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ACMG STATEMENT

DNA-based screening and personal health: a points to consider statement for individuals and health-care providers 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

This points to consider (PTC) explores the opportunities and challenges presented by exome and genome sequencing (ES/GS) for apparently healthy individuals to inform a genetic predisposition to a disease or disorder. Although the use of DNA-based assays such as ES/GS has become well established in clinical care,[1] the potential to inform diagnosis, prognosis, treatment, and prevention of disease in the absence of a clinical indication is an active area of study but remains unproven.[1–4] Clinical practice, research studies, and consumer-directed commercial offerings allow greater availability to ES/GS data than ever before, although with noted differences in uptake based on demographic factors.[5,6] It is important to consider how this emerging shift toward greater availability of ES/GS testing will change genomic medicine.

The American College of Medical Genetics and Genomics (ACMG) has generated this PTC document to guide individuals and health-care providers who are considering undertaking DNA-based health screening. Those leading programs and sponsoring organizations who are providing DNA-based screening are encouraged to review the ACMG document on DNA-based screening and population health for addition points to consider.[7]

The ACMG seeks to promote the most effective use of genetic and genomic information by offering this PTC document that may help guide discussions about potential benefits, potential harms, and limitations of ES/GS for healthy adults through each essential step in the testing process. Current models for delivery of genetic testing services include a traditional genetic health-care model of coordinated services between genetics health-care providers and a patient's referring primary care provider and a nontraditional genetic health-care model where genetic services are integrated within primary care and other specialties.[8] We have also considered another model, an emerging consumer-directed genetic health-care model in which consumers initiate the genomic medicine process on their own without direction from a health-care provider. A framework for the delivery of molecular genetic tests according to the preanalytical, analytical, and postanalytical phases of the genetic testing process has been described.[9] While the actions performed for each step involved in delivery of genetic testing services will vary, in general, all steps should occur for any clinical scenario. Therefore, we will consider opportunities and challenges for each step in the testing process for each health-care model as well as forward-looking strategies to address them. Of particular focus is the likely shift to the emerging approach of consumers seeking ES/GS on their

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own (the consumer-directed model). For each step in the testing process, the accompanying text provides brief considerations as background (usually describing the current state) and strategies for maintaining clinical standards while moving to a wider variety of genetic health-care models.

DEFINITIONS

Exome and genome sequencing (ES/GS) refers to the methodologies currently used to carry out large-scale DNA sequencing: either the coding region (exome) following a capture procedure or all genome sequence. Other commonly used terms include whole exome sequencing (WES), whole genome sequencing (WGS), and genomic sequencing.

An ES/GS screening test, as opposed to a diagnostic test, refers to the use of ES/GS as a clinical test to assess genotypes that identify individuals at risk for:

- Recessive or X-linked carrier status,
- Dominant or recessive Mendelian disease with variable penetrance or later onset,
- Pharmacogenomic drug response,
- Polygenic risk score for susceptibility to multifactorial disease.

In this document, a clinical ES/GS screening test will refer to the ES/GS test performed for an individual in whom ES/GS is not clinically indicated by currently accepted standards, but the results are intended to inform medical decision-making. This testing paradigm has also been referred to as "elective ES/GS testing."[10] A clinical ES/GS test will refer to the assay itself performed in a CLIA-certified laboratory. In this context, the term "screening" is being applied to indicate that the test is not being done for a specific symptomatic presentation or for a specific indication, but is being done to determine risk for future medical use.

An ES/GS screening test may be motivated by many factors such as curiosity, personal or family history of a genetic disorder that does not meet guidelines for diagnostic testing, concern of not knowing family history, or desire to know future health or reproductive risks. We also recognize the ambiguity associated with an attempt to distinguish a screening test from an indication-based diagnostic test, when both may be used to direct clinical care.

The models for delivery of genetic health care, including genetic testing, include:

- A traditional genetic health-care model: coordinated services between geneticists and other physicians.[8]
- A nontraditional genetic health-care model: genetic testing is ordered and managed within primary care and other specialties.[8]
- An emerging consumer-directed genetic health-care model: consumers access genetic services on their own without direction from their personal health-care provider. This model may utilize physicians employed by the testing service to order the testing, but who do not take long-term responsibility for medical management of the consumer.

SCOPE

This document focuses on the emerging state of clinical ES/GS screening tests performed on apparently healthy individuals to inform individualized options for early disease detection, disease prevention, targeted treatments, and reproductive decisions. Variants associated with nutritional status, ancestry, or other non–medically relevant phenotype traits and ancestry will not be discussed. Other technologies such as chromosomal microarray or G-banded chromosome analysis, as well as more limited sequencing assays such as gene panels, will not be discussed. However, if such analyses were requested as a screening test, then the same basic concepts would apply. There are additional clinical and ethical considerations in the potential use of clinical ES/GS screening in minors, particularly for adult-onset conditions. This PTC will pertain to ES/GS in the healthy adult.

ASSUMPTIONS

To explore the future of ES/GS screening tests, certain assumptions were made:

- The demand for ES/GS screening tests by consumers will continue to increase.
- Regulatory agencies will not prohibit consumer-directed genetic health care, enabling expansion of ES/GS screening test availability.
- Laboratories performing ES/GS screening tests will all be held to the same standards regardless of which genetic health-care model is accessed.
- The cost of the ES/GS screening test will be paid by the patient/consumer or for the patient/consumer by another entity such as their health insurer or employer, regardless of how the test is ordered.

For each of the genetic health-care models, we describe the potential challenges and opportunities of ES/GS screening related to the preanalytical phase (Table 1), the analytical phase (Table 2), and the postanalytical phase (Table 3). Below we summarize these challenges and opportunities and also provide some strategies that could address those challenges and leverage opportunities.

PREANALYTICAL PHASE (TABLE 1)

Preanalytical step 1: education/knowledge transfer

Opportunities and challenges. Under the traditional model, genetics professionals, knowledgeable about genetic principles underlying disease and health, are able to identify the optimum strategy for establishing a genetic diagnosis or genetic contribution to disease, which typically includes a comprehensive review of an individual's medical history and family history with pedigree analysis to assess possible modes of inheritance. They also provide genetic counseling and patient education techniques to appreciate and integrate an individual's genetic literacy, beliefs, and preferences. However, the time required for a typical clinical encounter under the traditional genetic health-care model is not scalable, given the limited number of genetics health-care providers. Under the nontraditional model, while primary care providers and other specialists may have less expertise in genetics,[11–13] they may be more readily available to provide ES/GS screening tests than genetics providers. Additionally, they are likely to be familiar with the health status, preferences, and medical literacy of a patient, and are trained to deal with complex medical issues and seek expert genetics consultation, as needed. In a consumer-directed health-care model, consumers can seek out information and resources that suit their perceived needs at a convenient time and without having to participate in a clinical encounter. The capacity for a consumer to seek out information about an ES/GS screening test is limited only by their own time, interest, and the availability of reliable and understandable information from consumer-directed testing entities. Each genetic health-care model must appreciate the wide range of medical and technical literacy of consumers and patients.[5,6] Genetics professionals and other health-care providers are trained to educate and transfer knowledge to patients in an individualized medical context, whereas the consumer-directed model relies on the consumer to navigate through the available information and identify what is most relevant for them.

Strategies. Greater availability of ES/GS screening tests will necessitate the development of effective educational materials

Table 1. Preanalytical challenges and opportunities in genomic screening of apparently healthy individuals.

Essential Steps	Traditional genetic healthcare[a]	Non-traditional genetic healthcare[b]	Consumer-directed genetic healthcare[c]
1. Education/ Knowledge transfer	**Opportunity:** Highly trained genetics professionals prepared to deal with all aspects of genetic testing and healthcare.	**Opportunity:** Primary care or other clinicians provide familiarity with patient in a medical home.	**Opportunities:** Consumer-friendly, attractive, convenient information and resources. Rapid adjustments to educational materials based on consumer feedback.
	Shared Opportunity: Genetics professionals and other healthcare providers are trained to educate and transfer knowledge to patients in a medical context. A healthcare professional has the training to recognize a personal or familial risk of a genetic disorder and discuss and/or recommend diagnostic genetics testing.		
	Challenge: Insufficient number of genetics healthcare providers	**Challenge:** Tools that aid in test interpretation and teach genetic/genomic principles are limited.	**Challenge:** Trustworthy sources of accurate information difficult to identify
	Shared Challenge: Time required for education and knowledge transfer limited by time allowed for medical appointment.		
2. Consent for genomic screening	**Opportunity:** Genetics professionals are knowledgeable about elements of informed consent relevant to genetic tests	**Opportunities:** Patient can consent for genetic testing in context of an established relationship with their healthcare provider. Patient-centered community practice already familiar with cultural, socioeconomic, and other influences.	**Opportunities:** Resources devoted to consumer-friendly, easy to access consent process (i.e., videos, on-line chat, attractive materials, choices for paper or computer-based forms) Cultural, socioeconomic, or other influences may be less likely to restrict free choice if testing is not desired after education/knowledge transfer
	Shared Opportunity: Consent occurring in a medical setting with established procedures, requirements, and oversight.		
	Challenge: Genetics professionals not familiar with consumer's preferences, cultural norms, etc.	**Challenge:** Provider may have limited knowledge about informed consent issues related to genetic testing.	**Challenges:** The informed consent may not be individualized to the consumer's health issues; limited ability to dialogue about benefits, harms, limitations.
3. Understanding sample and data ownership models and uses	**Opportunities:** Providers work within fields/institutions with focus on Health Insurance Portability and Accountability Act (HIPAA) requirements and compliance. Healthcare institutions have existing frameworks for research that meet state and federal regulations. Tools and platforms to support sharing of data and results federally coordinated.		**Opportunity:** Pressure to align policies with consumer preferences for data control and availability.
	Shared Challenge: Healthcare institutions may be slow to adopt progressive data sharing policies.		**Challenges:** Data security protocols likely to vary and may be breached. Need to develop methods to facilitate sharing with clinical databases (e.g., ClinVar). Selling of data is a business model – not driven by needs of patient.
		Shared Challenge: Provider or consumer may be unfamiliar with risks of data exposure	
	Shared Challenges: Ability to control downstream uses of data or samples may be limited or obscure. Data sharing policies of laboratories of other data-holders may not be clear/disclosed or may change with time.		
4. Selection of laboratory performing test	**Opportunity:** Genetics professionals knowledgeable about and familiar with laboratories offering ES/GS testing	**Opportunity:** Provider knowledgeable about and familiar with clinical laboratories and clinical testing.	**Opportunity:** Consumer engaged in the process of lab selection and establishes direct relationship with laboratory.
	Shared Opportunity: If testing is widely offered and/or advertised, regulators will hold laboratories to, at minimum, CLIA standards, as well as potentially professional standards.		
		Challenge: Non-genetics physicians may not have background to understand the laboratory methods used and their limitations.	**Challenges:** Consumer limited by how many laboratories they can investigate. Consumer may be unaware of relative importance of laboratory qualities (i.e., regulatory licensure vs. attractiveness of marketing materials).
	Shared Challenge: Provider may be swayed by cost vs. result quality.		

that teach genetic/genomic principles and aid in test interpretation aimed at a variety of education levels. These educational materials will be of particular importance for both the nontraditional health-care model and the consumer-directed model. The nontraditional model can benefit from decision support tools in the electronic health record that assist the nongeneticist clinician in obtaining consent and performing genetic risk assessment, identifying indications for genetic testing, interpreting test results,

Table 2. Analytical challenges and opportunities in genomic screening of apparently healthy individuals.

Essential Steps	Traditional genetic healthcare[a]	Non-traditional genetic healthcare[b]	Consumer-directed genetic healthcare[c]
1. Testing performed	**Shared Opportunities:** Clinical laboratories adhering to professional standards perform testing; Increased volume of tests ordered allow economies of scale for the laboratory; Additional large datasets can be generated and shared to inform variant interpretation		
	Shared Challenges: Clinical sensitivity is reduced by technical limitations of ES/GS. The interpretation of variants will change with time. Methodologies and standards for interpretation will vary between laboratories and are likely to change with time. Current standards and regulatory requirement for storing and sharing large data sets are inadequate. Cost of meeting regulatory demands and producing quality results must be balanced against competitive pricing and market forces.		

Table 3. Postanalytical challenges and opportunities in genomic screening of apparently healthy individuals.

Essential Steps	Traditional genetic healthcare[a]	Non-traditional genetic healthcare[b]	Consumer-directed genetic healthcare[c]
1. Laboratory reporting	**Shared Opportunity:** Healthcare providers have a well-established mechanism to receive laboratory report and are accustomed to formats and standards for communication of genetic test results. Test information may be incorporated into the patient's medical record.		**Opportunity:** Consumers will drive accessible, understandable laboratory reporting with the potential for feedback for educational and consent materials. Report format could be non-traditional (i.e., videos, on-line chat, computer-based).
	Challenge: Limited genetics resources may be stretched by patients who want to discuss test results	**Challenge:** Non-geneticist providers may have difficulty understanding genetic test reports.	**Challenge:** The average consumer may have difficulty understanding uncertainties in the result.
	Shared Challenge: There are no guidelines for reporting variants not associated with a current condition or family history-based risk. Methodology, advantages and limitations must be described by the laboratory at different levels depending on the healthcare model.		
2. Understanding current result(s) interpretation	**Opportunities:** Genetics professionals knowledgeable about and trained to explain complexities of genetic test results; Genetics professional may use test result to refine and expand personal/family history.	**Opportunities:** Provider has or establishes relationship with patient Provider is aware of patient's health concerns.	**Opportunities:** Consumer receives report at home and can review without time constraint. Consumer has unlimited time to review information returned.
	Challenge: Lack of information about penetrance.		
		Shared Challenge: Lack of familiarity/understanding of genetic test result may lead to over- or under-interpretation.	
3. Result(s) specific medical evaluation, follow-up, and on-going care	**Opportunity:** Genetics professionals trained to assess phenotype associated with genetic disorders	**Opportunity:** A provider in a medical home more familiar with health issues in patient and family	**Opportunity:** Consumer tested outside of healthcare system may be motivated to seek medical attention to discuss risk and next steps
	Shared Opportunity: Provider can coordinate diagnostic evaluation Unanticipated findings provide opportunity to revisit family history, initiate surveillance, and determined need for indication-based testing as new phenotypes arise.		
	Shared Opportunities: Opportunities to incorporate results (e.g., PGx results) into future treatment plans. Opportunity to incorporate carrier status into future reproductive planning.		
	Challenge: Follow up studies may be difficult to coordinate if genetics professional not affiliated with patient's/consumer's medical home/health care system	**Challenge:** Clinician may not attend to rare conditions or conditions outside their knowledge areas.	**Challenges:** Consumer must be able to recognize the medical importance of findings from genetic testing Consumer may lack access to medical provider who can offer context, integrate with family history and examination
		Shared Challenge: May over utilize diagnostic tests in follow up to ES/GS test results	
	Shared Challenge: Patients bringing a test result generated through a consumer-directed testing into the healthcare system need to be assessed for efficacy and understanding of PRE-TESTING steps.		**Challenge:** Consumer understanding dependent upon efficacy of education and consent process.
	Shared Challenge: Patient/consumer will receive a large amount of complex information which must be understood, digested and internalized.		

and making management recommendations.[14–16] Genetics health-care professionals will be instrumental in developing these novel tools to efficiently and effectively communicate information and educate patients. Access to such experts via telemedicine could further reduce resource gaps.[17]

Preanalytical step 2: consent for genomic testing

Opportunities and challenges. Professional organizations have consistently endorsed an informed consent process prior to germline genetic testing to review the potential benefits, harms, and limitations of testing, including the implications of results for the patient and their family member.[18,19] Generally accepted and expected elements of informed consent for germline genetic testing include ensuring an understanding of:

- Indications and limitations of the testing.
- Possible outcomes of the testing.
- Implications of results for the tested individual and their relatives (e.g., potential benefits and risks).
- Ethical considerations (e.g., testing children).
- How to access genetic resources when needed (e.g., medical geneticist, genetic counselor, advocacy organizations).

Individuals undergoing genomic testing report benefit from pretest counseling.[20] Irrespective of the mode of care in which ES/GS screening tests are performed, the essential elements of informed consent must be accomplished. However, informed consent for an ES/GS screening test might be best accomplished with a member of the individual's primary care team, who is knowledgeable about their medical problems, beliefs, and preferences. Under the consumer-directed model, informed consent processes may be less standardized and comprehensive,[21] which raises concerns for the consent process, especially among vulnerable populations.

The potential harms associated with the ES/GS screening test are different from those associated with diagnostic testing, and the consent process must address these special concerns (Table 2). For diagnostic testing, personal and family history is collected before genetic testing is offered to inform the indication and appropriateness of testing, differential diagnosis, mode of inheritance, and testing strategy. Under any of the health-care models, whoever is ordering the ES/GS screening test should ensure the patient/consumer gains sufficient understanding of the potential benefits and harms to make an informed decision about pursuing the testing. Ideally, with an ES/GS screening test, the complexities of potential test results that should be understood include:

- The potential positive and negative impact of ES/GS screening test results and their implications for family members.
- Awareness that the laws protecting genetic privacy and nondiscrimination are not comprehensive, and that those that do exist have not been fully tested; some groups may not be protected by existing laws.
- Lifetime disease risks are often not known, including penetrance and variable expressivity of a pathogenic variant.
- A false negative result: A person may be at risk for a health problem not identified by the ES/GS test due to technical (a pathogenic variant is present but not detected) or interpretive error (a pathogenic variant is interpreted as benign) or because not all gene–disease associations are known.
- A false positive result: A person may not be at risk for a health problem suggested by the ES/GS screening test results due to technical (a reported pathogenic variant is not actually present) or interpretive error (a benign variant is interpreted as pathogenic).
- Evolving interpretation: The results of a genetic test may indicate risk for disease; however, the clinical significance of variants, gene–disease associations, penetrance of pathogenic variants, and opportunities for clinical interventions can change with time.
- Evidence to support clinical actions based on ES/GS findings may not be available.
- Results may indicate a need for a medical evaluation, preventive services, or ongoing surveillance; however, access to health care may be limited or restricted due to out-of-pocket costs or lack of insurance.
- Options for the type of genetic test result to be reported such as carrier status for recessive conditions, adult-onset medically actionable or nonactionable findings, pharmacogenomics results.

Importantly, patients or consumers seeking an ES/GS screening test may self-select due to an enriched family history or subtle phenotypes such that they should be pursuing an indication-based test or population-targeted test, but instead pursue a screening non-indication-based test.[22,23] Therefore, it is vital for any consent process to ensure that screening questions for medical and family history that could indicate the need for diagnostic testing pursued through a health-care provider have been asked, either previously or as part of the pretest counseling. Additionally, the informed consent process should review data ownership and secondary uses of the ES/GS screening tests (see preanalytical step 3).

Strategies. Programs such as JScreen, a national Jewish genetic disease screening program,[24] All of Us,[25] and the ClinGen Consent and Disclosure Recommendations (CADRe) Workgroup[26] use materials developed by genetics experts to allow self-education by individuals interested in genetic testing that support informed consent. The JScreen program includes assessment of understanding as part of the consent process with follow-up (phone call or mailed report) dependent on result and mastery of the material. The All of Us consent process uses a series of short videos to explain each part of the process. Online decision aid tools developed for research or clinical use have been described[27] and could be used in an ES/GS screening test consent process in any of the genetic health-care models, but may be ideal for the consumer-driven model. It would be best to have input from genetics experts to help guide the informed consent process under the nontraditional and consumer-directed health-care models. Regulators will need to determine what constitutes adequate informed consent in the consumer-directed model and how these standards compare with the requirements of the health-care models.

Preanalytical step 3: discussion of data ownership and secondary uses

Opportunities and challenges. Data and residual specimens from ES/GS screening tests may be used for many purposes beyond their intended use, including gathering data for variant interpretation, identification of risk alleles, drug development, and discovery; therefore, these data have collective value. Third parties (employers, health-care systems, researchers, commercial entities) may be interested in these data for reasons such as aggregate analysis of population characteristics, development of marketable products, and sale or sharing of the data. Current practice has moved toward individuals having a right to access their medical records[28] and their personal data, including genomic data from research participation.[29,30] Many research projects require that genomic results be returned to participants when requested, including the All of Us program; however, protocols for returning such complex data to a diverse group of people with varying technical literacy have not been established.[5,6]

Strategies. Expansion of ES/GS screening tests performed under any model will be governed by HIPAA and CLIA requirements and will require regulatory oversight for ownership, storage, and use of

the data beyond their intended clinical purpose. Therefore, data storage approaches that are affordable, accessible, interoperable, and secure must be developed.

Preanalytical step 4: selection of laboratory performing test

Opportunities and challenges. Laboratories currently performing an ES/GS test that is intended to be returned to patients/consumers for any clinical purposes must hold a CLIA license. Commercialization of ES/GS screening tests may move testing away from genetic testing laboratories that perform clinical diagnostic testing under the traditional and nontraditional genetic health-care models to laboratories that cater to consumer-directed testing. Some payers may limit coverage to laboratories that share their data as a means of ensuring ongoing test result interpretation. Laboratories may freely share their data with various resources used by genetics professionals (e.g., ClinVar, GeneMatcher) or receive reimbursement for sharing data with a third party. Educational and consent materials for health-care providers and consumers will be different; therefore, a laboratory may need to provide different services depending on the health-care model. Factors influencing laboratory choice and ability to evaluate laboratory quality will likely vary among health-care models (Table 1). ES/GS testing becoming a primarily cost-driven commodity is a concern since the focus would be shifted away from patient care.

Strategies. Regulatory requirements for disclosure of a standard set of metrics that could include information on licensure held, laboratory leadership, professional guidelines followed, qualifications of staff, billing and cost structure, as well as clear disclosure as to whether the test is intended to be used for medical purposes, as opposed to recreational purposes, would allow transparent comparison among laboratories. Additionally, laboratories may need to meet new requirements for education and consent to offer consumer-directed testing. The extent to which the laboratory is responsible for the patient's/consumer's understanding of the ES/GS screening test purpose and results needs to be established.

ANALYTICAL PHASE (TABLE 2)

Analytical step 1: testing performed

Opportunities and challenges. Genomic data intended to be disclosed for medical purposes must be generated in CLIA-licensed laboratories. Critical information about the test performed, such as details about the methodology used, scope of testing performed, and limitations at the time of testing should be available for both pre- and post-test review. Optimal interpretations of ES/GS results are based on evaluations by board-certified individuals with appropriate training in medical genetics to interpret genomic data.[31] All testing should be performed in accordance with relevant regulatory requirements and professional standards. Therefore, unlike other steps in the testing process, the opportunities and challenges are the same for each of the genetic health-care models. Laboratories following current regulatory requirements confirm that testing is ordered by a qualified health-care provider. As a consumer-directed market for ES/GS testing emerges, changes in regulatory requirements to accommodate this model will be needed.

Analytical sensitivity of ES/GS testing is high, but also uneven across the genome with some areas of clinical relevance more difficult to sequence than others.[32] Some types of abnormalities are less likely or not able to be detected by ES/GS than by other technologies, such as copy-number variants, tandem repeats, and methylation status.[32] Genetics professionals working under the traditional genetic health-care model are educated about these issues and aware of the limitations of ES/GS. However, these limitations of ES/GS are not familiar to the typical health-care provider or consumer,[12,13] which could contribute to misinterpretation of results and could widen the disparities gap further.

Strategies. Technologies for sequencing difficult regions or detecting copy-number variants will continue to improve. Given that many interpretive and technical limitations will be overcome with time, recommendations for when to reinterpret data and when to repeat testing are needed. Standards and regulatory requirements for storing and sharing of large data sets will need to be updated or established as well.

POSTANALYTICAL PHASE (TABLE 3)

Postanalytical step 1: laboratory reporting

Opportunities and challenges. Professional standards for variant interpretation[33] and use of standard nomenclature,[34] as well as a suggested framework for assessing the validity of gene–disease association[35] and guidance for use of evidence level in diagnostic gene panels,[32] have been developed. However, the focus of these standards has been primarily on diagnostic testing for single-gene disorders. There are currently no standards for defining, developing, or reporting polygenic risk scores or relative risk for variants with non-Mendelian inheritance.[36] Current standards specify that variant classification and interpretation, such as diagnostic or likely carrier status, be clearly stated on the report.

Therefore, reporting of an ES/GS screening test in a healthy individual by current standards could include:

- Predictive (e.g., *BRCA1*) or carrier result (e.g., *CFTR*): pathogenic and likely pathogenic variants in genes associated with disease that meet a high standard of evidence of association with disease (e.g., definitive or strong evidence level by the ClinGen classification system are most appropriate for an ES/GS screening test). Note that rare or novel variants not predicted to result in loss of function (e.g., missense variants) identified in an apparently asymptomatic individual are likely to be classified as variants of uncertain significance (VUS), which would not usually be reportable for a screening test.
- Pharmacogenomic (PGx) result: to maximize clinical utility, variants need to be combined into haplotypes and reported using the star (*) allele designations and implications for health care including drug choice and/or dosage (https://cpicpgx.org/).
- Risk alleles: there are currently no reporting standards.

Variants most commonly associated with a condition have well-established pathogenicity claims and interpretation in the ES/GS test setting is straightforward. However, it is possible that a novel, predicted loss-of-function variant in a gene with a known loss-of-function disease mechanism could be interpreted as pathogenic or likely pathogenic by ACMG/AMP criteria, when in fact the variant is not disease causing. It is essential that clinicians and individuals understand the probabilistic nature of genetic testing in the absence of a clinical indication.

Gene-level evidence is also a concern for ES/GS screening tests. Genes tested in a diagnostic context may include definitive, strong, and moderate levels of evidence for disease association, but may also assess genes with limited evidence to be as comprehensive as possible. For example, a recent study of diagnostic panels for Brugada syndrome found that of 21 genes commonly tested, only *SCN5A* was classified as having a definitive disease association.[37]

Patients/consumers may request ES/GS results that do not meet any established criteria such as variants for genes associated with a specific condition. Patient/consumer data should not necessarily be withheld (see preanalytical step 3), but the consent process should encompass the implications of receiving such information (see preanalytical step 2).

Strategies. Standards need to be developed for the level of gene evidence and variant classifications that should be analyzed and

reported for an ES/GS screening test, which are not addressed by current recommendations.[32,35] Interpretation of variants changes over time, and new gene–disease associations are discovered, therefore revetting of previously reported variants as well as reanalysis and reinterpretation of next-generation sequencing data will be an important and recurring process in genomic testing and standards will need to be developed.[38–41] Development and incorporation of machine learning into interpretation pipelines continue to evolve and will likely aid this process.[42] A plan to communicate reporting changes to the patient/consumer will need to be developed (see future considerations step 1).

Currently, laboratory reports are written with the traditional genetic health-care model in mind. Reporting standards including format and content will need to accommodate the nontraditional and consumer-directed model (see Table 3).

Postanalytical step 2: understanding current results interpretation

Opportunities and challenges. The type of information obtained from an ES/GS test performed for no obvious clinical indication is likely to be used for future reproductive decisions, medical planning, and decision-making by learning carrier status for recessive conditions or X-linked conditions, identifying pharmacogenomic variants and variants associated with adult-onset disorders.[3,4,43–45] Most ES/GS tests will have an effectively "negative" or nonactionable result. Many will reveal carrier status for several genes and some will predict risk for later-onset disease. Nearly all could have pharmacogenetic results. Adding to the complexity is the fact that people perceive risk differently from each other when presented with genomic data,[46] and pilot studies that assess participant response to genomic information have been limited by lack of socioeconomic diversity.[4,23]

In the presence of a clinical indication (e.g., family history), the prior risk of a specific genetic disease is increased and those with a subsequent positive ES/GS test result will, therefore, have a higher positive predictive value compared with an individual from the general population with the same test result whose prior risk will be lower. Regardless of the prior risk, the predictive value may also be reduced in both scenarios by other factors such as incomplete penetrance or findings of a likely pathogenic variant.[47–50] Causes of clinical variability, attributed to either gene–gene interaction, genotype–phenotype variability, or gene–environment interaction, are not defined and not predictable.[51] For many conditions, there are no practice guidelines for managing a genomic finding in an asymptomatic individual with a negative family history. For example, a young adult with a pathogenic variant in *KCNQ1* that is associated with long QT syndrome and sudden cardiac death might be treated by one cardiologist with reassurance, by another with yearly electrocardiograms, and by a third with an implantable defibrillator. Therefore, there is a knowledge gap that limits use of ES/GS for making informed health-care decisions.

In each health-care model, the opportunities and challenges of understanding the implications of the results for health care and reproductive decision-making are important to consider (see Table 3). The patient's or consumer's reaction to the ES/GS test result must be considered. A review of pre- and post-testing psychological reactions among people undergoing clinical testing for cancer predisposition, cardiovascular disease, or neurodegenerative disorders found no significant increase in distress or anxiety, except in the extreme case of Huntington disease.[52] The nuances of result interpretation including the possibility of incomplete penetrance and likely variable expressivity of a gene variant must be conveyed to the patient/consumer to prevent unnecessary worry or medical procedures due to relatively low positive predictive value.

Strategies. Under any of the genetic health-care models, a patient/consumer will receive a large amount of complex information that must be understood, assimilated, and internalized. Therefore, effective approaches to prioritize and organize the breadth of results from ES/GS screening tests into manageable subsets of results need to be developed. Effective pretest education and consent strategies (see preanalytical steps 1 and 2) are critical. In addition, effective professional and regulatory standards will need to be established to ensure access to adequate information after testing and to relay information back to a health-care provider when needed. To improve understanding of disease penetrance, it is increasingly important that longitudinal clinical data from asymptomatic individuals with a genetic susceptibility to a condition be shared in publicly accessible databases. While it is true that genetic test results, at least in the traditional genetic health-care model, do not increase anxiety or depression, some individuals will react adversely to such results, and pathways to appropriate counseling should be provided, regardless of the testing model. Telemedicine can improve access to genetics expertise to help address these concerns.[17]

Education for genetics professionals and other health-care providers will also be needed for ES/GS screening test results interpretation, as no provider has expertise in the interpretation of all disease-associated genes. Disease area experts will need to develop educational materials or information resources tailored to the needs and preferences of clinicians on a wide array of disease-associated gene findings. Ideally these materials and resources will be integrated into electronic health record systems to support interpretation and clinical actions at the point-of-care.[53]

Postanalytical step 3: results-specific medical evaluation, follow-up, and ongoing care

Opportunities and challenges. Despite many efforts to provide affordable health care to more Americans, health disparities persist due to patient demographics, health-care provider practice patterns, and the complexity of health systems in the United States. The magnitude of these disparities is particularly large in genetics and genomics.[5,6] Following disclosure of ES/GS testing results, medical follow-up is often required, for example, pertaining to the pathogenic or likely pathogenic variant from any gene on the ACMG secondary findings list.[54] Both cancer and cardiovascular risk results associated with genes on that list may require specialist consultation, as well as consideration of further testing to surveil patients or evaluate for subclinical disease. Given the patchwork of health systems and insurance coverage in the United States, there is a significant chance of some individuals being denied coverage or being unable to afford recommended follow-up for genetic conditions for which they have a risk identified through ES/GS testing. These challenges must be balanced with the potential benefit of detecting a susceptibility for which intervention could be lifesaving. It remains to be determined whether ES/GS screening tests will change health-care utilization and lifestyle choices by consumers and patients for the better, or if these results will lead to unnecessary use of health-care resources, or alternative and potentially harmful therapies.[3,4,23,55,56]

Strategies. Clear and authoritative recommendations on the best practices for clinical management of patients with variants associated with genetic disorders are needed to fully realize the benefits of ES/GS screening tests.

FUTURE CONSIDERATIONS (TABLE 4)

Future considerations step 1: making a plan for reanalysis and reinterpretation of results

Opportunities and challenges. There are currently no professional guidelines for frequency of reanalysis.[38] Information from ES/GS testing will evolve with time and new information from existing data must be managed (see postanalytical step 1).[39–41] Individuals

Table 4. Future considerations: challenges and opportunities in genomic screening of apparently healthy individuals.

<table>
<tr><th>Essential Steps</th><th>Traditional genetic healthcare[a]</th><th>Non-traditional genetic healthcare[b]</th><th>Consumer-directed genetic healthcare[c]</th></tr>
<tr><td rowspan="5">1. Making a plan for re-analysis and re-interpretation of results</td><td>Opportunity: Genetics professional may initiate reanalysis of the genetic data based on knowledge of new disorders and evolving medical information about patient or patient's family.</td><td>Opportunity: Provider with long-standing relationship with patient has opportunity to revisit results</td><td>Opportunity: Consumer has opportunity to be directly involved in request for and notification of changes to interpretation.</td></tr>
<tr><td colspan="2">Shared Opportunity: Updated variant classification and report released to the healthcare provider using established mechanism.</td><td rowspan="3">Challenges: Standards or regulations for handling re-analysis requests, performing re-analysis and disclosing updated results need to be established.

Long-term sustainability of entity holding data cannot be known.

Consumer must update contact information.</td></tr>
<tr><td>Challenge: Unlikely to establish long-term care relationship with patient</td><td>Challenge: Provider unlikely to initiate re-analysis based on new knowledge of genetic disorders</td></tr>
<tr><td colspan="2">Shared Challenges: New health care providers will need mechanism to order a re-analysis on a test ordered by a different HCP
Patient may be lost to follow-up</td></tr>
<tr><td colspan="3">Shared Challenge:
Policies for reanalysis, including fees, may vary by testing laboratory.</td></tr>
<tr><td rowspan="4">2. Strategy for cascade testing of at-risk family members</td><td rowspan="2">Opportunities: Genetics professionals routinely obtain and document family structure and relationships; have expertise with mode of inheritance and understand penetrance, variable expressivity. Familiar with effective family communication strategies.</td><td>Opportunity: Provider likely to be familiar with patient's family structure and dynamics.</td><td>Opportunity: Model incentivizes testing of additional individuals, therefore, cascade testing could be encouraged.</td></tr>
<tr><td rowspan="2">Challenge: Lack of understanding for mode of inheritance, penetrance, and variable expressivity.
Implications for family members not typically addressed.</td><td rowspan="2">Challenges: Consumer may not appreciate mode of inheritance, penetrance, variable expressivity, family members at risk.

Consumer's family members may not have same economic resources to pursue testing.</td></tr>
<tr><td>Challenge: Workforce limitations</td></tr>
<tr><td colspan="2">Shared Challenge: HIPAA limits the ability to share medically relevant information with family members.</td></tr>
<tr><td colspan="3">Shared Challenges: Initiation of discussion with relatives could be overwhelming and resulting uptake of testing by relative may be low.
Economic barriers will exist including lack of insurance coverage for initial sequencing/targeted testing or follow-up medical care.</td></tr>
</table>

being tested should be aware of this possibility and discuss if, how, and to whom will new information be delivered.

Strategies. Strategies to deal with a constant need to incorporate new data should involve the laboratory, the health-care provider (if part of the process), and the patient/consumer. Laboratory policies should account for reanalysis of data, including regulatory and technical challenges, cost, allowed frequency of reanalysis, and the practical issue of maintaining contact information over time. Plans to disseminate new information should include the ordering health-care provider for the original and reanalysis test, as well as the patient/consumer. The latter will require development of tools, such as a patient portal, to maintain contact over long periods of time. Due to constant improvement in analytical technology and cost reduction, and given the possibility of a laboratory no longer operating, the ultimate strategy for reanalysis may be retesting. Coverage and reimbursement policies that support reanalysis are essential—neither laboratories nor clinicians can be expected to provide such services without being paid.

Educational tools for patients to recognize the limitations of ES/GS screening tests and the circumstances that necessitate reinterpretation of genomic results are needed.

Future considerations step 2: strategy for cascade testing of at-risk family members

Opportunities and challenges. Genetic data have implications not only for the person being tested, but family members as well. For example, the risk of a first-degree relative also having a pathogenic variant in a gene for a dominant disorder may be as high as 50%. Carrier status for variants associated with a recessive disorder may be of no consequence to patients/consumers who no longer intend to have children, but may be critical to their younger relatives who are still of reproductive age. Regardless of inheritance pattern, a positive result in one individual will imply the likelihood of other family members being at risk. These possibilities should be conveyed to the patient or consumer with resources to help inform and guide testing of relatives as part of the education and consent process (see preanalytical step 2). Family dynamics may be negatively affected by ES/GS results; it may be difficult to discuss these findings and there is the possibility of revealing previously unknown nonpaternity or adoption status.[57] Understanding and conveying the implications of a genetic diagnosis or test result for family members and the impact on family dynamics may present challenges for providers working under the nontraditional model and for the consumer in the consumer-directed model (see Table 4).

Strategies. Patients/consumers must be informed of who in their family may be at risk, how to inform them of this risk (e.g., providing a sample letter they can send to relatives), and how relatives can access testing should they so desire. Models to address this challenging issue have been suggested.[12,58] Importantly, regulations and laws pertaining to sharing protected health information with family members under the consumer-directed model need to be developed, as those that currently exist are designed for patients receiving care from a clinical entity and are a barrier to sharing information.

SUMMARY

Even though the application of ES/GS screening tests for apparently healthy individuals is in its infancy, the public's interest in obtaining their own genomic information is likely to increase along with demands on health-care providers to assist patients in

accessing testing, interpreting results, and using results in medical care. Much remains to be learned about the clinical utility from genomic sequencing in a healthy population. There will likely be well-documented pathogenic or likely pathogenic variants in genes with valid disease associations for which screening an asymptomatic patient may be beneficial. However, there will be many instances where the gene–disease associations are not understood outside of the context of a personal or family history. With existing gaps in evidence regarding the positive predictive value of ES/GS screening test results, recommendations from practice guidelines may not be applicable. As effective strategies for implementation throughout the genetic testing process are developed, there will likely be an increase in ES/GS screening tests pursued via the nontraditional and consumer-directed genetic health-care models. A patient/consumer may enter the testing process through one model, then access services through another model. For example, consumers and patients with ES/GS screening results received under the nontraditional or consumer-directed models will still need the expertise of genetics providers for interpretation of complex results or management of rare genetic disorders, while more common genetic concerns could be addressed by nongenetics health-care providers supported by implementation strategies that effectively guide appropriate care.

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ADDITIONAL INFORMATION

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