The issues raised by signs, symptoms, and family history should be handled as part of appropriate clinical care by medical professionals.

A woman with a strong family history of breast cancer who undergoes a limited DNA-based screening approach, such as a few common pathogenic *BRCA1* and *BRCA2* variants, can provide an instructive example of the potential harms of substituting DNA-based screening for a diagnostic assessment. While this screening, if positive, may give sufficient diagnostic information and thereby end the DNA-based evaluation, if negative it could offer false reassurance and truncate a more complete evaluation. The more complete DNA-based diagnostic evaluation would potentially include a review of a larger panel of genes, more complete analysis of known variants including higher resolution copy-number analysis, detection of other known structural variants as well as strategies to address difficult to sequence regions (e.g., PMS2 for Lynch syndrome), a more comprehensive variant evaluation to include variants of uncertain clinical significance (VUS), or potential follow-up of VUS to include segregation studies within the family. The more complete clinical follow-up would potentially include familial breast cancer–based risk assessment and recommendations for risk-reducing clinical care in the absence of identifying a pathogenic DNA variant.

We acknowledge that the potential exists for a multistage evaluation process for a person in need of a diagnostic assessment. Wherein, a positive DNA-based screening result completes the genetic evaluation but a negative screening result triggers a second stage of testing and evaluation. However, an effective use of this type of multistaged approach has not been demonstrated.

Disease risks identified through screening should not include DNA VUS

Standards and guidelines for the interpretation of sequence variants were set forth by the ACMG and the Association for Molecular Pathology in 2015.[16] There are five categories of variant interpretation under this standard, and resulting of diagnostic tests typically returns three of those categories, namely pathogenic (P), likely pathogenic (LP), and VUS. The two remaining categories are benign (B) and likely benign (LB).

Table 2. Wilson and Jungner criteria in the context of DNA-based screening and population health.

	Wilson and Jungner criteria	Criteria in DNA-based screening and population health context
1	The condition sought should be an important health problem.	Screening should focus on the identification of genomic risk(s) for important health problems.
2	There should be an accepted treatment for patients with recognized disease.	Options for evidence-based clinical actions should be communicated to patients in whom the genomic risk is identified.
3	Facilities for diagnosis and treatment should be available.	Clinical implementation strategies should be in place and available to anyone identified as having genomic risk.
4	There should be a recognizable latent or early symptomatic stage.	Screening should have the capability of identifying at-risk individuals during both presymptomatic and early symptomatic disease stages.
5	There should be a suitable test or examination.	The DNA-based strategy should constitute an improvement over existing strategies for risk identification and risk reduction.
6	The test should be acceptable to the population.	Proven screening applications should be available to all but individual participation should be optional.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.	Anticipated penetrance and expressivity (i.e., natural history) should be understood based on data from comparable populations.
8	There should be an agreed policy on whom to treat as patients.	Consensus should exist on clinical classification and management for those patients who screen positive for genomic risk but in whom the evidence of the associated health problems is absent (i.e., nonpenetrant risk).
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	Appropriate health economic analyses should be in place to understand programmatic costs and benefits.
10	Case-finding should be a continuing process and not a "once and for all" project.	There should exist plans for both: - Periodic *reanalysis of DNA variants* using updated information. - Periodic *clinical re-evaluation* of individuals with nonpenetrant risk.

It is important to note that these interpretation categories are reflective of the state of the evidence within the field of clinical genomics at a given point in time. Programs involved in DNA-based screening need to operate with the expectation that within any established workflow, the list of reportable variants will change with time. For instance, at any specific point in time the discrete set of variants that prompt reporting to participants will likely differ from the set that will prompt reporting 12 months later due to the evolving evidence base. The evolving evidence sets up a need in every ongoing program to periodically review the data against an updated standard data set. This review could reveal that the interpretation for one of the participant's previously identified DNA variants has moved closer to or further from pathogenic. Workflows should be established within programs to proactively identify changes in variant categories. Follow-up reporting of any significant revision should be communicated to the patient and their provider so that appropriate clinical follow-up can be pursued.

In a DNA-based screening approach, only P and LP should be reported in order to drive risk-reducing clinical care.[16] There is some debate about whether LP should be included in screening because over time it may not reliably be reclassified to P. Recent analyses have demonstrated that a majority of LP reclassifications from ClinVar (2016 to 2019) were LP to P.[17] It is important however for organizations and providers engaged in DNA-based screening to understand the potential for reclassification of variants (upgraded or downgraded), and to address this in any screening approach by communicating this potential reclassification to individuals receiving disease risk information.[4]

There is, however, strong consensus that the category of VUS, which by definition is composed of those variants with insufficient information to interpret,[16] should be excluded from DNA-based screening results. VUS are one of the motivating factors in the need for periodic reanalysis of DNA variants using new information including population database updates and updates to variant classification recommendations (Table 2). With time many VUS will become interpretable and a small subset of those will potentially drive risk-reducing clinical care.

DNA-based screening should be linked to opportunities for evidence-based risk-reducing clinical care

The Wilson and Jungner criteria call for the availability of facilities for diagnosis and treatment following health screening.[3] In the context of DNA-based screening, clearly articulated clinical implementation strategies need to be in place and available to anyone identified as having genomic risk in this manner (see Table 2), since identification of DNA-based risk without opportunities for risk-reducing clinical care would result in missed opportunities to improve health.[18–20]

Risk-reducing clinical follow-up for DNA-based screening should be consistent with best practices outlined by professional societies with appropriate expertise

Clinical practice guidelines exist for the diagnosis and management of many genomic conditions, including HBOC, LS, and FH.[21–23] These guidelines are based on evidence from cases typically ascertained through diagnostic (Fig. 1a) rather than screening approaches (Fig. 1b, c). For cases ascertained through DNA-based screening, the existing diagnosis and management recommendations have clear value but may, with time, need to be modified for this mode of case ascertainment. As data regarding penetrance and expressivity from DNA-screened cohorts accrue, recommendations for the management of individuals with risk identified via screening may require a distinct set of guidelines due to the expected reduced penetrance. Clinical practice guidelines should be based

Table 3. Ten frequently cited gene–condition pairs for DNA-based screening and population health.

Gene(s)	Condition	ClinGen actionability score[32]	Major disease risk	Follow-up (secondary) test or procedure (per guidelines)	Goal of follow-up test or procedure	Estimated penetrance in screened populations	Estimated penetrance in cohorts ascertained based on personal and familial disease
BRCA1	Hereditary breast and ovarian cancer syndrome (HBOC)	8–10	Breast cancer	Breast imaging and prophylactic surgery	Identify existing disease at early stage	Not established	F: 46–87%[33] M: 1.2%[33]
			Ovarian cancer	Prophylactic surgery	Reduce cancer risk	Not established	F: 39–63%[33]
		ND	Prostate cancer	Routine screening	Identify existing disease at early stage	Not established	M: 8.6% (by 65 years old)[33]
BRCA2	Hereditary breast and ovarian cancer syndrome (HBOC)	8–10	Breast cancer	Breast imaging and prophylactic surgery	Identify existing disease at early stage	Not established	F: 38–84%[33] M: up to 8.9%[33]
			Ovarian cancer	Prophylactic surgery	Reduce cancer risk	Not established	F: 16.5–27%[33]
		ND	Prostate cancer	Routine screening	Identify existing disease at early stage	Not established	M: 15% (by 65 years old)[33] M: 20% (lifetime)[33]
MLH1 MSH2	Lynch syndrome (LS)	10	Colorectal cancer (CRC)	Colonoscopy	Identify precursor lesions and existing disease at early stage	Not established	F: 22–53%[34] M: 27–74%[34]
		8–9	Endometrial cancer	Surveillance and prophylactic surgery	Identify existing disease at early stage	Not established	F: 14–54%[34]
MSH6	Lynch syndrome (LS)	10	Colorectal cancer (CRC)	Colonoscopy	Identify precursor lesions and existing disease at early stage	Not established	F: 10%[34] M: 22%[34]
		8–9	Endometrial cancer	Surveillance and prophylactic surgery	Identify existing disease at early stage	Not established	F: 16–26%[34]
PMS2	Lynch syndrome (LS)	10	Colorectal cancer (CRC)	Colonoscopy	Identify precursor lesions and existing disease at early stage	Not established	F: 15%[34] M: 20%[34]
		8–9	Endometrial cancer	Surveillance and prophylactic surgery	Identify existing disease at early stage	Not established	F: 15%[34]
EPCAM	Lynch syndrome (LS)	10	Colorectal cancer (CRC)	Colonoscopy	Identify precursor lesions and existing disease at early stage	Not established	Not established
		8–9	Endometrial cancer	Surveillance and prophylactic surgery	Identify existing disease at early stage	Not established	Not established
LDLR	Familial hypercholesterolemia (FH)	11	Coronary artery disease (CAD)	Serum LDL cholesterol	Guide therapeutic interventions	Not established	Not established
			Stroke	Serum LDL cholesterol	Guide therapeutic interventions	Not established	Not established
APOB	Familial hypercholesterolemia (FH)	11	Coronary artery disease (CAD)	Serum LDL cholesterol	Guide therapeutic interventions	Not established	Not established
			Stroke	Serum LDL cholesterol	Guide therapeutic interventions	Not established	Not established
PCSK9	Familial hypercholesterolemia (FH)	11	Coronary artery disease (CAD)	Serum LDL cholesterol	Guide therapeutic interventions	Not established	Not established
			Stroke	Serum LDL cholesterol	Guide therapeutic interventions	Not established	Not established

on best available evidence at the time of testing. Registries that standardize and aggregate data could foster evidence-based updates to management recommendations.

Organizations and providers offering DNA-based screening need to implement or facilitate the implementation of existing guidelines for the individuals who screen positive for risk variants and evaluate both health and implementation outcomes to foster continuous quality improvement.

Organizations involved in DNA-based screening should share the outcomes-related data

If the goal of improving population health through DNA-based screening is to be achieved, then the aggregation of outcomes data from many screened individuals is essential.[24] All organizations, both public and private, should share de-identified outcomes data, including P and LP variants and their frequencies, health outcomes of risk-reducing clinical care, and clinical outcomes related to penetrance and expressivity. To aid in the aggregation and analysis of outcomes, definitions should be harmonized and broadly disseminated.[25,26] Since these efforts are aimed at contributing to the greater good, outcome sharing should not be limited to health-care organizations. Shared databases optimized for screening may need to be created. Currently, deposition of data in public databases (such as ClinVar) and peer-reviewed publication are among the existing avenues that can be used for sharing aimed at improving efforts to prevent disease.

DNA-based screening applications with proven beneficial clinical outcomes should be made available to entire populations to promote health-care equity and limit health disparities

There are persistent racial, ethnic, and socioeconomic disparities in health care and health status.[27] The concern has been raised that genomic testing has the potential to increase health disparities.[28] The National Academy of Medicine sponsored a 2018 workshop that focused on understanding inequities in access to genomic medicine including social and language barriers, training of health-care providers, the limited genomics workforce, patient awareness, and privacy and potential discrimination related to insurance coverage.[29]

Given that inequities and disparities exist, and genomic medicine may exacerbate these differences, the ACMG supports efforts to make DNA-based screening applications that are shown to improve population health available to everyone. Namely, once a use-case is demonstrated to improve population health through DNA-based risk identification combined with risk-reducing clinical care, it should be made readily available to everyone based on appropriate data.[30] The routine population-wide offering of newborn screening (NBS) through collaborations between state departments of public health and health-care delivery systems demonstrates the type of collaborative efforts that can achieve this goal.

In the near term, organizations that are carrying out DNA-based screening should seek inclusiveness across racial, ethnic, and socioeconomic groups, so that evidence for improved health outcomes, as well as an infrastructure that supports population-wide screening applications, are being built in parallel.

CONCLUSION

If DNA-based screening is to improve population health, then it must be combined with effective risk-reducing clinical care. This will be a continual process, or as Wilson and Jungner framed it, not a "once and for all" project (Table 2). Evolving management guidelines that are implemented will require (1) periodic reanalysis of DNA variants informed by updated databases (e.g., ClinVar), (2) periodic clinical re-evaluation of disease status in at-risk individuals, and (3) periodic assessment of the effectiveness of strategies that support implementation of DNA-based screening and subsequent clinical management.

This points to consider document has focused on DNA-based screening and population health related to a limited number of common and well-studied monogenic conditions. Additional potential screening use-cases include pharmacogenomics, polygenic risk scores (PRS), and additional monogenic conditions. Depending upon the DNA data sets generated from DNA-based screening and the goals of the organizations involved, there is the potential to carry out multiple types of screens either simultaneously or in tandem.

The use of DNA variant identification as the screening tool to guide the decision of who should be offered enhanced risk-reducing clinical care is a new application of a longstanding practice in health care. The interest in this new application for DNA-based screening is high, and the evidence gaps are large.[31] There are many longstanding examples of evidence-based health screening (Supplemental Table S1) that provide useful examples for those seeking to initiate new screening efforts.

The ACMG continues to encourage further ascertainment of genotype–phenotype correlations and research to establish the effectiveness of risk-reducing interventions in asymptomatic patients with P and LP variants in known associated genes.[7] Collaborative research will be needed to create an adequate evidence base to support DNA-based screening to improve population health.[31] Additionally, public health systems and health-care organizations will need to be ready for dissemination and implementation of population-based DNA screening.

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REFERENCES

1. Wald, N. J. The definition of screening. *J. Med. Screen.* **8**, 1 (2001).
2. Gilbert, W. DNA sequencing, today and tomorrow. *Hosp. Pract. (Off. Ed.)* **26**, 165–169, 172, 174 (1991).
3. Wilson, J. M. & Jungner, Y. G. Principles and practice of mass screening for disease. *Bol. Oficina Sanit. Panam.* **65**, 281–393 (1968).
4. Bean, L. et al. DNA-based screening and personal health: a points to consider statement for individuals and healthcare providers from the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* (in press).
5. Green, R. C. et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet. Med.* **15**, 565–574 (2013).
6. Kalia, S. S. et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet. Med.* **19**, 249–255 (2017).
7. ACMG Board of Directors. The use of ACMG secondary findings recommendations for general population screening: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* **21**, 1467–1468 (2019).
8. Khoury, M. J. et al. A collaborative translational research framework for evaluating and implementing the appropriate use of human genome sequencing to improve health. *PLoS Med.* **15**, e1002631 (2018).
9. McClain, M. R., Palomaki, G. E., Nathanson, K. L. & Haddow, J. E. Adjusting the estimated proportion of breast cancer cases associated with BRCA1 and BRCA2 mutations: public health implications. *Genet. Med.* **7**, 28–33 (2005).
10. Murray, M. F. Your DNA is not your diagnosis: getting diagnoses right following secondary genomic findings. *Genet. Med.* **18**, 765–767 (2016).
11. Biesecker, L. G., Nussbaum, R. L. & Rehm, H. L. Distinguishing variant pathogenicity from genetic diagnosis: how to know whether a variant causes a condition. *JAMA.* **320**, 1929–1930 (2018).
12. Schwartz, M. L. B. et al. A model for genome-first care: returning secondary genomic findings to participants and their healthcare providers in a large research cohort. *Am. J. Hum. Genet.* **103**, 328–337 (2018).
13. Levy, H. & Farrell, P. M. New challenges in the diagnosis and management of cystic fibrosis. *J. Pediatr.* **166**, 1337–1341 (2015).

14. Hunter, J. E. et al. A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation. *Genet. Med.* **18**, 1258–1268 (2016).
15. Hagenkord, J. et al. Design and reporting considerations for genetic screening tests. *J. Mol. Diagn.* **22**, 599–609 (2020).
16. Richards, S. et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* **17**, 405–424 (2015).
17. Harrison, S. M. & Rehm, H. L. Is 'likely pathogenic' really 90% likely? Reclassification data in ClinVar. *Genome Med.* **11**, 72 (2019).
18. Vrečar, I., Hristovski, D. & Peterlin, B. Telegenetics: an update on availability and use of telemedicine in clinical genetics service. *J. Med. Syst.* **41**, 21 (2017).
19. Penon-Portmann, M., Chang, J., Cheng, M. & Shieh, J. T. Genetics workforce: distribution of genetics services and challenges to health care in California. *Genet. Med.* **22**, 227–231 (2020).
20. Institute of Medicine (US) Roundtable on Translating Genomic-Based Research for Health. *The Value of Genetic and Genomic Technologies: Workshop Summary*. (National Academies Press, Washington, DC, 2010).
21. National Comprehensive Cancer Network. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf (2020).
22. National Comprehensive Cancer Network. Genetic/familial high-risk assessment: colorectal. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf (2020).
23. Goldberg, A. C. et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J. Clin. Lipidol.* **5** (3 Suppl), S1–S8 (2011).
24. ACMG Board of Directors. Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics. *Genet. Med.* **19**, 721–722 (2017).
25. Peterson, J. F., Roden, D. M., Orlando, L. A., Ramirez, A. H., Mensah, G. A. & Williams, M. S. Building evidence and measuring clinical outcomes for genomic medicine. *Lancet.* **394**, 604–610 (2019).
26. Williams, J. L. et al. Harmonizing outcomes for genomic medicine: comparison of eMERGE outcomes to ClinGen outcome/intervention pairs. *Healthcare (Basel)* **6**, 83 (2018).
27. Meyer, P. A., Penman-Aguilar, A., Campbell, V. A., Graffunder, C., O'Connor, A. E. & Yoon, P. W., Centers for Disease Control and Prevention (CDC). Conclusion and future directions: CDC Health Disparities and Inequalities Report – United States, 2013. *MMWR Suppl.* **62**, 184–186 (2013).
28. West, K. M., Blacksher, E. & Burke, W. Genomics, health disparities, and missed opportunities for the nation's research agenda. *JAMA.* **317**, 1831–1832 (2017).
29. National Academies of Sciences, Engineering, and Medicine. *Understanding Disparities in Access to Genomic Medicine: Proceedings of a Workshop*. (The National Academies Press, Washington, DC, 2018).
30. Manrai, A. K. et al. Genetic misdiagnoses and the potential for health disparities. *N. Engl. J. Med.* **375**, 655–665 (2016).
31. Murray, M. F., Evans, J. P. & Khoury, M. J. DNA-based population screening: potential suitability and important knowledge gaps. *JAMA.* **323**, 307–308 (2020).
32. Hunter, J. E. et al. A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation. *Genet. Med.* **18**, 1258–1268 (2016).
33. Petrucelli, N., Daly, M. B. & Pal, T. in *GeneReviews* (eds Adam, M. P. et al.) BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. (University of Washington, Seattle, 2016).
34. Kohlmann, W. & Gruber, S. B. in *GeneReviews* (eds Adam, M. P. et al.) Lynch syndrome. (University of Washington, Seattle, 2018).

COMPETING INTERESTS

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SUPPLEMENTAL TABLE

TABLE S1. Established Examples of Population Screens in Health Care

	Primary Screening Measure	Goal of Screening	Target Population	Disease Risk Identified	Secondary Testing Measure	Intervention	DPH Based Engagement
Non-DNA based screening	Phenylalanine quantitation	Prevent Acquired Intellectual Disability	All newborns first day of life	Phenylketonuria (PKU)	Repeat or DNA	Dietary Management (modification of dietary proteins)	yes
	Immunoreactive trypsinogen quantitation (IRT)	Identify cystic fibrosis (CF)	All newborns first day of life	CF	Repeat IRT or sweat chloride or DNA	Proactive detection of clinical signs and symptoms followed by diagnostic and therapeutic interventions	yes
	Blood Pressure measurement	Identify Hypertension and prevent CAD and Stroke	All	CAD Stroke	Confirm elevated BP over multiple checks	Lifestyle changes and Pharmacologic Agents	no
	Periodic Colonoscopy	Identifies precursor lesions and existing disease at early stage	All adults over 50	Colorectal Cancer	Pathology	Biopsy	no
	Periodic Mammogram	Identifies existing disease at early stage	All women over 50 years	Breast Cancer	Pathology	Biopsy	no

Incidental finding in DNA-based screening	*CFTR* variant panel	Identification of *CFTR* heterozygotes	Prospective parents	Cystic Fibrosis in individuals with two incidental *CFTR* pathogenic variants	Sweat chloride	Proactive detection of clinical signs and symptoms followed by diagnostic and therapeutic interventions	no

DPH = state departments of public health