Technical Brief

Genomic Testing for Screening or Disease Risk Prediction: A Technical Brief to Support the U.S. Preventive Services Task Force

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This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2015-00007-I). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

The information in this report is intended to help healthcare decision makers, patients and clinicians, health system leaders, and policymakers make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Preface

AHRQ, through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new healthcare technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy, or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

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In designing the study questions, the EPC consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the technical brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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Abbreviations

ACA: Affordable Care Act
ACCE: Analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social implications
ACMG: American College of Medical Genetics and Genomics
ACS: American Cancer Society
AHRQ: Agency for Healthcare Research and Quality
BMI: body mass index
CDC: Centers for Disease Control and Prevention
ClinGen: Clinical Genome Resource
CMS: Centers for Medicare & Medicaid Services
DTC: direct-to-consumer
EHR: electronic health record
eMERGE: Electronic Medical Records and Genomics
EPC: Evidence-based Practice Center
FDA: Food and Drug Administration
GINA: Genetic Information Nondiscrimination Act
HIPAA: Health Insurance Portability and Accountability Act
IGNITE: Implementing GeNomics In pracTicE
NASEM: National Academy of Science, Engineering, and Medicine
NCGENE: North Carolina Clinical Genomic Evaluation by Next-generation Exome Sequencing
NHGRI: National Human Genome Research Institute
NHIS: National Health Interview Survey
NIH: National Institutes of Health
PGen: Impact of Personal Genomics study
PRoGRESS: Pediatric Reporting of Adult-Onset Genomic Results
RIGHT: Right Drug, Right Dose, Right Time study
USPSTF: U.S. Preventive Services Task Force
VALID: Verifying Accurate, Leading-edge In Vitro Clinical Trial Development
WISDOM: Women Informed to Screen Depending on Measures of risk study

Structured Abstract

Background: Genomic testing for otherwise healthy individuals is increasingly available both clinically and through direct-to-consumer (DTC) testing. Genomic testing increasingly may become a routine part of clinical risk assessment and is relevant to multiple topics in the U.S. Preventive Services Task Force's (USPSTF's) portfolio of recommendations.

Purpose: The purpose of this technical brief is to provide an overview of genomic testing (genome or exome sequencing, multigene panels, array of single gene polymorphisms [SNP arrays]) for screening and disease risk assessment. This technical brief will describe the landscape and regulatory environment pertaining to genomic testing, the use of clinically ordered and DTC genomic tests in primary care, available evidence about the benefits and harms of genomic testing, and important issues, controversies, and research gaps related to genomic testing. The USPSTF will use this technical brief to assist it in considering the implications of genomic testing for its portfolio and methods.

Methods: This Technical Brief integrates a systematic search of peer-reviewed literature, hand-searches of gray literature, and discussions with Key Informants to inform four Guiding Questions (GQs): landscape of genomic testing (GQ1); clinical context (GQ2); evidence on benefits and harms (GQ3); and issues and controversies (GQ4). We included DTC and clinician-ordered tests for broad genomic panels, exome sequencing, and genome sequencing. We excluded testing for diagnostic purposes, cascade screening within families with a known genetic variant, testing for somatic mutations, carrier testing as part of preconception or prenatal counseling, and non-health–related genetic tests. The evidence for each GQ was synthesized in a narrative format, with supporting summary tables appropriate to the identified evidence.

Findings: The use of clinically ordered and DTC genomic testing is growing and is likely to affect primary care practice. While many care models, risk assessment tools, and resources are available to aid primary care clinicians in integrating genomic testing data into their practice, challenges remain. The evidence base for health outcomes and harms associated with genomic screening and risk prediction is beginning to develop, and information on health outcomes should be available within the next 5 years. Potential implications of genomic screening for USPSTF methods include unique considerations of test accuracy, inclusion of nontraditional harms and secondary findings, and consideration of expanded positive outcomes, such as personal utility and benefits to family members.

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Chapter 1. Background

Significance and Purpose

Our understanding of how genetic variants increase disease risk, aid in diagnosis, and inform clinical management is evolving rapidly. Testing for these and other variants with clinical actionability is increasingly available both clinically and through *direct-to-consumer* (DTC) testing. Genomic testing increasingly may become a routine part of clinical risk assessment and is relevant to multiple topics in the U.S. Preventive Services Task Force's (USPSTF's) portfolio of recommendations. However, questions remain about whom and when to test and how to respond to patient-generated genomic data.

In general, single-gene tests are used to diagnose conditions suspected of involving a specific variant. Until recently, these were the focus of clinical testing, largely because of the high cost of genetic testing. As the price of testing has rapidly decreased, genomic testing (*multigene panels* or *exome sequencing* or *genome sequencing* or *arrays of single gene polymorphisms* [*SNP arrays*]) has become increasingly available and may be ordered even when only clinically relevant variation in a single gene is suspected. These tests can be used for diagnosis, screening, and clinical management,[1-3] and can be conducted without the need for a specific clinical indication, resulting in identification of disease or disease risk that may have certain or uncertain clinical implications.

The USPSTF will use this technical brief to assist in considering the implications of genomic testing with multigene panels or exome/genome sequencing for its portfolio and methods.

Definitions

Genetic testing identifies changes in DNA sequence or chromosome structure. Genetic testing may also include testing of biochemical changes in the protein activity; however, these tests are not included in this report. In clinical care, genetic information is typically analyzed through a sample of blood or saliva. The results of a genomic test can help determine a person's chance of developing or passing on a genetic disorder (screening or risk prediction); confirm or rule out a suspected genetic condition (diagnostic); or guide clinical management with either dosing or medication choices or a selection of targeted therapies (*pharmacogenomics*), most commonly cancer drugs.

In the context of this technical brief, genomic tests will be limited to those conducted for screening or disease risk prediction. Tests included in this technical brief include multigene panels, exome or genome sequencing, or SNP arrays.

Additionally, in this technical brief, the term *genomic test* will refer to *multiplex next-generation sequencing*, which includes both exome or genome sequencing and multigene panels.

This technical brief focuses on *germline variants* as opposed to *somatic variants*. Germline variants are gene changes in a reproductive cell (egg or sperm) that become incorporated into the

DNA of every cell in the body of the offspring. A variant contained within the germline can be passed from parent to offspring and is, therefore, hereditary. In contrast, somatic variants can occur in any cell except germ cells and therefore are not passed on to children. Somatic mutation occurs frequently and rarely causes disease, usually only after accumulation of multiple mutations. Further definitions of all italicized terms in this technical brief are provided in **Appendix A**.

Relevance to Prevention and Primary Care

Among people who have an identified high genetic risk for certain conditions but are otherwise healthy, genomic screening can improve health outcomes through early intervention or enhanced surveillance. Genomic risk prediction might also improve health outcomes if the receipt of genetic risk information leads to behavior change (e.g., diet, smoking cessation) that modifies disease risk. In addition, family members of patients might also experience improved health outcomes if genetic risk is identified through *cascade screening* (a systematic process for identifying individuals at risk for a hereditary condition by extending genetic testing to at-risk biological relatives and repeating the process as more carriers are identified).

Genomic testing may impact primary care practice, as clinicians may be asked to interpret or advise on tests that they did not order. These include DTC tests that offer clinical and/or nonclinical results (e.g., *ancestry testing*), as well as results of panel testing or sequencing ordered by a clinician for one purpose that might return other, *secondary findings* unrelated to the primary purpose for the testing. Further, in areas where there is limited access to genomic specialty care, primary care providers may assume a larger role in providing testing, interpretation, and followup care.

Related USPSTF Recommendations

The USPSTF portfolio has one recommendation on genetic testing for purposes of screening for disease risk (*BRCA*-Related Cancer). Other USPSTF recommendations pertaining to diseases with a genetic component (e.g., colorectal cancer, pancreatic cancer, familial hypercholesterolemia) explicitly exclude genetic testing. Typically, the rationale for these exclusions is a lack of relevance to primary care practice.

In its 2019 statement, the USPSTF recommended that primary care clinicians assess women who have a personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry (such as Ashkenazi Jewish ancestry) associated with increased frequency of pathogenic variants in the *BRCA1* or *BRCA2* genes, using an appropriate brief familial risk assessment tool (B recommendation). The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing of women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations (D recommendation).[4] The accompanying evidence review focused on *BRCA*-related breast and ovarian cancer only; it did not address multigene panels or other genes associated with increased risk of breast and ovarian cancer (e.g., *ATM*, *PALB2*, *TP53*). In addition, the review and recommendation did not consider

other *BRCA*-related cancers, such as pancreatic cancer, melanoma, and prostate cancer; nor did it consider the benefits and harms of risk assessment and genetic counseling in men.

The USPSTF's portfolio intentionally excludes or does not address other well-described genetic syndromes that increase disease risk. In 2016, the USPSTF found insufficient evidence for screening with lipid panels for either multifactorial hypercholesterolemia or familial hypercholesterolemia in children and adolescents.[5-7] The accompanying evidence review on screening for familial hypercholesterolemia addressed the effectiveness of screening, diagnostic yield of universal or selective screening with lipid panels, and treatment of familial hypercholesterolemia;[7] genetic screening alone and cascade screening in family members were both excluded from the review.

The USPSTF has not made a recommendation on genetic screening for Lynch syndrome, which has been reported to occur as in many as 1 in 279 individuals[8] and is associated with an increased risk of ovarian, endometrial, colon, pancreatic and other cancers.[9] In the USPSTF's recommendation on screening for colorectal cancer, genetic syndromes such as Lynch syndrome are intentionally excluded.

The USPSTF does not have any recommendations on DTC genomic tests.

Recommendations of Other Groups

We did not locate any guidelines or recommendations that support the use of genomic testing for population-based screening. In 2013, the American College of Medical Genetics and Genomics (ACMG) first published a list of identified known pathogenic or expected pathogenic variants in specific genes that it recommends being reported back to patients, even when these are secondary findings (unrelated to the original reason for testing); in 2017, this list was updated to include 59 genes.[10, 11] This return of secondary findings could be considered a form of "opportunistic screening." However, in 2019, the ACMG issued a clarification that this list of genes should not be used for population-based screening until *penetrance* (the likelihood that a clinical condition will occur when a particular *genotype* is present) is better understood in asymptomatic individuals and appropriate followup care approaches can be assured.[12]

Most guidelines on clinical genomic testing center on screening for individuals who meet clinical criteria for a condition or who have been identified based on a positive family history. Many organizations (e.g., American College of Obstetricians and Gynecologists,[9] National Comprehensive Cancer Network,[13, 14] ACMG,[15] National Society of Genetic Counselors[15]) recommend risk-based genomic screening for hereditary cancer risk, similar to the USPSTF's *BRCA* guideline. Family history–based risk assessment as a proxy for genetic testing and diagnostic testing of those meeting clinical criteria are areas outside the scope of this technical brief; therefore, these guidelines are not addressed in detail here.

Many organizations have published position statements related to DTC genomic testing. Several organizations outside of the United States have recommended against DTC testing, and although some U.S.-based organizations have discouraged its use,[16] most support informed personal decision making about DTC testing with certain stipulations. For example, multiple

organizations have recommended that clinicians with specialized genomics training be involved in interpreting results and clinical management of DTC genomic tests, and that consumers have access to comprehensive information about DTC genomic tests, including explanation of specific tests' scientific evidence, limitations, the risk that a test will neither confirm nor eliminate disease potential, and potential implications for relatives. Multiple specialty medical societies support healthcare professional education in genomics, including for primary care providers, so clinicians can counsel patients on the value and limitations of DTC testing. More information on recommendations of other groups related to DTC testing is in **Appendix B**.

The international Clinical Pharmacogenetics Implementation Consortium issues systematic grading of the evidence for how individual pharmacogenomic targets might be used—not whether testing should be done—in clinical care.[17]

Chapter 2. Methods

This Technical Brief integrates discussions with Key Informants with searches of the published literature and gray literature to inform the Guiding Questions (GQs) (**Appendix C Figure 1**). Additional details on the Methods for this Technical Brief are available in **Appendix C**.

Guiding Questions

The focus of this Technical Brief is on genomic testing and its implications for primary care. Specifically, we address four GQs shown in the Box below and **Figure 1**.

Box. Guiding Questions and Page Numbers

Guiding Question	Page numbers
Guiding Question 1: Landscape of genomic testing	
1a. What types of clinically relevant genomic tests and panels are currently available to primary care clinicians and patients?	15-16
1b. What is the current regulatory environment around genomic testing?	13-15
1c. What is the short-term (3–5 year) future horizon of genomic testing available to primary care clinicians and patients?	30-31
Guiding Question 2: Clinical context and use of genomic testing in primary care	
2a. How widely used are direct-to-consumer genomic tests? How often are primary care clinicians ordering exome sequencing and broad genomic panels?	16-18
2b. How often are patients sharing direct-to-consumer genomic test results with their primary care clinicians?	18-19
2c. What challenges are primary care clinicians facing in interpreting and addressing direct-to-consumer genomic test results with patients?	19-22
2d. What care models, tools, resources, and guidance are being used to help primary care clinicians talk with patients about genomic test results?	22-24
Guiding Question 3: Available evidence about the benefits and harms of genomic testing	
3a. What are potential outcomes related to genomic testing that are not traditionally considered by the USPSTF as benefits or harms?	24-30; 33-34
3b. What results have been reported on the benefits or harms of genomic testing?	24-30
Guiding Question 4: Important issues and controversies	
4a. What are the important issues and controversies related to genomic testing, including issues related to test characteristics?	8-12; 21-22
4b. What are the primary care–relevant research gaps related to genomic testing?	24-30; 34-35

Inclusion and Exclusion Criteria

For all GQs, we prioritized research focused on genomic testing for the purposes of screening and risk prediction, as these testing indications have the most relevance for the USPSTF (**Appendix C Table 1**). We included DTC and clinician-ordered tests for broad genomic panels, exome sequencing, or genome sequencing. We excluded testing for diagnostic purposes, cascade

screening within families with a known genetic variant, as well as tests for somatic mutations. We did not include research on *carrier testing* as part of preconception or prenatal counseling or on non-health–related genetic tests such as those for ancestry, paternity, or forensic purposes. We included research conducted in adult and pediatric populations, including newborns. For GQ3, included outcomes were any benefits related to health or shared decision making, as well as any harms, tradeoffs, unintended consequences, or secondary/incidental findings. While pharmacogenomic testing was included in this technical brief, only those tests for pre-emptive (i.e., screening) purposes were included, not those conducted in the course of clinical care (e.g., to determine drug dosage).

Literature Searches

For GQ3 (benefits/harms), we conducted a systematic search of English-language primary published literature to identify completed or ongoing genomic screening studies. We worked with a research librarian to develop our search strategy, which was peer reviewed by a second research librarian. Because of the large volume (more than 100,000 references) of genome science discovery studies, we modified our search strategy to pursue a "best-evidence" approach to identifying the most relevant screening studies. This approach included searching the Cochrane Central Register of Controlled Trials, MEDLINE, and PubMed, publisher-supplied, for systematic reviews and clinical trials published from 2016 to January 30, 2019. The rationale for this date is based on the publication of several relevant systematic reviews in 2016 or later, as well as the publication of results from the MedSeq trial in 2017.

For all GQs, we conducted hand searches of the published literature, reviewed reference lists from recent systematic reviews, and conducted cited-by searches using Google Scholar. We also searched gray literature sources, including websites of relevant professional organizations, grants and clinical trials registries, regulatory agencies, conference proceedings, and gray literature repositories. Key Informants also suggested potential sources of information.

Key Informant Interviews

We conducted semistructured telephone interviews with 12 Key Informants to obtain additional insight on our guiding questions. The 12 Key Informants (4 from federal agencies and 8 from nonfederal organizations) represented the following stakeholder areas: research, clinical care, policy, ethics, patients, regulation, and industry. Interview audio recordings were transcribed via a professional transcription service. One team member reviewed each transcript and categorized segments of interviewee responses by one or more GQ. The team then integrated findings from Key Informants' interviews with evidence from the published and gray literature.

Data Management and Presentation

Data from the published literature was integrated with information from the gray literature and discussions with Key Informants. Following the standard procedures for technical briefs, quality assessment (i.e., critical appraisal) of identified studies was not conducted. The evidence for each GQ was synthesized in a narrative format, with supporting summary tables appropriate to the identified evidence.

For GQ 3, we audited outcomes reported in relevant studies to outline for the USPSTF the types of evidence available related to the use of genomic testing. We prioritized outcomes that are most relevant to the USPSTF portfolio and added nontraditional outcomes after team discussion. We narratively summarized the findings and conclusions of these articles as reported by the study authors but did not abstract specific data from the studies or evaluate the quality or accuracy of the author-generated conclusions.

Expert Reviewers

Expert reviewers were invited to provide written comments on the draft Technical Brief. Reviewer comments on the preliminary draft of the Technical Brief were considered by the Evidence-based Practice Center in preparation of the final draft of the Technical Brief.

Chapter 3. Findings

Discussion of each of the four GQs is interwoven throughout the Background, Findings, and Implications sections of the report; the **Box** on page 5 provides page numbers where specific GQs are addressed.

Evaluating the Outcomes of Genomic Testing

In the context of rapidly advancing genetic technology and the decreasing price of testing, methods for evaluating the actionability of genetic results have emerged. The Centers for Disease Control and Prevention's (CDC's) Office of Public Health Genomics established and supported the ACCE Model Project (2000–2004), which developed from between analytical process for evaluating scientific data on emerging genetic tests.[18] This framework, called ACCE, includes four main components: analytic validity (A); clinical validity (C); clinical utility (C); and ethical, legal, and social implications (E) (these concepts are described in further detail below). However, the ACCE framework was developed for single-gene tests, and its applicability to multigene panels or sequencing is not yet clear.[19]

A 2018 systematic review of genetic testing evaluation frameworks found 29 frameworks; the four ACCE domains were the most commonly used, with less attention to contextual, economic, consumer-focused, or organizational aspects. Most frameworks were focused on genetic testing in general, including for risk prediction, rather than specifically on sequencing or multigene panels.[20]

Test Accuracy: Analytic and Clinical Validity

Analytic validity refers to the ability of the test to accurately and reliably measure the genotype(s) of interest. This is typically strictly a measure of laboratory accuracy and is regulated for clinical testing through the Centers for Medicare & Medicaid Services (CMS). This type of evidence is not typically reviewed for USPSTF topics addressing test accuracy.

Clinical validity is the ability of a genetic test to detect or predict a patient's clinical status (*phenotype*). For many variants, particularly rare ones, the association with clinically important states is unclear.[21] The Clinical Genome Resource (ClinGen) has developed a framework for the assessment of the validity of gene–disease relationships for monogenic or Mendelian disorders.[22] Clinical validity is dependent on the genetic and functional evidence that variation in a given gene leads to symptoms of the condition.

ACMG and the Association of Molecular Pathologists outline a categorical system to define whether a variant is pathogenic, likely pathogenic, a variant of uncertain significance, likely benign, or benign, with respect to a given monogenic condition.[23] This framework includes both an assertion about a pathogenic or benign effect, as well as the confidence in that assertion. For any test, a clinician must subsequently perform clinical correlation of the genetic finding with the patient's phenotype to determine the relevance of the finding, regardless of whether the result is "positive," "negative," or "uncertain."

Penetrance is the probability of a phenotype being expressed in the presence of a given variant, and it can be variable depending on the condition. Penetrance can be highly dependent on age, typically when a phenotype (such as cancer) is far more likely to be expressed at older ages. A related construct is *expressivity*, which refers to variation in phenotypic expression when a given allele is penetrant. These constructs have bearing on the determination of traditional measures of test accuracy (sensitivity, specificity, and predictive value). This would be a test accuracy consideration for the USPSTF, particularly around age to begin screening, as a phenotype may not typically appear until later in life. Even a highly pathogenic, well-characterized variant, if not penetrant in a given individual, would and could represent a form of overdiagnosis.[24, 25]

In the context of population-based genomic screening for monogenic disorders, test accuracy depends on what types of variants, in terms of pathogenicity, would be included in screening algorithms to register a "positive" screening result. An analysis of exome data from participants in the NCGENE (North Carolina clinical Genomic Evaluation by Next-generation Exome sequencing) study (n=478) considered five different variation selection algorithms with increasingly relaxed inclusion criteria—from rare variants classified as pathogenic to *missense variants* of uncertain clinical significance. The most restrictive algorithm was the least sensitive and most specific, while the most relaxed algorithm was the most sensitive but least specific, raising concerns about how to balance efforts to maximize case finding with efforts to reduce false-positive results in genomic screening.[24] The etiology is more complex in multifactorial conditions, and thus the interpretation of genetic testing (e.g., polygenic risk scores) is fundamentally different than in monogenic disorders.

The introduction of patient-initiated DTC tests, and inconsistencies in regulation of DTC tests for clinical use, have resulted in potentially conflicting interpretations between DTC and clinician interpretation that could result in harms.[26] Most variants reported in current DTC tests are derived from genotyping arrays, which primarily provide information about common population variants and therefore multifactorial disease risk, but sometimes can include a subset of rare variants that are more well-characterized. Cases of false-positive results have been reported in which a DTC test has reported the presence of a rare pathogenic variant that is later confirmed to be negative on clinical confirmation with Clinical Laboratory Improvement Amendments (CLIA)–certified testing.[27] In addition, false-negative results from DTC testing may lead to false reassurance. For example, the 23andMe *BRCA* test only tests for three pathogenic variants found in 2% of women of Ashkenazi Jewish ancestry but rarely in other populations (0.1%).[28] These three founder variants represent just a few of the more than 1,000 known *BRCA* mutations, and negative test results could be misinterpreted to indicate an absence of any *BRCA* mutations and lead to false reassurance about disease risk. This could be particularly problematic in individuals who meet clinical indications for testing.[29]

Another trend raising concerns about clinical validity is the use of third-party automated DNA interpretation services, wherein consumers have the option of downloading their raw data file from DTC testing companies. In one study, 89% of respondents reported uploading their raw data into third-party interpretation services to receive automated genetic risk reports beyond those provided by the DTC testing company.[30] Many DTC companies warn that these interpretation services are not validated for accuracy or intended to guide medical care. For example, a study of referrals for clinical diagnostic testing at Ambry Genetics for people with

variants previously identified as pathogenic through third-party interpretation of DTC testing (n=49) found a 40% false-positive rate in third party interpretation of DTC raw data, including 8 false-positive results for *BRCA1* or *BRCA2* variants.[31]

Benefits: Clinical Utility

Clinical utility traditionally refers to the ability of a test to demonstrate, in the tested individual, prevention of disease or improvements in health outcomes such as mortality, morbidity, or disability through the adoption of treatments based on test results. This definition is analogous to the USPSTF's health outcomes domains. While clinical utility can be assessed in a given individual, outcomes of testing may vary from person to person. Therefore, clinical utility is typically evaluated at the level of the population undergoing testing.

Under traditional definitions, making an accurate diagnosis based on a test result alone, without evidence of benefit with accompanying intervention, would be said to lack clinical utility. However, ACMG has proposed a policy statement arguing that multiple utilities accrue beyond these traditional outcomes, to individuals (through preventing diagnostic odysseys, unnecessary further testing, and providing actionable risk information to biologic relatives); families (through *cascade testing*, enabling informed reproductive decision making, and enabling social support opportunities), and to society (through understanding of disease etiology).[32]

Personal utility refers to the value an individual places on the knowledge associated with their genomic test result independent of its clinical implications; for example, value of getting a definitive diagnosis even without clinical intervention or value related to life planning.[33, 34] Personal utility has been studied for some time, with consensus emerging only recently about the domains within this construct. A 2017 systematic review found the construct of personal utility is likely multifactorial, including affective (e.g., preparation, spiritual well-being), cognitive (e.g., knowledge, curiosity, future planning), behavioral (e.g., reproductive planning, communication with relatives), and social (e.g., concerns about discrimination, privacy, and social support).[35] While measures of personal utility are still emerging, the extent to which aspects of personal utility are related to quality of life may be relevant to the USPSTF in assessing the outcomes of genomic screening.[36] For example, in the MedSeq trial, patients receiving genome sequencing expressed different conceptions of clinical utility than the clinician-defined conception of clinical actionability, with a more fluid conception of ideas of the preventability and treatability of diseases across the risk spectrum.[37] A review of studies of health-related quality of life in people receiving genetic testing for neurodegenerative disease such as Alzheimer's, Huntington's, and Parkinson's disease found little evidence of harm and evidence of quality-of-life-related benefits to individuals receiving genetic information even in the absence of a clinical intervention that can alter the disease course. Benefits included sense of control, ability to do future planning, reproductive decision making, participation in disease-specific communities and support systems, and participation in advocacy on behalf of family members.[38]

Family-Level Outcomes

Clinically actionable test results may also be applicable to a patient's biologic relatives, making family-level outcomes important and uniquely relevant in studies of the benefits of genomic

screening.[21] For certain conditions, *cascade testing* may be recommended, a process of testing first-degree relatives of an individual with a known pathogenic variant (e.g., in *BRCA1* or *BRCA2*). Disclosure or nondisclosure of results to relatives also can impact family distress or other outcomes. Traditionally, USPSTF reviews have not included family-level outcomes or cascade testing as an outcome of testing an individual, but some of these outcomes may be relevant for consideration as they relate to a patient's quality of life or to relatives' receipt of testing and subsequent outcomes. Benefits to family members may constitute indirect clinical utility.[39]

Harms: Ethical, Legal, and Social Issues

Since the beginning of the Human Genome Project, ethical issues have been at the forefront for all aspects of genomic research and clinical care.[40, 41] In the first decade of the genetic era, where the idea was novel, disruptive, and focused primarily on single-gene diseases, the primary concerns about harms were on psychosocial harms, mainly anxiety, depression, or distress; on receipt of genetic test results; and on concerns about genetic discrimination in health, disability, or long-term care insurance and in employment. As the genetic era has evolved into the genomic era, where large panels and sequencing are more common, the focus of harms has expanded to include false-positive results and harms associated with unnecessary testing or workup resulting from uncertain or incorrect genomic information.[39] Additionally, false reassurance is a potential harm, particularly of DTC services that test only a limited number of variants.[42] Harms to relatives, such as learning something they did not wish to know, are also possible.[43] Typically, USPSTF reviews have not addressed ethical, legal, or societal-level harms in screening or risk prediction recommendations.

A review of ethical, legal, and social issues research studies (k=299) published from 2008–2012 found the most common study topics were informed consent, data sharing and privacy, issues related to return of results including secondary findings, issues related to specific populations according to ancestry or socioeconomic status, and Institutional Review Board issues. Topics seeing the most growth in research over time were results disclosure and concepts of group-level harm.[44]

Clinical Actionability and Secondary Findings

Clinical actionability refers to the extent to which genetic testing provides information about the risk of serious disease that could be prevented or mitigated if the risk were known. Typically this construct is measured at the level of a gene-disease relationship. ClinGen has developed a framework for assessing the clinical actionability of secondary findings.[45, 46] The first consideration is whether a finding has clinical validity (whether there is sufficient strength of the evidence linking the gene to a disease or disease risk). In many cases, the clinical actionability associated with a given condition is not well established, either because interventions do not exist or have not been proven effective in presymptomatic individuals, or because little is known about the manifestation of the disease due to the rarity of the condition.

There is consensus about the clinical actionability of variants associated with only a relatively small number of conditions. The CDC's Office of Genomics and Precision Public Health

designed a tiered system to track genomic applications that might have significant potential for positive impact on public health based on available evidence-based guidelines and recommendations (**Appendix B Table 2**). As a result, CDC has focused its public health genomics efforts on three main conditions, each of which has various scenarios when genetic screening may be appropriate: hereditary breast and ovarian cancer (specifically due to the *BRCA1* and *BRCA2* genes), Lynch syndrome, and familial hypercholesterolemia.[47] Currently, the USPSTF addresses two of these topics, *BRCA*-related breast and ovarian cancer and familial hypercholesterolemia (within the review on screening for lipid disorders in children and adolescents). As genomic discoveries are made and targeted therapies and/or management strategies are developed, more genetic conditions will be identified as having clinical actionability or clinical utility.

The examination of genome or exome data can lead to the identification of secondary findings, those findings beyond the original indication for testing. Some of these findings have been identified as opportunities to implement a medical intervention that could improve future health outcomes (e.g., identification of a *BRCA1* variant associated with hereditary breast and ovarian cancer).[11, 45, 46] However, there is also some debate in the field about whether and how to report secondary findings.[48, 49] Several resources are available to clinicians seeking to understand potential clinical actionability of secondary findings, such as ACMG's list of 59 genes with sufficient clinical actionability to be returned to patients even if they were not the original reason for testing[11] (**Appendix B Table 3**).

ACMG also recommends giving patients undergoing clinical genomic sequencing the option to opt out of receiving secondary findings following appropriate genetic counseling.[11] ACMG has stated that it intends to update this list over time based on evidence-based work from groups such as the ClinGen Actionability Working Group.[45, 46] ACMG has a standing Secondary Findings Maintenance Working Group that uses a standardized methodology to assess the evidence for inclusion of a gene on the list.

Research studies have typically identified secondary findings in 1% to 3% of individuals.[50-59] For example, in a study of sites participating in the Clinical Sequencing Evidence-Generating Research consortium (n=6,240 individuals undergoing sequencing), prevalence of secondary findings (defined by ACMG guidelines) was 1.2% (adjusted prevalence of 1.7%); no psychological adverse events associated with the return of these results were noted.[53] A 2019 health technology assessment on diagnostic exome sequencing calculated that 3.9% (95% CI, 2.4% to 5.3%) of individuals with a suspected germline disorder would have an additional medically actionable variant based on data from 13 studies (6,653 participants).[60] Additional studies reported a secondary finding rate of 0% to 10%.[60] These estimates depend on several factors, including the number of genes included in the analysis of secondary findings, the population prevalence of conditions associated with those genes, and the threshold used to define a variant as likely pathogenic.

Regulatory Considerations Related to Genomic Testing

Regulation of Clinical and DTC Testing

In general, federal oversight is primarily focused on the analytic validity of tests, with limited consideration of clinical validity or utility. Two federal agencies have primary authority to regulate genetic tests in the United States: CMS and FDA. Currently, how tests are regulated depends on whether they are available commercially or developed and conducted by a single laboratory.[61-63] The regulatory landscape is evolving and there is uncertainty about how multigene panels and sequencing will be regulated in the future.

Most clinically available genetic tests are laboratory-developed tests, typically single gene tests that are developed and performed by a single laboratory (also called "home brew" tests). Under the CLIA, the CMS establishes certification processes that laboratories must pass to legally conduct clinical testing.[64] The objective of this testing is to determine the clinical testing quality, verification of procedures, qualifications of technicians, and in some cases proficiency testing. CLIA considers only analytic validity, not clinical validity or clinical utility.

Like CMS and CLIA, the FDA limits regulation to analytic validity, although it has required consumer comprehension studies for DTC tests. The FDA does not require collection of postmarket data.[65] It has exercised "enforcement discretion" of laboratory-developed tests and begun regulatory enforcement of commercially marketed "kits" (a group of reagents packaged together) as medical devices.[61] Although the FDA has increasingly regulated DTC tests through this mechanism, there are no clear standards for regulatory oversight of next-generation sequencing and multigene panels.

FDA regulation of DTC genetic testing began after a 2010 Government Accountability Office report identified multiple concerns about misleading results and questionable practices.[66] The FDA also sent letters to the largest DTC companies informing them that their products constituted medical devices.[67] In 2013, the FDA sent cease-and-desist letters ordering DTC companies to immediately stop marketing sales of health-related testing until they had received FDA approval.[68]

In 2015, 23andMe became the first DTC company to receive FDA approval for the sale of a DTC genetic test with its carrier screening test for Bloom syndrome, based on studies of user understanding and analytic validation studies. Since then 23andMe has received FDA approval for additional carrier screening conditions, tests for genetic health risks (e.g., Alzheimer's disease, hereditary breast and ovarian cancer), and pharmacogenomic tests.[69] While these tests were approved on the basis of analytic validity, the FDA has noted that these tests should not be used to make medical decisions and should be confirmed via clinical confirmatory testing.[69] At this time, the FDA provides no oversight or recommendation on followup care or support provided to DTC consumers. Questions have been raised about the purpose of confirmatory testing, generally through a non-FDA–approved laboratory-developed test, when the DTC test has received FDA approval for analytic validity.[70]

The FDA has proposed draft policies to further extend its oversight of laboratory-developed tests and to include clinical validity in its regulations.[71] These policies outline considerations for designing, developing, and validating next-generation sequencing tests used for exome sequencing or targeted sequencing to aid in the diagnosis of symptomatic individuals with suspected germline diseases. In 2018, legislation was introduced into Congress based on input from the laboratory industry and the FDA. The Verifying Accurate, Leading-edge In Vitro Clinical Test Development (VALID) Act seeks to establish a risk-based approach to regulation of in vitro clinical tests. Under the legislation, the FDA would operate a precertification program for lower-risk tests, while high-risk tests (such as novel tests) would be required to undergo premarket review to verify analytical and clinical validity.[72] Congress has not yet voted on this legislation, so these policies remain in draft form and have not been implemented.

Key Informants reflected on this complex and evolving regulatory structure in interviews. Many said the current regulatory structure cannot keep up with the speed of innovation in genomic testing. Others expressed concern about whether the FDA has capacity to review large volumes of applications, whether it has a clear framework for evaluating these tests, and whether the FDA policies reflect the complexity of how these tests move through the healthcare system. Some Key Informants felt the FDA was not going far enough, expressing a need for required collection of postmarketing data. However, others felt FDA enforcement was likely to diminish in the future and revert to the CLIA regulation model due to pressure from industry for reduced regulations.

Regulations on Data Sharing and Patient Privacy

The Genetic Information Nondiscrimination Act (GINA) of 2008 amended the Health Insurance Portability and Accountability Act (HIPAA) to state that genetic information is considered health information.[73] Health insurers may not request or require genetic information to make eligibility, coverage, underwriting, or premium-related decisions under some conditions. Health insurance protection is also provided by the Affordable Care Act (ACA) of 2010, which prohibits insurers from refusing coverage for patients with genetic diseases because of protections for pre-existing conditions. GINA also offers protection from employment discrimination by preventing employers from using genetic information in employment-related decisions; however, these protections do not apply to employers with less than 15 employees.[73] GINA does not cover other forms of insurance, including federal and military insurance, long-term care insurance, life insurance, or disability insurance. Some states (e.g., Maine, Vermont) have passed additional laws expanding the scope of GINA to other forms of insurance such as long-term care insurance, life insurance, and disability insurance.[74, 75] In 2011, California extended protections further to prohibit genetic discrimination in housing, mortgage lending, emergency medical services, education, and state-funded programs.[73]

HIPAA does not apply in all situations. Numerous exceptions (e.g., judicial proceedings, workers' compensation, insurance and commercial transactions) permit access to individual health information. In cases where this information becomes available outside of healthcare institutions, or in other settings such as forensics, HIPAA protections do not apply. In addition, DTC genetic testing companies largely are not governed by HIPAA policies. Instead, these companies operate through user agreements about their genetic data practices, and retain broad

rights to commercializing data resulting from testing, which may include sharing data with third parties.[76]

Available Genomic Tests

Genomic Tests Available to Primary Care Clinicians and Consumers

According to an analysis of a claims database conducted from 2014 to 2017, there were about 75,000 clinical genetic tests on the market in August 2017.[1] The majority of these (86%) were for single genes, and the remaining 14% were multigene tests, including 873 exome or genome sequencing tests. Highest spending was for prenatal tests (33%–43% of total during study period) and hereditary cancer tests (approximately 30%). The analysis also found rapid growth in the number of new tests entering the market, with 14,000 new tests emerging between 2014 and 2017, for a rate of about 10 new tests per day. Most new tests entering the market target multiple genes.[1]

Along with the increase in genomic testing available to clinicians, the marketing of testing panels directly to patients has increased following completion of the Human Genome Project. In 2019, more than 100 companies offered DTC testing for multifactorial health-related variants (selected monogenic variants such as carrier status for cystic fibrosis and sickle cell anemia, genetic risk reports for certain variants in *BRCA1*, *BRCA2*, Lynch syndrome, and familial hypercholesterolemia), drug sensitivity reports, and/or "wellness" reports (for topics such as lactose intolerance and muscle composition, and diet).[77] Several DTC testing companies also offer genome and/or exome sequencing. Examples of health-related genetic tests currently marketed to U.S. consumers are listed in **Table 1**.

Individuals can order some of these tests, such as those offered by 23andMe, directly without clinician involvement.[78] Other DTC testing companies have a hybrid consumer-initiated, physician-mediated model wherein clinicians order the tests and return the results. Many of these hybrid DTC testing companies have their own networks of clinicians who provide review and authorization as part of the test ordering process.[79]

Most DTC testing companies allow consumers to download their raw genetic data. Some consumers may opt to share their raw data with collective genomic research efforts such as Open Humans and openSNP. In addition, many DTC consumers upload their raw data to third-party interpretation services such as Promethease or GEDmatch, which then provide automated reports on topics such as health risks, ancestry, and genealogy.[30] These third-party services are not associated with the DTC companies and frequently do not require payment for their automated interpretation reports. One survey of nearly 500 DTC consumers found that about two-thirds of them had taken their raw genetic data to a third-party service for interpretation.[80]

Primary Care Clinician Ordering of Genomic Tests

Primary care clinicians appear to have a varying degree of familiarity with genetic testing. While genetic test ordering appears somewhat common, a substantial proportion of clinicians have

never ordered any type of genetic testing. Further, there are limited data on ordering of multigene tests or sequencing in primary care, possibly reflecting that ordering happens after referral to medical genetics.

A survey conducted from 2014–2016 among 488 primary care physicians found that in the prior year, about 38% had referred a patient for genetic counseling, 36% had ordered a genetic test, and 30% had returned genetic test results.[81] The study did not indicate the percentage of genetic tests ordered for screening purposes. Similarly, a survey conducted in 2017 among 130 family practice and internal medicine physicians found that 44% had never ordered a genetic test, while 34% had ordered 1 to 3 genetic tests in the past year. Among those who had ordered a genetic test in the previous year, the most common types were presymptomatic or susceptibility tests (56%), carrier tests (48%), and diagnostic tests (43%). Most of the tests ordered were single-gene tests (44%) rather than gene panels (29%) or karyotypes (tests that examine chromosomes) (14%).[82] While exact estimates are not available, it is likely that primary care clinicians rarely order exome and genome sequencing as these tests are more commonly under the purview of medical genetics.[83]

Use of genomic tests for risk-based screening purposes appears to be fairly uncommon.[84, 85] According to an analysis of a nationally representative sample of 18,601 women surveyed in the 2015 National Health Interview Survey (NHIS), very few women had ever discussed genetic testing with their clinician (4.55%), had genetic counseling (2.78%), or had genetic testing (1.64%). Among those with a high familial risk of *BRCA1/2*-related cancers based on family history, only 7.35% had received genetic testing.[84] Another analysis of NHIS data from 2000, 2010, and 2015 estimated that 1.2 to 1.3 million eligible women did not receive genetic testing for cancer risk.[86] A separate study looked at 552 women who fulfilled the USPSTF's criteria for increased risk of *BRCA1/2*-related cancers and found that 90% had shared their family history with their clinician, but less than 20% had been referred for genetic counseling and only 8% had undergone genetic testing.[87] In addition, data from the Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia registry show that only 3.9% of individuals in the registry with a clinical diagnosis of familial hypercholesterolemia have received genetic testing.[88] An analysis of a cohort of insured women with and without incident breast cancer at Kaiser Permanente found low rates of *BRCA* testing between 2000 and 2015; in this study no ordering by primary care clinicians was observed, likely reflecting standard practice within the organization.[89]

We found no data on primary care clinician ordering of genomic tests for the purposes of screening in unselected, asymptomatic populations.

Use of Genomic Testing by Consumers

Consumer Use of Genomic Testing

The market for DTC genomic tests and consumer awareness of these services have grown rapidly in recent years. In 2019, the total number of people who had taken any DTC genomic test was more than 26 million worldwide, up from about 12 million in 2017.[90, 91] This includes more

than 14 million people tested by Ancestry.com and more than 9 million tested by the next largest company, 23andMe.[90]

Sales data specific to health-related DTC tests are not publicly available, but interest in health-related DTC tests appears to be growing.[92] In the United States, the percentage of residents who had heard of DTC genomic tests that provide health risk information increased from 29% in 2008 to 38% in 2014.[93-95] While updated figures are not available, it is likely that awareness and use of health-related DTC genomic testing has continued to grow in recent years, as evidenced by the fact that 23andMe's bundled genealogy and health DNA test kit was among the top five Black Friday sellers on Amazon.com in 2017.[92]

Awareness of health-related DTC genomic tests is highest among Internet users, people with high incomes, college graduates, urban residents, non-Hispanic white individuals, people with a regular source of healthcare, and people with a prior cancer diagnosis.[93-95] Similar demographic groups have the highest levels of use of health-related DTC genomic tests. In the Impact of Personal Genomics (PGen) study, which includes 1,464 consumers of DTC genomic testing, most have health insurance (94.7%), are white (84.3%), have annual incomes of greater than $40,000 (83.2%), and are college graduates (78.2%).[96).]

While many consumers of DTC genomic testing services are interested in their ancestry and genealogy, they also report high levels of interest in health-related reports. According to a survey of DTC genomic testing consumers (n=1,648) participating in the PGen study, a similar proportion of consumers are "very interested" in ancestry information (74%) and disease risk information (72%). Specifically, participants reported being "very interested" in learning about their risk for heart disease (67.8%), breast cancer (66.9%; women only), Alzheimer's disease (66.3%), prostate cancer (59.9%; men only), skin cancer (59.4%), diabetes (55.3%), and colon cancer (52.7%).[97] Another survey from the PGen study (n=1,487) found similar levels of interest in DTC testing across White individuals and racial minority groups, with greater proportion of Black consumers compared with White consumers reported being "very interested" in testing for nonclinical genetic traits (91.9% vs. 70.8%; p=0.009).[98]

Consumer Sharing of Genomic Test Results in Primary Care

Available survey data suggest that 20% to 30% of people who use DTC testing share their results with a primary care clinician. Far less share their results with a genetics or other clinical specialist, suggesting primary care is by far the most common first stop for people who wish to share their DTC results with a clinician.

A meta-analysis of eight studies (n=3,921) found that about one-third of DTC genomic testing consumers (33% [95% CI, 18% to 48%]) had shared their results with a clinician, including 23% who had shared with their primary care provider and 5% who had shared with a genetics specialist. Seven percent of consumers had received followup screening, laboratory tests, or other preventive care as a result of their DTC genomic testing.[99]

In the PGen Study (n=1,026), 63% of consumers obtaining DTC testing in 2012 reported intentions to share their results with a healthcare provider. Six months after receiving their

results, 27% of participants had actually shared their results with their primary care clinician, 8% had shared their results with another type of healthcare provider,[100] and 4% had attended or scheduled a genetic counseling appointment.[101] A separate study of U.S. DTC consumers (n=1,046) conducted in 2010 found that 28% of consumers had shared their results with at least one clinician, including 20% who had shared with their primary care provider, 19% who had shared with another type of clinician, 1% who had shared with a genetic counselor, and 11% who had shared with more than one clinician. Almost 10% of participants reported obtaining followup laboratory tests as a result of receiving their DTC genomic testing data.[102]

In a 2017–2018 survey of Kaiser Permanente primary care and specialist providers (n=1,502), 35% reported receiving at least one DTC health risk result from a patient in the past year, and 12% reported receiving at least one pharmacogenomics result. Of the clinicians who had received DTC results from patients, about 40% had referred those patients to other clinicians, primarily to clinical geneticists.[103]

Another study suggested that consumers who share DTC test results with clinicians may be more health conscious than those who do not. In this study (n=2,024), 26.5% of DTC genomic test consumers had shared their results with a healthcare provider. Those who did so reported higher levels of exercise, lower fat intake, fewer overall concerns about genetic testing, and fewer concerns about the privacy of their genomic information than those who did not share their results with a clinician.[104]

Some consumers opt to download their raw genetic data and use third-party DNA interpretation services to provide health-related reports. In a 2016 survey of 321 users of third-party DNA interpretation services, 62% cited learning about their health as a "highly important" motivator for exploring their raw DNA, and 30% reported sharing their results with a medical provider.[80] Among those who shared their results with a medical provider, 80% reported sharing with a primary care clinician, 10% with a nurse practitioner, 14% with a genetic counselor, and 25% with another specialist. Twenty-one percent of participants shared their results with multiple medical providers. When asked about the outcomes of sharing their results, respondents reported that their medical provider was interested in the results (29%), used the results to modify medication or supplements (12%), and ordered followup testing or treatment (12%). Twenty-three percent of respondents said their doctor was uninterested in the results.[80]

In the coming years, primary care clinicians are expected to receive more requests for interpretation of DTC or other patient-generated genomic data.[105] Given the history of DTC companies that bypass the medical model by making genetic data available directly to consumers, and the recent regulatory environment under which the FDA considers DTC testing a medical device, there may be a greater integration of DTC and medically generated genomic data in the future, as patients can effectively self-order tests that may require clinical followup.[63]

The National Academies of Science, Engineering, and Medicine, in a workshop about the acceleration of research on precision health and genomics, predicted emerging opportunities for genomics and digital health. The authors predicted increasing opportunities for consumers to engage directly with their genomic data through DTC services and associated data platforms. The group noted the potential for improved population health with this development, and the

potential for reduced disparities in increasing direct patient access to testing as the cost of testing decreases. The group also noted an emerging hybrid model wherein clinicians order and interpret DTC health-related tests for patients rather than patients bringing the test results to them. However, as testing increases, a massive amount of data is created, introducing new questions about data quality, management, sharing, and maintaining consumer privacy.[106]

Challenges Integrating Genomic Testing Into Primary Care Practice

As the use of genetic testing grows, so does the need for genetic counselors and genetics professionals to meet the need for clinical support.[107-109] A study by the Genetic Counselor Workforce Working Group estimated that the United States had a shortfall of about 1,900 genetic counselors in 2017, or about 44% of what would be needed to provide clinical services if there were 1 counselor per 75,000 people.[110] A survey of ACMG members involved in clinical care found that 62% of medical geneticists said their practices were full, and 45% reported that their organization had job vacancies.[111]

These workforce issues are among many barriers to clinical integration of genomic testing into primary care. Several studies and Key Informant interviews suggest that despite widespread acknowledgment of the potential value of genomic testing in clinical care, multiple barriers remain: lack of consensus about clinical utility; uncertainty about standard practices for communicating genomic results to patients; lack of data infrastructure to support clinical decision making (including integration with electronic health records [EHRs]); uncertainty about clinical workflow, including downstream management, surveillance strategies, and re-interrogation of test results as evidence emerges; and uncertainty about knowledge or training about genomics more broadly. Coverage and reimbursement inconsistencies as well as liability concerns also were noted.

According to a 2019 systematic review of genetic cancer risk assessment tools available to primary care providers, a majority of studies found that clinicians considered genetics in primary care to be important but that self-reported provider knowledge was low and providers had concerns about time pressure, competing demands, and expansion of the general practitioner role.[112] A Delphi panel study published in 2016 found several barriers relevant to primary care providers. Cited as key barriers were the lack of data sharing among testing companies, which slowed the identification of clinically actionable mutations; inconsistencies in coverage and reimbursement due to varying evidentiary standards for assessing clinical utility; and the lack of standardization for reporting and communicating test results.[113] Other barriers included the lack of provider training in genomics, lack of standardization of the role of genetic counseling in routine clinical practice, and the lack of data infrastructure for genomic data within EHRs to facilitate clinical decision making. The lack of clear legal guidance on the scope of potential liability for clinicians regarding the reporting and interpreting tests was also noted.[113]

A survey of physicians conducted from 2014 to 2016 (n=285 physicians, 49% working in community settings, subspecialty not reported) from five institutions conducting studies funded through Implementing GeNomics In pracTicE (IGNITE; National Institutes of Health [NIH]

grant number RFA-HG-12-006), primarily disease genetics studies (73%), explored attitudes on barriers to clinical implementation of genomics. Two-thirds of physicians thought sequencing was relevant to clinical practice, and one-third felt their ability to care for patients would improve if genetic risk data were available during patient visits. However, only one-third reported that their training had prepared them to deal with patients at genetic risk, and only 15% felt confident in their ability to use genetic data in practice. Physicians with less than 5 years of practice experience reported higher levels of confidence.[114] Another survey of IGNITE members and affiliates found the top factors related to genomic program sustainability were expanded provider education in genomics; availability of clinical decision support tools; consideration of the addition of genomics to clinical workflow; implementation research; clarity in liability laws related to genomic medicine; and long-term data on health outcomes and harms.[115]

An interview study of physicians (n=25) associated with four sites participating in the NIH-funded Electronic Medical Records and Genomics (eMERGE) network on attitudes regarding the receipt of unsolicited genetic test results in practice found that clinical actionability was important to physicians, specifically because it could alter a patient's disease course. Many noted a need for evidence or data on test characteristics, predictive value, and patient outcomes, and the lack of evidentiary standards for genetic data compared to other tests. Although several potential benefits to patients were noted (e.g., improved care), many potential harms also were noted (e.g., anxiety/regret, insurance discrimination, false reassurance, unclear long-term impacts). Multiple workflow barriers were cited, including unreimbursed time and unclear liability.[116] Questions remain about how to resolve the complexity of integrating genomic data into EHRs and clinical care.[117] In an interview study with genetics professionals about issues related to the return of incidental findings from exome or genome sequencing, participants similarly expressed a need for standardized workflows that included genetic counseling; preference for clinical integration varied by clinical role, but there was wide agreement about the need for a multidisciplinary team to be involved in returning results.[118]

Multiple studies have noted the perceived lack of knowledge or training of nongenetics clinicians as a significant barrier. A 2017 systematic review of studies of primary care provider knowledge and attitudes found that while assessments of clinical utility were generally favorable, self-reported knowledge was often limited.[119] Further, a survey of medical genetics course directors (n=157; 73% response rate) found that most medical schools incorporate genetics education primarily into didactic years 1 and 2 of medical school, but only 26% of courses incorporated genomics into clinical years 3 and 4.[120]

A Delphi study of researchers, clinicians, law and policymakers, industry representatives, and patient advocates with experience in genetics published in 2016 found that 71% (24/34) of participants agreed or strongly agreed that next-generation sequencing would be a valuable tool spanning multiple areas of clinical practice within the following 5 years. The most common clinical area indicated was oncology, and most (74%) of the panel reported that potential risks to patients were moderate to low.[113]

Key Informants noted similar challenges: uncertainty regarding best practices for genetic risk assessment, criteria for referral for genetic testing, which tests to order, and management of high-risk patients in primary care. Primary care clinicians reported concern about a potential increase

in requests to interpret DTC testing results, including clinical followup of secondary findings and workflow concerns. Inconsistent insurance coverage for genetic testing also was noted as a challenge.

When discussing challenges for integrating genomics into primary care, several Key Informants mentioned a lack of clinical practice guidance and a lack of a minimum core competency for genomics in primary care. They suggested that lack of guidance contributed to a variation in practice. Key Informants thought there was confusion about primary care clinicians' role in communicating, testing, and caring for family members of patients at high risk of genetic conditions, and about any role they might play beyond referral to medical genetics. Training needs were frequently cited, including limited genomics training in most medical schools (especially for older cohorts) and lack of continuing education opportunities. However, some Key Informants did not think there was a shortage of training resources; rather, they felt the challenge was competing clinical priorities and time demands. Genomic screening is still relatively rare in actual practice, so clinicians may not prioritize the need for training.

Key Informants identified several contextual issues relevant to the integration of genomics in primary care. First, genomic science is rapidly advancing, and both guideline makers and clinicians have encountered challenges keeping up with clinical implications and knowing what results to return to patients. Further, it remains unclear how genomic data should be stored and stewarded in a fragmented healthcare system, as well as what the processes should be for re-interrogating genomic data and returning relevant results to patients. Finally, standards regarding the use of genomics in clinical care are still evolving, most notably the implications of genomics in pediatric settings, including best practices for sequencing newborns; uncertain recommendations about the optimal age to return risk data on adult-onset conditions to patients; and duties of clinicians in communicating test results to patients and families.

Genomics and Health Equity

The literature about genomics and health disparities highlighted two particular concerns. First, the potential clinical validity of genomic testing for population groups of non-European ancestry is likely limited because of underrepresentation of these groups in genetic research studies.[121, 122] An analysis of the NIH Genome-Wide Association Study Catalog found that non-European participants represented only 19% of individuals studied, and most of these non-European participants were of Asian ancestry.[123] Together, individuals with African, Latin American, and Native or Indigenous ancestry account for less than 4% of samples analyzed.[123] NIH has made increasing diversity in genomic discovery research a priority.[124]

Second are the widely recognized disparities in health outcomes and access to care, including genomic care. A survey of ACMG members found that rural populations, people living on Native American reservations, non-English speakers, and uninsured individuals were at risk for not accessing genetic services. Barriers to accessing genetic services included distance to care, a lack of recognition among primary care providers about the need for a genetics referral, genetic provider workforce shortages, and insufficient insurance coverage.[111] An analysis of the 2015 NHIS data found disparities in genetic testing for people of Hispanic ethnicity, people who were uninsured, noncitizens, and people with less than a high school education.[125] In a healthcare

system with finite resources, spending on genomic medicine could shift the focus from more structural determinants of health—such as poverty, environmental exposures, and geographic disparities—and potentially exacerbate existing health disparities[122, 126] as well as financial barriers to followup care or behavioral changes.[127] Other possible sources of disparities in accessing testing include perceptions about the nature and intent of genetic services and geographic distance to clinics.[128]

Strategies to address these two concerns include efforts to increase representation of diverse populations in genomic research, implementing genomic medicine programs in diverse healthcare settings and underserved communities, and engaging communities and healthcare providers in genomics research.[126] State public health genomics programs might also help reach populations with barriers to accessing genomics services.[129]

Several Key Informants also pointed out that disparities in access to testing could grow even more without intentional policies focused on equity. While inexpensive testing can in theory reach more people, reduced access to genetic counseling, testing, and followup care over time was cited as a possibility. Additionally, some Key Informants noted that a lack of USPSTF screening recommendations for people at increased genetic risk can result in inconsistent coverage of testing for people and families at increased risk.

Care Models to Support Primary Care Clinicians' Communication With Patients

To date, the role of the primary care physician in genomic medicine has been primarily limited to genetic risk assessment, typically through family history assessment followed by specialty referral, and possibly clinical management of genetic conditions after diagnosis. This type of care has been provided for single-gene conditions for many years, and may be instructive looking forward to more multigene testing.

A 2019 systematic review of genetic service delivery models identified 148 genetics services programs worldwide, 35 of which were based in the United States.[130] Worldwide, the most common model was geneticist-led (13 U.S.-based programs), where patients receive all genetic counseling and care within a medical genetics specialty setting. Less common were primary care–based models (3 U.S.-based programs); here, the primary care clinician conducts an initial risk assessment and then refers the patient to genetic services or delivers genetic counseling, orders testing, and returns results to the patient. *Population-based genetic screening programs* also were identified (16 U.S.-based programs). In this model, patients receive genetics services as part of a population-based screening program, typically through a primary care physician or other nongenetics subspecialist, and testing is typically focused on detecting specific conditions in defined populations (e.g., newborn screening, hereditary breast and ovarian cancer, or genetic screening for individuals with Ashkenazi Jewish ancestry). Other, less prevalent care models are those that call for nongenetics subspecialists (e.g., oncologists) to test, counsel, and return results, as well as DTC models in which the testing company provides testing, counseling, and return of results, and sometimes also genetic counseling and referrals.[130]

Most care models rely on genetic counselors and medical geneticists to provide pre- and post-test genetic counseling, interpret and return results, and support informed decision making about followup care. However, in light of the growing shortage of genetics professionals, researchers and healthcare systems are exploring alternative models for providing genetic counseling services.[108] Such models include:

- **Group education with individual counseling.** Genetic counselors provide genetic education to multiple nonrelated patients in a group setting (such as a prenatal group visit), and individual appointments are available if patients desire them.[131, 132]
- **Post-test counseling only.** Patients receive print, video, or web-based educational materials prior to genetic testing, with opportunities to speak with genetic counselors by phone after receiving their results.[133-136]
- **Digital tools for risk assessment or counseling.** Technology such as smartphone applications and "chatbots" (digital simulated conversation tools) facilitate communication with patients about genomic testing, including risk assessment, consent, post-test result followup, and cascade testing for relatives.[137, 138]
- **Telegenetics.** Genetic counselors provide counseling services directly to patients via phone or telemedicine.[139, 140] This can also include group visits via telemedicine with multiple patients at various locations[108] or remote appointments for specific clinical functions, such as consultation with medical genetics only for complex cases,[141] while a local team provides relatively uncomplicated services.[142, 143] The use of telemedicine may help alleviate the genetic counselor shortage and improve access to genetics services for underserved areas.

Multiple studies have found that telegenetics is more convenient and less expensive than in-person counseling, although uptake of genetic testing is lower among patients receiving phone- or video-based counseling.[139, 140, 144, 145] Patients' knowledge, test-related distress, anxiety, decisional conflict, perceived personal control, and satisfaction with counseling are similar between those receiving telegenetics and in-person genetic counseling.[139, 140, 145, 146]

Although family history collection in primary care is routinely practiced, challenges persist in updating family history and in reaching underserved populations. In a survey of U.S. pediatricians and family medicine physicians (n=1,200), 77% reported collecting family history on a first visit, but only 42% routinely update family history at wellness visits.[147] Further, clinic-based family history collection is limited to serving people who attend clinical visits and have continuity of care. However, an increased demand on primary care providers with regard to genomic testing seems imminent. The cost of genomic tests has decreased, removing a substantial barrier to exploratory test ordering without clear expected benefit. Also, the widely projected shortage of genomic medicine clinicians is likely to increase the involvement of primary care providers in genomic medicine. Further, as insights into gene-disease associations (e.g., cardiovascular disease, cancer, dementia, mental health conditions) expand, the availability of multiple-gene panels has skyrocketed. Because of the availability and marketing of testing panels directly to patients, it is increasingly likely that primary care physicians will be asked to interpret or determine clinical actionability for test results that they did not order.

Tools and Resources Available to Clinicians

There are multiple educational resources for clinicians.[117] For example, the National Human Genome Research Institute (NHGRI)'s Genetics/Genomics Competency Center for Education is a curated repository of high-quality curricula on genomic medicine for physicians and other healthcare providers.[148] In addition, NHGRI's Inter-Society Coordinating Committee on Practitioner Education in Genomics has developed a framework for developing physician competencies in genomic medicine. The framework includes five "entrustable professional activities" comprising a core set of genomic skills, namely: family history taking, genomic testing, treatment based on genomic results, somatic genomics, and microbial genomics.[149]

There are also several tools for use in assessing genetic risk. A systematic review published in 2019[112] identified eight genetic cancer risk assessment tools, including the Gail model,[150] MeTree,[151] Genetic Risk Assessment in an Intranet and Decision Support (GRAIDS),[152] and Your Health Snapshot.[153] A 2019 systematic evidence review in support of the USPSTF recommendation on *BRCA* testing found eight tools that use family history to assess breast cancer risk.[154] These include the seven-question Family History Screening (FHS-7),[155] the Ontario Family History Assessment Tool (FHAT),[156] and BRCAPRO.[157]

ClinGen's Consent and Disclosure Recommendations workgroup has pilot-tested two rubrics designed to support clinicians in communicating with patients about consent for genetic testing and return of genetic testing results.[158] Digital tools may also hold promise for enhancing communication about genetic test results. For example, the Gen-Equip project has developed online training and resources to support primary care clinicians in providing genomics services, including information on how to take a family history, make a referral, and explain genetic concepts to patients.[159] Clinicians have reported high levels of satisfaction with the tools, as well as improvements in knowledge, skills, confidence, and practice behavior after using the resources.[160]

Key Informants highlighted several strategies and resources to support communication about genetic testing. These include risk assessment questionnaires to identify patients who might benefit from genetic testing; third-party telephone-based genetic counseling; coordinated efforts to connect patients with genetic counselors while providing primary care clinicians with information to help manage test results; "action sheets" (called ACT sheets) for clinicians on pathogenic variants from the ACMG secondary findings list; clinical decision support alerts related to pharmacogenetics; online trainings and continuing medical educations for primary care clinicians; training programs to support nurses in delivering genetic counseling; and telephone-based genetic testing–related consultations for clinicians, health plans, and health systems.

Results of Literature Review: Outcomes of Genomic Screening and Risk Prediction Testing in Primary Care

Our audit reveals that published and ongoing genomic studies are exploring a wide range of outcomes (**Appendix D Table 1, Appendix D Figure 1**). Most of these—test accuracy, intermediate outcomes, health outcomes, other positive outcomes (beliefs and intentions), and

harms and unintended consequences/tradeoffs—are similar to those assessed in other USPSTF screening topics.

Test accuracy–related outcomes include frequency of disease or disease predisposition detection (yield) and traditional measures of sensitivity or specificity. Intermediate outcomes include disease incidence, physiologic outcomes such as changes in body mass index (BMI) or blood pressure, lifestyle or behavioral changes as a result of exposure to genetic risk information, and healthcare utilization. Health outcomes include measures of quality of life and morbidity and mortality. Other positive outcomes are related to beliefs and behavior change intentions, including personal utility, self-efficacy, attitudes, information seeking, and participant understanding. Reported harms include false-positive results, false reassurance, and psychosocial distress.

The outcomes most commonly published to date in screening studies relate to harms, most commonly psychosocial distress—likely reflecting the focus on individual psychosocial harms that was prevalent at the beginning of the genetic era. Other commonly reported outcomes include detection of disease predisposition and beliefs and intentions, such as participant understanding and information seeking or sharing (**Appendix D Table 1**).

Many studies are still ongoing, with planned—but not yet reported—outcomes. These include harms, mortality (MyPeBS[161]), morbidity (MyPeBS[161] and WISDOM[162]), quality of life (MilSeq,[163] MyPeBs,[161] PopSeq,[164] MVP-ROAR,[165] PRoGRESS[166]), stage at detection, and disease incidence. Three studies reported planned outcomes of cascade screening of relatives (PRoGRESS,[166] PopSeq,[164] MVP-ROAR[165]) In general, both existing and ongoing or new studies are examining similar outcomes. Health outcomes (quality of life, morbidity, and mortality) were not reported in any published reports, but some newer or ongoing screening studies do plan studies with these outcomes (**Appendix D Figure 1**).

Key Informants reported potential benefits and harms associated with genomic screening similar to those identified in the literature search. The main potential benefit mentioned was improvement in health outcomes through medication management with pharmacogenomics, enhanced surveillance or prevention strategies, or individual personal engagement with health, possibly fueling behavioral modifications relevant to disease risk reduction. Psychosocial benefits related to personal utility and potential health benefits to relatives also were mentioned. Potential harms included psychosocial distress, insurance discrimination, privacy concerns, and false reassurance from receiving a negative test result.

Evidence for Benefits or Harms of Genomic Screening and Risk Prediction Testing in Primary Care

Our literature search identified nine published studies that met our inclusion criteria (**Table 2**).[51, 167-173] Included studies ranged from randomized clinical trials (RCTs) (k=3)[167-169] to implementation programs within health systems.[51]

The three RCTs (n=507)[167-169] examined the impacts associated with genomic testing for screening or risk prediction purposes. In the BabySeq trial (n=257), healthy infants in the

intervention group received genome sequencing in addition to conventional newborn screening, while infants in the control group received conventional newborn screening alone. Outcomes include healthcare use, family and personal distress, personal utility, and the identification of disease risk variants.[167] In the MedSeq trial (n=100), healthy primary care patients received genome sequencing. Intervention patients and their physicians received a report based on genome sequencing results and family history, while comparison group participants received a family history-only report. Outcomes of interest include psychosocial outcomes, behavior changes, healthcare use, personal utility, and cost.[168, 174] In the Predictive Genetic Risk Assessment Trial (PGT, n=150), intervention participants received DTC testing for predisposition for 12 conditions (such as breast cancer, colon cancer, obesity, and osteoarthritis), while comparison group participants receive usual care. The outcomes are disease risk perception and worry.[169]

All three trials reported psychosocial outcomes, and 2 of 3 reported yield of screening for detecting disease or disease predisposition, healthcare use, and participant understanding and information seeking, as well as personal utility. No trials have reported or planned outcomes of morbidity or mortality.

Six observational studies met our inclusion criteria (k=6, n=60,408).[51, 170-173, 175] All are single-arm observational cohorts observing the impacts of genomic screening in healthy adults. One of the six (Geisinger MyCode) is a clinical implementation project and has the largest sample size (N=57,758).[51]

Studies varied in settings, testing protocols, scope, and design. No observational studies included comparison groups. In the one pilot study (GeneScreen, n=1086), screening for clinically actionable variants was undertaken in a healthy adult internal medicine population in a large university medical center.[170] In the other clinic-based study, the MyCode initiative at Geisinger (n=50,726), the team is building a research biorepository, with exome sequencing results linked to Geisinger patients' medical records, and is returning clinically actionable results (adapted from ACMG guidelines) to participants.[51, 176-179] One cohort study (ClinSeq) is a pilot study of sequencing conducted by NHGRI. The primary intention of this cohort is to create a research cohort for future studies; however, relevant findings are returned to participants when identified.[175]

By contrast, two other cohorts observed outcomes in people who had elected to receive genomic screening, either by DTC testing (PGen, n=1,648)[171, 180-183] or by early adoption of genome sequencing (PeopleSeq, n=658).[172] In the Scripps Genomic Health Initiative (n=3,640), adults received a panel of disease risk information judged to have risks modifiable by changing individual behavior.[173]

All six cohort studies reported healthcare utilization outcomes.[168, 171, 172, 180, 184-186] Five of the cohort studies (all except MyCode) have or will be reporting participant intentions to change behavior based on testing results, as well as psychosocial distress outcomes such as worry, anxiety, or regret, and participant comprehension.[170-173, 184] Four cohort studies (GeneScreen, PeopleSeq, PGen, and Scripps) reported lifestyle changes such as modifications to diet, physical activity, and smoking behaviors.[170, 172, 173, 182, 183] Three cohort studies (PeopleSeq, PGen, and

Scripps) reported personal utility measures and information seeking.[172, 173, 182-184] One study (GeneScreen) includes family-level distress outcomes.[170] Three studies (MyCode, GeneScreen, and ClinSeq) reported overall screening findings and rates of disease/disease predisposition detection.[176-179, 185, 187]

Study Findings

No evidence was available on the impact of genomic screening on morbidity, mortality, or quality of life. There is a substantial body of evidence suggesting that psychosocial harms of testing (including DTC testing) are minimal, but no evidence reported on the potential harm of unnecessary workup related to false-positive results or on false reassurance related to incomplete understanding of negative findings. Likewise, several studies and reviews have found that exposure to genetic risk information has little impact on behavioral outcomes (e.g., diet, exercise, smoking). Testing can detect variants in population-based samples, but little evidence was available from the included studies on other measures of test accuracy. Likewise, there is little evidence in the included studies on secondary findings or their impacts, or on benefits or harms to relatives.

Test Accuracy and Yield

Identification of disease predisposition was the main outcome reported, and based on two trials and the MyCode, GeneScreen, and ClinSeq cohorts, it appears that genomic screening can identify risk variants in relatively unselected populations (e.g., *BRCA1/BRCA2*), carrier status for recessive variants, and variants associated with familial hypercholesterolemia or other cardiovascular disease.[51, 167, 168, 176-179, 185, 187]

Intermediate Outcomes

Three screening studies reported changes in medication use following genomic screening.[168, 171, 178] In two of three studies, no medication changes were reported.[168, 178] In the third, 5.6% of participants reported a change in medication after screening.[171] Similarly, in five screening studies, participant behavior changes were rarely demonstrated as a result of genomic screening.[168, 170, 172, 182, 183] One study reported similar rates of self-reported diet and exercise changes in both the screening and family history–only groups.[168] In the other studies, smoking and general lifestyle behaviors were similar at baseline and followup in screened populations.[170, 172, 182, 183]

Health Outcomes

No included studies reported disease incidence, morbidity, mortality, or quality-of-life outcomes. However, several included studies are relatively recent, so data may be available over time on these outcomes.

Harms

There was limited evidence in seven studies that the receipt of genomic screening results did not impact anxiety or depression or induce decisional regret.[168-174, 184] This is consistent with several

reviews suggesting that there is minimal evidence for persistent psychosocial harm resulting from genetic testing, and there has not been substantial reporting of genetic discrimination.[39, 188-190]

Studies of Behavior Change After Exposure to Genetic Risk Information

In addition to the nine studies on genomic testing for screening or risk prediction, we identified six additional trials that tested the impact of providing polygenic risk score information on individual health behavior (**Appendix D Table 2**).[191-196] In general, these trials included only populations already at risk for a condition, such as people with a high BMI, smokers, or people at increased risk for heart disease as determined by risk assessment scores. These studies found little to no impact on clinical markers such as BMI, cholesterol, or weight; similarly, they found little to no impact on smoking cessation, physical activity, or diet. This is consistent with a 2016 Cochrane review suggesting exposure to genetic risk information is not a sufficient motivator to change individual behavior (**Appendix D Table 3**).[197, 198]

Ongoing Studies

We identified nine ongoing studies that address genomic screening, risk prediction, or both (**Table 5**).[161-166, 199-201] Four of these studies are RCTs.[161, 162, 165, 199] The Cancer Health Assessment Reaching Many (CHARM) study aims to assess clinical exome sequencing in healthy individuals in primary care who are identified based on screening to be at high risk for a hereditary cancer syndrome (or unknown risk in the absence of family history information).[199] Along with examining the rates of positive findings on exome sequencing, this trial will compare the benefits of traditional genetic counseling and a modified genetic counseling model tailored for lower health literacy. The Million Veteran Program Return of Actionable Results (MVP-ROAR) study will compare immediate vs. delayed return of medically actionable genetic test results to participants in the Million Veterans Program.[165] The study will explore how returning these results affects cholesterol levels, medical management, patient lifestyle behaviors, and quality of life. Two larger ongoing trials will examine the effectiveness of a risk-based breast cancer screening strategy compared with standard screening. The My Personalized Breast Screening (MyPeBS) is being conducted in Europe with an estimated enrollment of 85,000 and completion date of 2025.[161] The U.S.-based Women Informed to Screen Depending On Measures of Risk Study (WISDOM) seeks to enroll 100,000 women; expected end date is 2020.[162] Both of these studies will compare standard screening according to current guidelines with screening based on a clinical risk assessment combined with a genetic risk score. The primary outcome in both trials is incidence of breast cancer.

Four ongoing exome- or whole-genome sequencing cohort studies target more specific populations: military personnel (MilSeq),[163] newborns (NC_NEXUS),[200] pediatric patients in the ongoing Geisinger MyCode program (PRoGRESS),[166] and participants in the Framingham Heart Study and Jackson Heart Study (PopSeq).[164] These studies will focus on the implementation and psychological impact of screening in these populations. The Personalised Risk-based Breast Cancer Prevention and Screening study will explore the impact of stratifying breast cancer screening strategies based on genetic risk for female participants in the Estonian Genome Center Biobank.[201]

A systematic review underway by NHGRI is summarizing the available research addressing the manner by which ACMG secondary findings are returned and the outcome data to support their return.[202] Preliminary results from this review indicate that few studies have examined the disclosure process or followed recipients to evaluate clinical utility and family communication. In addition, studies identified in this review indicate that not all individuals report these findings to their primary care provider or family members.[202] Norms about whether secondary findings should be considered benefits (if they result in improved health outcomes) or harms are evolving.[203]

Health Systems and Biobanks

In addition to published research studies, our search also identified several health systems that have begun offering genomic screening to their patients (**Table 4**). These include Northshore's Genomic Health Initiative (Illinois), University of Colorado's Center for Personalized Medicine, the Mayo Clinic Gene Guide program, and Harvard/Massachusetts General Hospital's Personal Genome Project. While these may yield valuable clinical data relevant to our GQs, none is being conducted as a research study, so planned outcomes are not available.

In addition, several large projects are underway that are or will be returning genomic screening results to participants: NIH's All of Us program; the Alabama Genomic Health Initiative; the Healthy Nevada program; the Estonian Genome Project; and the PopSeq project, which is part of the TOPMed program. At the time of this report, only the Estonian Genome Project had published results, which include the return of genomic results for familial hypercholesterolemia, leading to changes in medication management and an increase in cascade testing.[204] Several large biobanks also have been formed, including the VA's Million Veterans Program, Kaiser Permanente Research Biobank, and Vanderbilt's de-identified biobank; none report planning to routinely return results to participants.

The NHGRI-funded Electronic Medical Records and Genomics (eMERGE) Network has supported nine study sites to screen biobank participants for the ACMG 59 variants and return results to participants with actionable findings. No published results are available on the results of these activities.

Studies of Testing for Pharmacogenomic Purposes

The majority of evidence related to pharmacogenomics centers is on the underlying effect of single variants on drug response and adverse effects, and thus is outside of the scope of this technical brief. Studies of the implementation of pharmacogenomics have used two primary strategies: point-of-care or pre-emptive. With a point-of-care strategy, testing occurs when the drug is first prescribed. The pre-emptive strategy is the most analogous to a screening model, where variant data are collected for multiple pharmacogenomic targets, stored within an EHR system, and ideally coupled with clinical decision support when prescriptions are considered.[205] However, current EHR systems may not support the implementation of these tools.

We identified a few studies that fell within the purview of this technical brief, using the pre-emptive model. The 1200 Patients Project (completed December 2018) at the University of

Chicago aimed to determine whether pharmacogenetic results made available to a patient's treating physician are used during routine healthcare.[206] The Vanderbilt Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment program tested more than 10,000 people with preemptive pharmacogenomic testing, finding that more than 90% carried at least one actionable variant.[207] The PREemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study aims to evaluate the use of pre-emptive genotyping of 12 genes with the goal of reducing adverse drug reactions related to 43 target drugs. This prospective, block RCT clinical study is being conducted in seven European countries and will examine the impact on patient outcomes and cost-effectiveness. The target enrollment of this study is 8,100 patients, with an estimated study completion of December 2019.[208] The Right Drug, Right Dose, Right Time (RIGHT Protocol) study uses pre-emptive screening among participants of the Mayo Clinic biobank and aims to develop EHR support infrastructure and clinical support tools to examine the effects of clinical practice and patient outcomes. The estimated enrollment of this program is 14,000 patients with an estimated completion of July 2024.[209]

More information about pharmacogenomics is in **Appendix E**.

Five-Year Future Horizon

There was wide consensus among Key Informants—consistent with forecasting in several published commentaries—that the cost of testing will continue to decrease in the next 5 years, accompanied by an increase in evidence about disease risk or pharmacogenomics potential.[1, 210, 211] Further, as genomics moves toward public health applications, a hybrid ethical and legal framework may emerge that includes a focus on prevention/population rather than treatment/individual, and on greatest net social good, equity and health disparities considerations, community consent considerations, and possible tensions between individual privacy and the common good.[65]

The clinical use of polygenic risk scores is also likely to increase. Polygenic risk scores typically provide a relative, rather than absolute, estimate of disease risk based on analyses of genome-wide association studies; methods for developing these scores still are evolving, and their clinical utility has not yet been established.[212] Multiple DTC and clinical testing companies have started to return these risk scores along with more traditional results. However, some Key Informants and commentaries have questioned the clinical value of this testing.[213] The eMERGE network (funded by NHGRI) will focus its next round of funding on the development and validation of polygenic risk scores for several complex diseases and assess the uptake of risk reduction recommendations based on these scores as well as their impact of clinical outcomes.[214]

Key Informants consistently predicted that testing availability will only increase, both to the public and to primary care clinicians (**Appendix F**). Key Informants also consistently predicted that models of care would soon emerge, providing data on best practices for clinical care and integration of genomic screening data with EHRs to support clinical decision making. The clinical genomic workforce shortage was widely predicted to continue, with related concerns about limited scalability of the current pre- and post-testing genetic counseling care model.

Predictions for the pace of these changes within 5 years were more variable. Some Key Informants felt that no obvious changes would be apparent in the next 5 years, while some thought that significant changes would be observable in that time, particularly as evidence emerges from demonstrations of care models for population-based genomic screening. While Key Informants agreed that tests would be ever more widely available to consumers, not all thought consumer demand would continue to increase. Some Key Informants predicted that consumers would find limited utility in clinical genetic data over time, with interest limited to "infotainment" provided by nonclinical genetic information (e.g., ancestry). Others pointed out that other types of health screenings (e.g., cancer, cholesterol) are underused by patients, suggesting that genomic screening could be similarly underused over time.

More distal predictions beyond 5 years included widespread use of genome sequencing, such as of newborns, and the emergence of a generation of clinicians with high levels of knowledge and comfort with genomic medicine.

Chapter 3. Summary and Implications

Rapidly emerging evidence about the genomics of disease risk and the increased availability of genomic tests for screening or risk prediction to both consumers and clinicians will likely impact primary care practice. The scope of practice for primary care clinicians, particularly in responding to patient-initiated genomic data, is unclear. Additionally, there is potential for disparities in access to genomic testing, especially considering the shortage of genomic medicine clinicians in the United States. Patient use of DTC services for genomic data is increasing and is likely to increasingly touch primary care practice.

The evidence base for the health outcomes and harms associated with genomic screening and risk prediction is only beginning to develop; some information on these outcomes should be available in the next 5 years. Further, genomic discovery research continues to rapidly evolve, creating challenges for setting standards of care and interpretation of results.

Evidence was sparse on the effect of broad population-based screening on less traditional outcomes (e.g., clinical benefit or harm to relatives, nonphysical harms such as discrimination, and test accuracy outcomes). Little trial evidence on health outcomes is expected in the short term, but several large genomic screening implementation projects in large health systems are ongoing and will provide observational evidence on the yield and potential benefits and harms of population-based screening. There are little data about the impact of DTC testing on health outcomes, intermediate outcomes, or harms.

There is a substantial evidence base suggesting a low prevalence of psychosocial harms related to testing and limited ability of genomic risk data as a cue to behavioral or lifestyle changes. Multiple early studies exploring the impact of genetic risk information suggest that such information is not a sufficient motivator for individual behavioral or lifestyle change.

Other concerns include the potential for exacerbated disparities in access to testing and the lack of genomic diversity in existing research resources, which limits the application of genomics beyond populations of European ancestry. The uncertain regulatory environment as it concerns genomic tests, specifically because clinical utility is not required for approval, is an important contextual factor. Further, the ethical, legal, and social issues related to population genomic screening are well discussed in the literature but still evolving.

Implications for Primary Care

This review has suggested several implications for primary care practice.

- There is not a robust evidence base about the benefits or harms of genomic testing to suggest a clear role for the primary care workforce in testing, interpretation, and management of genomic test results. Family history assessment already is practiced in primary care, and many risk assessment tools are available. Uncertainty about management of patient-generated genomic data, including DTC results, was prevalent.

- Our review identified evidence for both low confidence about genomic competencies and multiple resources for clinicians, including risk assessment tools, genomics education resources, and curated resources providing guidance on emerging clinically relevant genomic tests.
- Multiple other workflow-related factors also were noted as barriers, including EHR-based clinical decision support that allows continued care of patients as new evidence emerges, clarity on circumstances for referral to genetics, access to genetics subspecialists, and competing time demands.
- Continued concerns about disparities in access to genomic testing and followup may present an opportunity for primary care practice.

Considerations for the USPSTF Portfolio and Methods

The topic of genomic testing for screening or risk prediction is largely consistent with other screening and risk assessment topics in the USPSTF portfolio. However, several considerations may require revisions or adaptations to traditional USPSTF methods.

Scope: Test and Condition Selection

Future screening initiatives are likely to include screening for sequencing panels that can detect risks for multiple diseases. This might require processes for determining the scope for a USPSTF review and for addressing secondary findings. When the USPSTF considered screening with pelvic examinations—which similarly reviewed a nonspecific test that could detect numerous conditions—the USPSTF deliberated extensively during scoping to determine which outcomes and conditions to consider.

Outcome Selection

While most positive and negative outcomes of genomic screening could be the same as for a traditional review, an expanded set of outcomes might present a deviation from typical USPSTF methods, including indirect clinical utility (e.g., to relatives, personal utility), and nonphysical harms such as discrimination. Also, secondary findings are likely to be a part of any screening program using a large panel or sequencing. The USPSTF has addressed issues related to secondary findings for topics addressing computed tomography screening (lung cancer screening and colorectal cancer screening) and deliberated on whether each finding should be considered a benefit or potential harm of screening.

Test Accuracy

Assessing test accuracy could be a challenge, given the rapid rate of discovery of gene-disease associations and incomplete penetrance and expressivity between individuals. While the USPSTF has dealt with changes in laboratory tests over time, the rate of change in the underlying technology and interpretation of genetic tests will likely occur at a more rapid pace. Further, several potential accuracy-related harms are possible, including false positive results and unnecessary diagnostic workups and false reassurances with negative tests.

Patient-Generated Data

DTC testing does not fall within the traditional purview of the USPSTF, since these results are patient-generated rather than clinician-ordered. However, because patients may approach their clinician with questions about the results, the testing is clearly relevant to primary care practice. The USPSTF may wish to consider how to incorporate patient-generated test results into existing topics, including guidance about clinical confirmation of patient-generated tests. Considerations would likely extend beyond genetic testing and into the realm of all patient-generated data (e.g., cardiac screening via wearable devices).

Limitations of the Technical Brief

This technical brief has intentional limits on its scope. The technical brief was scoped to focus on the implications of multigene testing for primary care practice, with the intent of supporting the USPSTF in assessing its portfolio and methods. As such, many relevant aspects of genomics and precision medicine are not fully considered here, such as the value of population-based screening programs, the evidence base for benefits and harms of single-gene testing programs, genomic screening efforts that do not intersect with primary care, and frameworks for evaluating medical tests more broadly. Although our original inclusion criteria allowed for pharmacogenomics testing, pharmacogenomics is not fully addressed in this report. This is due to our focus on broad panel or sequencing tests and our exclusion of targeted, single-gene tests, which make up a large portion of pharmacogenomic tests. Therefore, the presentation of pharmacogenomics studies in this report should not be considered a complete picture.

Further, given the rapidly evolving state of genomic science, this review should be considered a snapshot in time.

We did not conduct a formal systematic evidence review or abstract data from included studies, but rather summarized the results. Originally this technical brief was intended to include a systematic review of the evidence of genomic panel testing or sequencing for screening and risk prediction covering the past decade. However, because of impractically large search yields, we switched to a more pragmatic literature search approach. Thus, this technical brief should be considered a narrative review of the landscape rather than a definitive systematic evidence review of current evidence on any one variant.

Research Gaps Related to Genomic Testing and Primary Care

Research needs include the continued development of research on gene-disease association, especially in diverse populations. Randomized trials and well-conducted nonrandomized studies examining test accuracy outcomes, health outcomes, and harms of genomic screening are needed, as are data on the impact of returning secondary findings. Several trials are ongoing, and ongoing large-scale implementation projects within health systems also may provide relevant evidence on clinical care models, the role of primary care, patient and family-level

considerations, and expanded consideration of benefits and harms of testing, as well as attention to mitigating disparities in access to genomic testing and followup care.

Chapter 4. Conclusions

Rapidly emerging evidence about the genomics of disease risk and the increased availability of genomic tests to clinicians as well as consumers likely will impact primary care practice, but the role of primary care clinicians in genomic medicine is unclear. Additionally, there is potential for disparities in access to genomic testing. As patient use of DTC services for genomic data increases, so, too, does the likelihood that primary care providers' involvement with genomic data will increase.

Genomic testing with panels or sequencing increasingly is being explored in trials and large implementation projects for its potential utility for screening or risk prediction purposes, but there currently are little data available on the impacts of testing on health outcomes. At the same time, genomic data are increasingly available directly to consumers. Potential implications for genomic screening for the USPSTF methods include outcome and condition selection, considerations of test accuracy, inclusion of nonphysical harms, and consideration of benefits that extend beyond individuals to family members.

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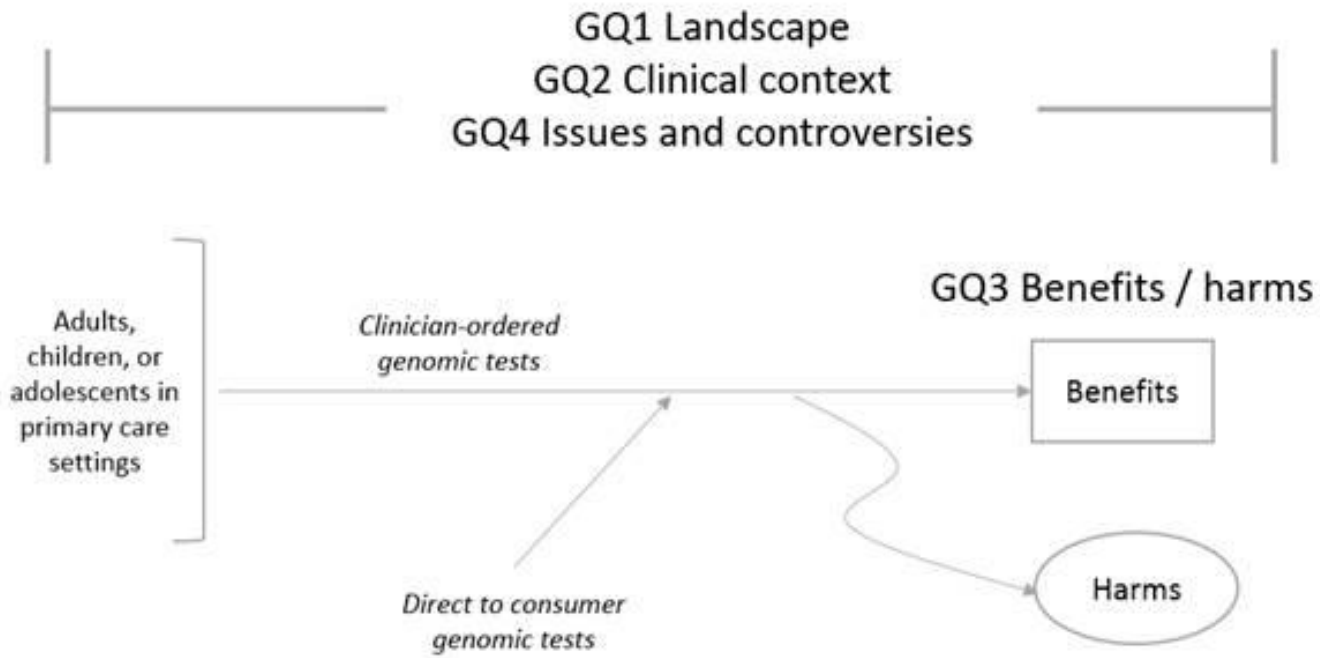
Figure 1. Analytic Framework



Abbreviation: GQ=guiding question.

Table 1. Selected Health-Related Direct-to-Consumer Tests Available in the United States, 2020

Company	Results available
23andMe	**Carrier status reports, including cystic fibrosis, sickle cell anemia; genetic risk reports (e.g., Mendelian disease risk, polygenic risk); wellness reports**
EasyDNA	**Wellness reports, including nutrition, skin care, health/fitness**
Full Genomes	**Exome sequencing; genome sequencing**
Xcode*	**Wellness reports; carrier status reports; genetic risk reports**
Gene by Gene	**Exome sequencing; genome sequencing** 250+ carrier status reports; ~300 genetic tests
Pathway Genomics	**Wellness reports, including nutrition and fitness, skin care, mental health, cardiac risk, medication use** Reports on genetics and healthy weight; women's health; 120+ carrier status reports
AncestryDNA	Carrier status reports, including cystic fibrosis, sickle cell anemia; cancer risk reports; cardiovascular risk reports
MyHeritage	Carrier status reports, including cystic fibrosis, Tay-Sachs disease, Gaucher disease; genetic risk reports, including heart disease, breast cancer, Alzheimer's disease
Invitae	Exome sequencing Hereditary cancer risk panels; cardiovascular health panels; carrier screening; prenatal screening; genetic risk reports for neurological disorders, blood disorders, childhood and rare diseases, and newborn conditions and metabolic disorders
Color Genomics†	30 cancer risk reports; 30 cardiac risk reports; pharmacogenomics reports; wellness reports, including lactose intolerance and taste perception
Counsyl	175+ carrier status reports; prenatal screen for trisomy 13, 18, and 21, sex chromosome abnormalities, and microdeletions; 25 cancer risk reports
Futura Genetics	Genetic risk reports for 28 conditions, including age-related macular degeneration, Alzheimer's disease, breast cancer, migraine, obesity
Genos	Exome sequencing
Helix	Carrier status reports; genetic risk reports; wellness reports, including calcium levels and body mass index
Sure Genomics	Genome sequencing
Promethease	Genetic risk report based on scientific findings cited in SNPedia*
Veritas	Genome sequencing; 18 genetic risk reports; "insights" on 650+ diseases; 225+ carrier status reports; 150+ drug sensitivity reports; *BRCA1/2* and HBOC panels; prenatal testing for trisomy 13, 18, and 21

Abbreviation: HBOC = hereditary breast and ovarian cancer.
Note: **Bold text** indicates results are available without clinician authorization. All other listed results require clinician authorization. Some testing companies provide clinician review and authorization as part of the test ordering process.

*Does not offer its own genetic testing kits; instead allows users to upload raw data from other tests (such as 23andMe) and then purchase wellness, carrier status, and genetic risk reports.
†Includes free genetic counseling services by phone.

Table 2. Characteristics of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Study	N	Years of data collection	Aim	Population	Intervention	Related outcomes (detail)
RCTs						
BabySeq[*167, 215-219]	257	2015 - 2020	Integrating genome sequencing into pediatric medicine through newborn sequencing	Well infants[†]	• Intervention: Conventional NBS + family history + genome sequencing • Comparison: Conventional NBS + family history	• Change in self-reported healthcare utilization • Change in family relationship and personal distress levels • Personal utility • Identification of disease risk variants
MedSeq[*168, 174, 220-224]	100	2012 - 2016	Study impact of incorporating information from a patient's genome sequence into the practice of clinical medicine	Healthy primary care patients (ages 40-65 years)[‡]	• Intervention: Patients and clinicians receive annotated report based on family history and genome sequencing • Comparison: Annotated report based on family history only	• Anxiety/depression based on the Hospital Anxiety and Depression score • Attitudes and trust of genetic information, provider, and medical system • Changes in diet, exercise, vitamin use, and supplement use • Change in healthcare utilization based on medical record review and Behavioral Risk Factor Surveillance System • Sharing genetic results with provider • Personal utility
Predictive Genetic Risk Assessment Trial (PGT)[169, 225]	150	2008 - 2010	Assess impact of DTC testing on perceived risk and worry in routine clinical care	Individuals in a preventive medicine executive healthcare clinic	• Intervention: DTC testing for 12 conditions • Comparison: Usual care (1- to 3-day preventive care visits)	• Disease risk perception • Worry
Cohorts						
ClinSeq[*]; ClinSeq A2[*175, 184, 187, 226-228]	2650	2007-2023	Pilot project to investigate the use of genome sequencing as	Individuals ages 45-65 years	• Intervention: Exome sequencing • Comparator: None	• Accuracy of sequencing • Detection to disease predisposition • Changes to disease surveillance • Behavioral change

Table 2. Characteristics of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Study	N	Years of data collection	Aim	Population	Intervention	Related outcomes (detail)
			a tool for clinical research			• Distress (Multidimensional Impact of Cancer Risk Assessment)
Geisinger MyCode[51, 176, 177, 179, 186]	50,726[§]	2007 - ongoing	Research biorepository of samples linked to EHR, allows for return of actionable findings to participants	Geisinger clinic patients	• Intervention: Exome sequencing • Comparator: None	• Rates of actionable findings • Medication changes • Disease and predisposition detection • Uptake of cascade testing in relatives
GeneScreen[170, 185, 229]	1,086	Feb 2016-May 2016	Pilot study of screening healthy adults for rare conditions that are related to clinically important genetic variants and that have prevention and/or treatment options using online education and e-consent	Healthy patients from General Medicine clinic at UNC and KPNW biobank	• Intervention: Screening 17 genes that confer risk for 11 rare, medically actionable conditions, most of which are related to a high risk for cancer or cardiovascular disease • Comparator: None	• Identification of disease risk variants • Disease risk perception • Changes in diet and exercise • Decision regret • Change in medical screening • Family support/family conflict
Impact of Personal Genomics (PGen) Study[98, 171, 180, 182, 183, 230-234]	1,648	May 2012 - July 2012	Determine consumers' reactions to genetic risk information for common diseases	DTC customers	• Intervention: Survey of DTC customers • Comparator: None	• Changes in diet, exercise, and smoking • Change in medication use • Likelihood of following up with genetic counselor • Disease risk perception • Harms from screening • Decisional regret

Table 2. Characteristics of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Study	N	Years of data collection	Aim	Population	Intervention	Related outcomes (detail)
PeopleSeq Consortium* **172, 235**	658§	2014 - 2017	Examining the medical, behavioral, and economic outcomes of returning genomic sequencing information to healthy individuals	Healthy individuals who were early adopters of genome sequencing	• Intervention: Survey of early adults in genome screening projects • Comparator: None	• Changes in diet, exercise, habits, and insurance coverage • Sharing genetic results with provider • Scheduling additional followup appointments with provider • Decisional regret • Harms from screening
Scripps Genomic Health Initiative* **104, 173, 236-242**	3,640	2008 - 2009	Determine the long term psychological, behavioral, and clinical impacts of genomic risk testing for common disease	Adults age 18 years or older	• Intervention: Navigenics Health Compass (assesses risk for over 20 common diseases) • Comparator: None	• Changes in diet and exercise • Anxiety related to test results • Sharing genetic results with provider • Likelihood of following up with physician and/or genetic counselor

Abbreviations: DTC = direct to consumer; EHR = electronic health record; KPNW = Kaiser Permanente Northwest; NBS = newborn screening; UNC = University of North Carolina.

* Ongoing; estimated completion in 2020 (BabySeq); 2022 (MedSeq); not reported (PeopleSeq); 2029 (Scripps Genomic Health Initiative).
† Study also included 68 neonatal intensive care unit patients not included here.
‡ Study also included 100 cardiology patients with cardiomyopathy.
§ Enrollment is ongoing.

Table 3. Summary of Results of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Relevant outcomes	Study	Author-reported findings
Test accuracy	BabySeq	• 10/127 (7.9%) of newborns had variants associated with previously unidentified monogenic disease risk that may be present and/or clinically managed in childhood.[167] • Adult-onset disease was identified in 1 child (*BRCA2*).[167] • Carrier status for recessive diseases and pharmacogenomics variants were reported in 140/159 (88%) and 8/159 (5%) of newborns, respectively.*[167]
	ClinSeq	• Compared with Sanger sequencing, next-generation sequencing was found to have a validation rate of 99.965%.[227] • Among 572 patients, 7 participants were found to have a deleterious *BRCA1* or *BRCA2* variant. One participant had a deleterious *SDHC* variant (paragangliomas).[187]

	GeneScreen	• 15/262 participants (5%) screened positive for genetic variants in one of the 11 genes tested. Of these:
		  ○ 5 patients already knew about their results.
		  ○ For those who did not previously know, they had not yet developed signs or symptoms, nor did the result explain any previous symptoms.[185]

	MyCode	• 49/1415 (3.5%) of the pilot cohort were estimated to have a pathogenic variant in the 76 clinically actionable genes examined.[51] • Of 50,726 patients who underwent exome sequencing, 267 (0.5%) were *BRCA1/2* carriers. Compared with previous clinical care, exome sequencing identified 5 times as many individuals with a pathogenic or likely pathogenic *BRCA1/2* variant.[179] • Among 55 participants with a *BRCA1/2* variant, 37 (17 females, 20 males) were previously unaware of their status and had no history of *BRCA*-associated cancer.[177] • Of 50,726 patients who underwent exome sequencing, 229 individuals had a variant associated with familial hypercholesterolemia. Of these 229 individuals, 109 (57.7%) were active statin users and 35 (15.3%) had been diagnosed with hypercholesterolemia or seen in a lipid clinic. Of the 63 statin users with recent LDL-C levels available, 29 (46.0%) had LDL levels below 100 mg/dL.[176] • Among 59 women who received pathogenic/likely pathogenic *BRCA1*/2 results, 48 (81.4%) had not previously undergone testing and were unaware of their status. A family history of *BRCA1/2*-related cancer was reported in 64.4%.[186]

Table 3. Summary of Results of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Relevant outcomes	Study	Author-reported findings

	MedSeq	• Of 50 primary care patients undergoing genome sequencing, 11 (22%) received results about monogenic disease risk previously unknown to them.[168]
		  ○ For 2 of these 11 patients, supporting phenotypic evidence for a new clinical diagnosis was identified within 6 months.[168]
		  ○ 2 of the findings were in medically actionable genes as defined by ACMG; these were classified as "likely pathogenic" and "VUS: favors pathogenic," respectively.[168]
		• All 50 patients had ≥1 carrier variant associated with a recessive condition (median 2, range 1-7).[168]
		• 48/50 patients (96%) received a pharmacogenomic result indicating abnormal response to at least one medication.[168]
		• Over the course of the study, 14 variants were reclassified and, upon reanalysis, 18 new variants met criteria for reporting.[243‡]

Intermediate outcomes: *Healthcare utilization*	ClinSeq	Of 29 patients who received a finding from their exome sequencing, 72% reported sharing their result with a healthcare provider, with 31% reporting a change to their healthcare.[184]
	GeneScreen	One asymptomatic individual with a pathogenic variant in the *RET* gene associated with multiple endocrine neoplasia type 2A underwent prophylactic thyroid surgery due to a positive family history.[185]

	MedSeq	• 11/50 (22%) of primary care patients undergoing genome sequencing received results about monogenic disease risk previously unknown to them.
		  ○ Of these 11 patients, 6 needed no additional management beyond examination and/or counseling and 5 received additional imaging, tests, or referrals.[168]
		  ○ An external panel determined clinicians' clinical management was appropriate for 8 of the 11 monogenic disease risk cases and neither appropriate nor inappropriate for 1 case. The panel judged clinicians' management as inappropriate for 2 cases, because of under-evaluation of a variant's disease risk or miscommunication about inheritance.[168]
		• Clinicians recommended clinical action for 17/50 (34%) of patients who underwent genome sequencing and for 8/50 (16%) of patients who received only family history reports.
		  ○ Costs of immediately attributable followup care averaged $41 in the family history group and $68 in the genome sequencing group.[168]
		  ○ Costs of followup care at 6 months averaged $1,142 in FH group and $1,490 in genome sequencing group.[168]

	MyCode	Of 59 women who received pathogenic/likely pathogenic *BRCA1/2* results, there were no changes in the number of outpatient or inpatient visits from pre- to post-disclosure. There was no statistically significant change in average total costs.[186]
	PeopleSeq	Of 543 healthy adults who underwent genome sequencing: • 65 (13.5%)[†] reported making a followup appointment with a healthcare provider specifically because of genomic test results.[172] • Of the 65 patients who discussed their results with a healthcare provider, most consulted a primary care physician (81.1%) or a genetics specialist (27.9%).[172]

Table 3. Summary of Results of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Relevant outcomes	Study	Author-reported findings
	PGen	• Of 992 customers of DTC genetic testing, 380 (41%) reported the test results had motivated them to use a healthcare service by 6-month followup.[180] • Of 961 customers of DTC genetic testing, 105 (10.9%) reported undergoing followup tests, examinations, or procedures based on DTC genomic test results.[171]
	Scripps	Among 1,325 individuals who underwent DTC testing: • Individuals who had undergone pharmacogenomic testing had an increase in physician visits at followup and were more likely to share their results with their physician than DTC participants who did not receive pharmacogenomic results. • Individuals who received pharmacogenomic results were more likely to report that their physician ordered additional tests based on their results and were more likely to discuss their results with a genetic counselor.[242]
Intermediate outcomes: *Medication adherence and changes*	MedSeq	• Of 50 primary care patients undergoing genome sequencing, 48 (96%) received a pharmacogenomic result indicating abnormal response to at least one medication. • Of those with a pharmacogenomic result, 6 were receiving a relevant medication at baseline. No prescription changes or adverse events were documented during the 6-month followup period.[168]
	MyCode	Of 23 individuals diagnosed with familial hypercholesterolemia based on genetic testing: • 9 (39%) made changes to their treatment, including increasing their medication intensity or dose (n=4), adding additional medication (n=4), or initiating new medication (n=1). • 9 (39%) individuals made no medication changes after receiving their genetic test result. • 5 (22%) individuals were not taking medication.[178]
	PGen	• Of 961 customers of DTC genetic testing, 54 (5.6%) reported changing a prescription medication they were already using or starting a new medication in the 6 months after receiving their DTC results. • Of the 54 patients who changed medication, 46 (85.2%) reported consulting a healthcare provider before doing so.[171]

Table 3. Summary of Results of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Relevant outcomes	Study	Author-reported findings
Intermediate outcomes: *Changes in disease surveillance/preventive measures*	ClinSeq	Of 29 patients who received results from sequencing, 5 underwent cancer screening based on the result, 2 underwent screening for heart disease, one had a skin examination, and 1 had an eye examination.[184]
	MedSeq	The proportion of patients receiving USPSTF guideline-concordant care at 6-month followup did not differ between the group receiving family history + genome sequencing (n=100) and the group receiving family history information alone (n=102).[168]
	MyCode	• Among 55 participants with a *BRCA1/2* variant, 37 (17 females, 20 males) were previously unaware of their status and had no history of *BRCA*-associated cancer. Of the 37 previously unaware patients, 33 were old enough for risk management and 26 had engaged in at least one risk-management behavior. Three of these patients were diagnosed with early-stage *BRCA*-associated cancer (1 ovarian cancer, 1 breast cancer, 1 prostate cancer).[177] • Among 59 women who received pathogenic/likely pathogenic *BRCA1/2* results, the following risk-reducing behaviors were taken up during the first year post-disclosure: 49% had undergone either mammography or breast MRI, 3.5% had a mastectomy, 12% had an oophorectomy, and 5% started chemoprevention.[186]
	GeneScreen	Among 131 individuals who underwent genetic testing for 11 medically actionable conditions and received normal/negative results, there was no change in perceived need for medical screening after receiving the test results.[170]
	PGen	Among 1,042 customers of DTC genetic testing: • The proportion who underwent cancer screening within the 6 months after receiving their DTC test results was 26% for mammography, 7% for colonoscopy, and 19% for PSA testing. • A small percentage of participants who reported no prior history of screening at baseline reported screening at 6-month followup (0.6% for mammography, 2.0% for colonoscopy, and 2.5% for PSA testing), with slightly higher rates of colonoscopy (6.5%) and PSA testing (7.1%) among participants age 50 years or older. • Participants who had received elevated cancer genetic risk scores on their DTC results were not significantly more likely to change their cancer screening behavior compared with individuals at average or reduced risk.[182]
	Scripps	2,240 participants underwent DTC genetic testing and completed either or both a 3-month and 1-year followup assessment. Between the 3-month and 1-year follow-up assessments: • No significant changes in the total number of health screening tests completed. • No significant changes in the number of screening tests participants intended to complete with greater frequency. • At the 1-year followup, 42.4% of the sample continued to report at least one screening test they intended to complete with greater frequency post-genomic testing.[173]

Table 3. Summary of Results of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Relevant outcomes	Study	Author-reported findings
Intermediate outcomes: *Lifestyle changes*	MedSeq	In this study, one group of participants received family history information alone (n=102) and one group received both family history information + genome sequencing (n=100). At 6-month followup, 30% of the family history group and 41% of the family history + genome sequencing group reported that their study results prompted a health behavior change, most frequently involving diet or exercise.[168]
	GeneScreen	131 individuals underwent genetic testing for 11 medically actionable conditions and received normal/negative results. At a 1-week followup survey, most reported they would not change their health-related behaviors in response to their results.[170]
	PeopleSeq	Of 543 healthy adults who underwent genome sequencing, 12.4% reported making changes to their lifestyle because of their test results. These include: • 9.0% who reported eating a healthier diet and 8.6% who reported exercising more. • Less than 1.0% who reported eating a less healthy diet and 0% who reported exercising less.[172]
	PGen	This study included 1,042 customers of DTC genetic testing. Six months after receiving their test results: • Less than one-third of patients had made changes to their diet (31%), exercise behavior (26%), use of vitamins/herbal supplements (21%), or advanced care planning behavior (6%) in response to their test results.[182] • 941/980 (96%) reported no changes in smoking status between baseline and 6-month followup.[183] • Of the 916 participants who were never or former smokers at baseline, 13 (1%) were current smokers at 6-month followup.[183] • Of the 64 current smokers at baseline, 14 (22%) reported having quit smoking by 6-month followup.[183]
	Scripps	1,325 participants underwent DTC genetic testing and completed the 1-year followup. Between baseline and followup, there were no significant changes in dietary fat intake or exercise behavior.[173]
Health outcomes	--	*No published studies reported change in health outcomes*
Beliefs and intentions: *Perceived utility*	MedSeq	Compared with participants receiving family history information alone (n=102), patients receiving both family history + genome sequencing (n=100) were significantly more likely at 6-month followup to report that their study results had: • Led to accurate identification of disease risks (OR, 7.45 [95% CI, 2.9-19.4]). • Influenced their current medical treatment (OR, 2.39 [95% CI, 1.2-4.6]).[244]
	PeopleSeq	Of 543 healthy adults who underwent genome sequencing: • 189 (39.5%)† somewhat or strongly agreed that they believed they learned something to improve their health that they did not know before. • 282 (58.4%)† somewhat or strongly agreed that having genome sequencing made them feel like they had more control over their health.[172]

Table 3. Summary of Results of Identified Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Relevant outcomes	Study	Author-reported findings
Harms	ClinSeq	Of 29 patients who received results from their sequencing, participants generally had high scores on the Positive Experiences subscale (mean, 15.2; SD, 5.6; range, 0–20) and low scores on the Distress (mean, 1.7; SD, 3.9; range, 0–30) and Uncertainty subscales (mean, 4.3; SD, 7.0; range, 0–45). Most participants (n=25) reported that their result had either a positive or neutral impact on their affect.[184]
	MedSeq	In this study, one group of participants received family history information alone (n=102) and one group received both family history information + genome sequencing (n=100). This study found: • Patients did not report significant changes in self-rated health, anxiety, or depression scores after receiving genome sequencing.[168] • Participants in the family history–only arm reported on average higher levels of decisional regret compared with participants in the family history + genome sequencing arm (mean, 17.8 vs. 7.1; p<0.001).[244]
	GeneScreen	Among 131 individuals who underwent genetic testing for 11 medically actionable conditions and received normal/negative results: • Levels of decisional regret were low (mean of 1.4 on a scale of 1=no regret to 6=maximum regret) • Levels of family support were high (mean of 2.14 on a scale from 0=not at all to 3=a lot) and levels of family conflict were low (mean of 0.06 on a scale from 0=not at all to 3=a lot).[170]
	PeopleSeq	Of 543 healthy adults who underwent genome sequencing, less than 3% reported regretting their decision to undergo genomic testing.[172]
	PGen	In this study, 998 individuals underwent DTC genetic testing and completed assessments at baseline and 6 months later. • There were no significant differences in the proportion of patients with a positive screen for anxiety at baseline (15.8%) and at 6-month followup (14.5%). • Decisional regret following DTC genetic testing was rare; 583/998 participants (58.4%) received a score of 0/100 (no decisional regret) and 972/998 (97.4%) received a score of 40/100 or lower.[171]
	PGT	In this study, patients received genetic risk information from a DTC genomic test plus usual care (n=74) or from usual care alone (n=76). At both the 1-week and 1-year followup, levels of worry were similar for both groups.[169]
	Scripps	1,325 participants underwent DTC genetic testing and completed the 1-year followup. • Between baseline and followup, there were no significant differences levels of anxiety and levels of test-related distress decreased significantly. • At 1-year followup, 99.7% of participants had a total score of ≤23 on the Impact of Events Scale-Revised (IES-R), indicating no clinically significant test-related distress.[173]

Abbreviations: ACMG = American College of Medical Genetics and Genomics; CI = confidence interval; DTC = direct-to-consumer; FH = familial hypercholesterolemia; OR, odds ratio; PSA = prostate-specific antigen; SD = standard deviation; USPSTF = U.S. Preventive Services Task Force; VUS = variant of uncertain significance.

* Carrier status and pharmacogenomics outcomes include neonatal intensive care unit patients; not reported separately for healthy infants.
† Percentages are not all based on denominator of 543 because of missing responses to some survey items.
‡ Results include those from the cardiomyopathy (N=50) and healthy patient cohorts (N=50).

Table 4. Overview of Health System-Led Genomic Sequencing Efforts

Name	Country	Type	Description	Genetic and clinical focus	Source Population	Planned enrollment	Latest posted enrollment	Returns Results to Participants?	Test Description
Northshore Genomic Health Initiative	U.S.-based healthcare network	Health system/ implementation	Northshore Genomic Health Initiative (GHI) is the research portion of Northshore's genetic testing and risk assessment service that falls under their Personalized Medicine division	Clinical conditions associated with a Geisinger defined gene list	Outpatient laboratories and research centers within Northshore health system	500,000	225,000	Y	Exome sequencing
Center for Personalized Medicine at UCHealth	U.S.-based healthcare network	Health system/ implementation	Biobank/genetic screening program for patients at UCHealth	Clinical conditions associated with a UCHealth defined gene list	Outpatient clinics and inpatient facilities at UCHealth	NR	87,000	Y	Genotyping
Mayo Clinic GeneGuide	U.S.-based healthcare network	Health system/ implementation	Mayo Clinic genetic screening program that is available to the general public and Mayo patients. Research areas include precision medicine, genome sequencing, pharmacogenomics, individualized medicine, genomics, and epigenomics.	Clinical conditions associated with a Mayo Clinic GeneGuide defined gene list	Collected from Mayo Clinics	NR	NR	Y	Next-generation sequencing
Harvard Personal Genome Project	U.S.	Research consortia	To allow scientists to connect human genetic information (human DNA sequence, gene expression, associated microbial sequence data) with human trait information (medical information, biospecimens and physical traits) and environmental exposures. Publicly shares genomic and trait data.	General genomic research	Publicly submitted samples	NR	5,000	N	Genome sequencing

Table 4. Overview of Health System-Led Genomic Sequencing Efforts

Name	Country	Type	Description	Genetic and clinical focus	Source Population	Planned enrollment	Latest posted enrollment	Returns Results to Participants?	Test Description
Electronic Medical Records and Genomics (eMERGE) Network	U.S.	Research consortia	The eMERGE Network develops, disseminates, and applies approaches to research that combine biorepositories with electronic medical record systems for genomic discovery and genomic medicine implementation research.	Clinical conditions associated with the ACMG 59 and other conditions	Clinics from any of the participating research sites	25,000	25,000	Y	Next-generation sequencing panel
All of Us	U.S.	Research consortia	Part of the Precision Medicine Initiative at the NIH. Goal is to build a research cohort of 1M+ participants that contains participant-provided information, including biospecimen for genetic analysis.	Clinical conditions associated with an All of Us defined gene list; risk measurement based on environmental exposures and genetic factors; pharmacogenomics	Publicly submitted samples	1M+	170,000	Y	Genotyping; genome sequencing
Alabama Genomic Health Initiative	U.S.	Health system/ implementation	Provides genomic testing, interpretation, and counseling free of charge to Alabama residents. 5 year program.	Clinical conditions associated with an Alabama Genomic Health Initiative defined gene list	Outpatient and inpatient facilities at UAB; community events	NR	NR	Y	Genome sequencing
Healthy Nevada	U.S.	Research consortia	A population health study with Renown Health (Nevada-based healthcare network) and Desert Research Institute to learn how genetics impact personal health trajectory within Nevada population. Uses the Helix sequencing laboratory.	Rare genetic diseases (familial hypercholesterolemia, hereditary breast and ovarian syndrome, and Lynch syndrome)	Publicly submitted samples	NR	NR	Y	Next-generation sequencing

Table 4. Overview of Health System-Led Genomic Sequencing Efforts

Name	Country	Type	Description	Genetic and clinical focus	Source Population	Planned enrollment	Latest posted enrollment	Returns Results to Participants?	Test Description
Clinical Sequencing Evidence-Generating Research (CSER)	U.S.	Research consortia	A national multisite research program (KPNW; Baylor; UNC; Mount Sinai; UCSF; HudsonAlpha; UW) studying the effectiveness of integrating genome sequencing into the clinical care of diverse and medically underserved individuals.	Clinical conditions associated with a defined gene list set by the participating research site	Clinics from the 7 participating research sites	NR	NR	Y	Exome sequencing; genome sequencing
Implementing Genomics in Practice (IGNITE)	U.S.	Research consortia	Multisite research study incorporating genomic information into the electronic medical record and providing clinical decision support for implementation of appropriate interventions or clinical advice.	Clinical conditions associated with a defined gene list set by the participating research site	Clinics from the 5 participating research sites	NR	NR	Y	Targeted sequencing
UK 100,000 Genomes	U.K.	Research consortia	A program part of the U.K. Government's Life Sciences Strategy to sequence 100,000 genomes.	Rare genetic disease and cancer	Participants throughout the U.K.	100,000	100,000	Y	Genome sequencing
Estonian Genome Project	Estonia	Biobank	Estonian Biobank is a population-based biobank of the Estonian Genome Center at the University of Tartu	Rare genetic disease and familial hyperlipidemia	Subjects that are randomly recruited by general practitioners and physicians in hospitals	150,000	51,535	Y	GWAS/ Genotyping

Table 4. Overview of Health System-Led Genomic Sequencing Efforts

Name	Country	Type	Description	Genetic and clinical focus	Source Population	Planned enrollment	Latest posted enrollment	Returns Results to Participants?	Test Description
Personal Genome Project Canada	Canada	Research consortia	The Personal Genome Project Canada constitutes a public resource of data from the population at large that supports evaluation of genome sequencing and its utility for personalized medical practice in Canada	General genomic research	Participants throughout Canada	NR	56	Y	Genome sequencing
Genome Canada	Canada	Research consortia	A not-for-profit organization funded by the Government of Canada. Acts as a catalyst for developing and applying genomic and genomic-based technologies to create economic and social benefits to Canadians.	Rare genetic disease	Participants throughout Canada	NR	NR	NR	NR
Brigham and Women's Hospital	U.S.-based healthcare network	Health system/ implementation	Provides innovative screening and cutting edge genomic information for healthy adults in order to predict and potentially prevent the onset of disease.	Clinical conditions associated with a Brigham and Women's Hospital defined gene list	Publicly submitted samples	NR	NR	Y	NR
Trans-Omics for Precision Medicine (TOPMed) / PopSeq	U.S.	Research consortia	The TOPMed program collects genome sequencing and genomics data and will integrate that data with molecular, behavioral, imaging, environmental, and clinical data to improve prevention and treatment of heart, lung, blood, and sleep disorders. The PopSeq program aims to deliver genomic information to a subset of the TOPMed population.	General genomic research	Participants in selected National Heart, Lung, and Blood Institute studies	NR	NR	Y	Genome sequencing

Table 4. Overview of Health System-Led Genomic Sequencing Efforts

Abbreviations: ACMG = American College of Medical Genetics; CSER = Clinical Sequencing Evidence-Generating Research; eMERGE = Electronic Medical Records and Genomics network; GWAS = genome-wide association study; IGNITE = Implementing Genomics in Practice; KPNW = Kaiser Permanente Northwest; NIH = National Institute of Health; NR = not reported; UAB = University of Alabama at Birmingham; UCSF = University of California, San Francisco; U.K. = United Kingdom; UNC = University of North Carolina; U.S. = United States; UW = University of Washington; Y = yes.

Table 5. Overview of Ongoing Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Study	Planned N	Estimated completion date	Aim	Population	Intervention	Planned outcomes
RCTs						
Cancer Health Assessments Reaching Many (CHARM)[199]	880	May 2021	Assess the utility of clinical exome sequencing and how it affects care in diverse populations	Healthy 18- to 50-year-olds in primary care at high risk for a hereditary cancer syndrome or unknown family history	• Intervention: Modified genetic counseling (modified for lower literacy) • Comparator: Traditional genetic counseling	• Positive finding for hereditary cancer syndromes* • Secondary findings (including carrier conditions) • Healthcare utilization • Participant understanding and satisfaction • Family communication • Personal utility
Million Veteran Program Return of Actionable Results (MVP-ROAR)[165]	254	April 2022	Develop a process to return medically actionable genetic results and determine the impact on medical management, patient outcomes, and quality of life	Participants in Million Veterans Program with a pathogenic or likely pathogenic variant	• Intervention: Immediate return of results • Control: 6-month delay in return of results	• LDL change* • Change in lipid-lowering treatment • Medication adherence • Cascade testing • Lifestyle behaviors (smoking, physical activity, fat intake) • Healthcare costs • Quality of life
My Personalized Breast Screening (MyPeBS)[161]	85,000	December 2025	Assess the effectiveness of a risk-based breast cancer screening strategy compared with standard screening	Women ages 40-70 years	• Intervention: Screening based on a risk assessment using clinical risk scores and polymorphisms • Comparison: Screening according to current guidelines	• Incidence of breast cancer stage 2+* • 10- and 15-year survival • Morbidity • Anxiety • Psychosocial concerns • Quality of life • Cost-effectiveness • Stage-specific incidence • Overdiagnosis • False negatives • False positives • Interval cancer

Table 5. Overview of Ongoing Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Study	Planned N	Estimated completion date	Aim	Population	Intervention	Planned outcomes
Women Informed to Screen Depending On Measures of risk (WISDOM) Study[162, 245]	100,000	December 2020	Assess the effectiveness of a risk-based breast cancer screening strategy compared to standard screening	Women ages 40-74 years	• Intervention: Screening based risk assessment using clinical risk scores and polymorphisms • Comparator: Annual screening	• Late-stage cancer* • Biopsy rate* • Interval cancers • Rate of systemic therapy • Mammograph recall rate • DCIS • Chemoprevention uptake • Choice of risk-based vs. annual screening • Adherence to screening schedule • Anxiety • Decisional regret • Rates of low cancer-risk
Cohorts						
Enabling Personalized Medicine Through Exome Sequencing in the U.S. Air Force (MilSeq)[163]	75	December 2019	Explore the implementation of exome sequencing into clinical medical care in the military health system	Healthy active Air Force airmen	• Intervention: Exome sequencing • Comparator: None	• Provider knowledge* • Perceived effect on career status* • Genomic findings* • Healthcare utilization* • Provider confidence with genomic data • Participant attitudes • Change in health
Implementation of a Model for Personalised Risk-Based Breast Cancer Prevention and Screening[201]	28,389	December 2020	Estimate the impact of genetic risk for breast cancer detection in the screening program	Female participants in Estonian Genome Center Biobank	• Intervention: Screening strategy stratified based on presence of moderate-high risk genetic variants or PRS calculation • Comparator: Standard mammography screening in ages 50-69 years	• Proportion of women with genetically higher risk of breast cancer* • Number of screen-detected breast cancers in different risk groups

Table 5. Overview of Ongoing Studies on Genomic Testing for Screening and Risk Prediction (k=9)

Study	Planned N	Estimated completion date	Aim	Population	Intervention	Planned outcomes
North Carolina Newborn Exome Sequencing for Universal Screening (NC_NEXUS)[200]	200†	June 2019	Utility of next generation sequencing in newborn screening and parental decision making	Newborns with no known conditions	• Intervention: Exome sequencing • Comparator: None	• Parental decision making*
Pediatric Reporting of Adult-Onset Genomic Results[166]	705	June 2023	Assess psychosocial and behavior outcomes of children receiving genomic results	Geisinger clinic patients enrolled in MyCode (ages 0-17 years)	• Intervention: Exome sequencing • Comparator: None	• Anxiety and depression* • Family functioning* • HRQoL* • Update of cascade testing* • Initiation of risk reduction behavior* • Body image and self esteem • Decisional regret • Satisfaction with genetic counseling • PTSD (Impact of events), psychologic adaptation • Health education impact
Return of Genomic Results and Aggregate Penetrance in Population-Based Cohorts (PopSeq)[164]	200	June 2023	Return clinically actionable genomic results, improve high-throughput methods, and evaluate aggregate penetrance for Mendelian diseases	Framingham Heart Study and Jackson Heart Study participants	Interventions: Whole genome sequencing and return of actionable findings from ACMG secondary findings list Comparator: None	• Follow through with disclosure* • Costs of disclosure* • New/modified diagnoses • Self-rated health • Physician recommendations • Healthcare utilization • Health behaviors • Disclosure-specific impact • Satisfaction with disclosure • Decisional regret • Sharing with relatives/family testing • General anxiety

Abbreviations: DCIS = ductal carcinoma in situ; LDL = low-density lipoprotein; HRQoL = health-related quality of life; PRS = polygenic risk score; PTSD = post-traumatic stress syndrome.

* Indicates primary outcome.
† Also includes a cohort of 200 infants with diagnosed conditions (not included in this table).

Specific genes named in report:

- *ATM*
- *BRCA1, BRCA2*
- *PALB2*
- *TP53*

Terms used in report:

Allele: One of two or more DNA sequences occurring at a particular gene locus. Typically one allele ("normal" DNA sequence) is common, and other alleles (mutations) are rare.

Analytic validity: The ability of the test to accurately and reliably measure the genotype(s) of interest.

Ancestry testing: Genetic ancestry testing, or genetic genealogy, involves the examination patterns of DNA variation that are often shared among people of particular backgrounds and can provide clues about where a person's ancestors might have come from and about relationships between families.

Carrier: In classical genetics, an individual who carries one deleterious allele for an autosomal recessive disorder. In clinical discussions, may refer to an individual who carries a deleterious allele that predisposes to disease.

Cascade testing/screening: A systematic process for the identification of individuals at risk for a hereditary condition. The process begins with the identification of an individual with the condition and/or a pathogenic variant associated with the condition, then extends genetic testing to his/her at-risk biological relatives. This process is repeated as more affected individuals or pathogenic variant carriers are identified.

Clinical actionability: The extent to which genetic testing provides information about the risk of serious disease that could be prevented or mitigated if the risk were known.

Clinical utility: Refers to the ability of the test to demonstrate, in the tested individual, prevention of disease or improvements in health outcomes such as mortality, morbidity, or disability through the adoption of treatments based on test results.

Clinical validity: The ability of a genetic test to detect or predict a patient's clinical status (phenotype). Clinical validity is dependent on the *penetrance* of a given variant.

De novo variant: A genetic alteration that is present for the first time in one family member as a result of a variant (or mutation) in a germ cell (egg or sperm) of one of the parents, or a variant that arises in the fertilized egg itself during early embryogenesis. Also called *de novo* mutation, new mutation, and new variant.

Direct-to-consumer testing: Genetic tests that are marketed directly to customers via television, print advertisements, or the Internet, and that can be bought online or in stores. Customers send the company a DNA sample and receive their results directly from a secure website or in a written report. Direct-to-consumer genetic testing provides people access to their genetic information without necessarily involving a healthcare provider or health insurance company in the process. Other names for direct-to-consumer genetic testing include DTC genetic testing, direct-access genetic testing, at-home genetic testing, and home DNA testing.

Expressivity: Refers to variation in phenotypic expression when a given allele is present.

Founder variant: A genetic alteration observed with high frequency in a group that is or was geographically or culturally isolated, in which one or more of the ancestors was a carrier of the altered gene. This phenomenon is often called a founder effect. Also called founder mutation.

Genetic test (mutation analysis): A germline genetic testing method targeted to detect a specific variant or mutation (such as a deleterious *MSH2* variant previously identified in a family), panel of variants (such as the 3 *BRCA* pathogenic variants comprising the founder mutation panel for individuals of Ashkenazi Jewish ancestry) or type of variant (such as large deletions or insertions in the *BRCA1* gene).

Genetic variant (mutation): An alteration in the most common DNA nucleotide sequence. The term variant can be used to describe an alteration that may be benign, pathogenic, or of unknown significance. The term variant is increasingly being used in place of the term mutation.

Genotype: At its broadest level, genotype includes the entire genetic constitution of an individual. It is often applied more narrowly to the set of alleles present at one or more specific loci.

Germline: The cells from which eggs or sperm (i.e., gametes) are derived.

Germline variant: A gene change in a reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. A variant contained within the germline can be passed from parent to offspring, and is, therefore, hereditary.

Missense variant: Refers to when the change of a single base pair causes the substitution of a different amino acid in the resulting protein. This amino acid substitution may have no effect, or it may render the protein nonfunctional.

Multi-gene panel test (sequencing panel): Genetic tests that use next-generation sequencing to test multiple genes simultaneously.

Multiplex genomic test (genomic test): A method for detecting multiple genetic alterations (i.e., gene mutations or single nucleotide polymorphisms in a single gene or across the genome) simultaneously.

Next generation sequencing (NGS): A high-throughput method used to determine a portion of the nucleotide sequence of an individual's genome. This technique utilizes DNA sequencing technologies that are capable of processing multiple DNA sequences in parallel.

Pathogenic variant: A genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder. When such a variant (or mutation) is inherited, development of symptoms is more likely, but not certain. Also called deleterious mutation, disease-causing mutation, predisposing mutation, and susceptibility gene.

Penetrance: Penetrance refers to the likelihood that a clinical condition will occur when a particular genotype is present. For adult-onset diseases, penetrance is usually described by the individual carrier's age, sex, and organ site. For example, the penetrance for breast cancer in female carriers of *BRCA1* pathogenic variants is often quoted by age 50 years and by age 70 years.

Personal utility: Refers to the value an individual places on the knowledge associated with their genomic testing result independent of its clinical implications.

Pharmacogenomics: The study of how genes affect a person's response to drugs by combining pharmacology and genomics to develop and identify effective, safe medications and doses that are tailored to variations in a person's genes.

Phenotype: The observable characteristics in an individual resulting from the expression of genes; the clinical presentation of an individual with a particular genotype.

Population-based genetic screening programs: Programs that offer genetic services within an organized population screening program, such as newborn screening, colorectal cancer screening, or genetic screening for individuals with Ashkenazi Jewish ancestry.

Secondary finding: Genetic results that provide information about variants unrelated to the primary purpose for the testing.

Somatic variant: An alteration in DNA that occurs after conception and is not present within the germline. Somatic variants can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. Somatic variants can (but do not always) cause cancer or other diseases.

Variable expression: Variation in the manner in which a trait is manifested. When there is variable expressivity, the trait may vary in clinical expression from mild to severe. For example, neurofibromatosis type 1 may be mild, presenting with café-au-lait spots only, or severe, presenting with neurofibromas and brain tumors.

Variant of unknown significance: A variation in a genetic sequence whose association with disease risk is unknown. Also called unclassified variant, variant of uncertain significance, and VUS.

Exome sequencing: A laboratory process that is used to determine the nucleotide sequence primarily of the exonic (or protein-coding) regions of an individual's genome and related sequences, representing approximately 1% of the complete DNA sequence.

Genome sequencing: A laboratory process that is used to determine nearly all of the approximately 3 billion nucleotides of an individual's complete DNA sequence, including non-coding sequence.

Sources: Unless otherwise noted, definitions come from the National Cancer Institute Dictionary of Genetic Terms (available at: https://www.cancer.gov/publications/dictionaries/genetics-dictionary) of the Genetics Home Reference (available at: https://ghr.nlm.nih.gov/primer). Some definitions have been adapted from their original language.

Appendix B. Recommendations of Other Groups

Many organizations have published recommendations related to direct-to-consumer (DTC) genetic testing and other genetic testing services. For example:

- One U.S. organization and four European organizations **do not support DTC genetic testing**, typically because of the lack of medical indication or supervision as well as the potential harms of misinterpreted or inaccurate test results. These organizations are:
    - American College of Obstetricians and Gynecologists (2017)[1]
    - Austrian Bioethics Commission (2010)[2]
    - German National Academy of Sciences (2010)[3]
    - Council of Europe (2009)[4]
    - Portugal's National Council of Ethics for the Life Sciences (2008)[5]

- In contrast, the U.S.-based National Society of Genetic Counselors (2015) states that patients interested in DTC genetic testing have a right to make an **independent, informed decision** about whether to pursue this form of testing.[6]

- Five organizations recommend that **clinicians with specialized genetics training** be involved in interpreting genetic test results, including the results of DTC genetic tests. These organizations include:
    - American College of Obstetricians and Gynecologists (2017)[1]
    - American College of Medical Genetics and Genomics (2016)[7]
    - National Society of Genetic Counselors (2012)[8]
    - International Society of Nurses in Genetics (2017)[9]
    - Portugal's National Council of Ethics for the Life Sciences (2008)[5]

- Eleven organizations recommend that **consumers receive comprehensive information about DTC genetic tests**, including explanation of the test's scientific evidence, clinical validity, limitations, the risk that a test will neither confirm nor eliminate disease potential, and potential implications for relatives. These organizations include:
    - American College of Obstetricians and Gynecologists (2017)[1]
    - American College of Medical Genetics and Genomics (2016)[7]
    - American Society of Clinical Oncology (2015)[10]
    - National Society of Genetic Counselors (2012)[8]
    - American Society of Human Genetics (2007)[11]
    - Canadian College of Medical Geneticists (2015)[12]
    - International Society of Nurses in Genetics (2017)[9]
    - European Society of Human Genetics (2013)[13]
    - United Kingdom's Human Genetics Commission (2010)[14]
    - Council of Europe (2009)[4]
    - Portugal's National Council of Ethics for the Life Sciences (2008)[5]
    - Belgian Advisory Committee on Bioethics (2004)[15]

- The European Society of Human Genetics (2013) recommends that clinicians who order genetic tests **use a targeted approach first** to avoid unsolicited findings or findings that cannot be interpreted.[13]

Appendix B. Recommendations of Other Groups

Only a few organizations have issued specific guidance on how healthcare providers should respond when patients present them with DTC genetic test results. Some recommendations from U.S. and international organizations include:

Recommendations about clinician management of patient-generated genetic test results

- The American College of Obstetricians and Gynecologists (2017) recommends that providers presented with a patient's DTC genetic test results refer the patient to a clinician who is skilled in risk assessment and interpretation of genetic test results in the context of the individual's medical and family history.[1]
- The International Society of Nurses in Genetics (2017) recommends that nurses be receptive to open communication with patients about DTC genetic testing, provide patient education about genetic risk assessment and the benefits and limitations of testing, and facilitate access to appropriate genetic counseling services for patients as needed.[9]
- The American College of Clinical Pharmacology (2009) recommends that clinical pharmacologists advise patients about the availability of genetic counseling services since many DTC genetic testing services do not provide interpretation of test results.[16]

Recommendations about providing clinicians with education about genetic testing

- The American Society of Clinical Oncology (2015) recommends that oncologists and other healthcare professionals receive continuing education in the areas of cancer risk assessment and management of individuals with an inherited predisposition to cancer.[10]
- The European Society of Human Genetics (2013) recommends clinicians receive education in genetics to help them inform, counsel, and refer patients appropriately.[13]
- The Austrian Bioethics Commission (2010) recommends that professional medical societies educate their members about the scientific, legal, and ethical dimensions of DTC genetic testing.[2]
- The United Kingdom's Nuffield Council on Bioethics (2010) recommends that healthcare professionals receive training in best practices for advising patients about DTC genetic testing services, addressing the limitations of the tests, and determining when to refer patients to specialist services.[17]
- The American Society of Human Genetics (2007) recommends that professional medical organizations educate their members about DTC genetic tests so clinicians can counsel their patients about the value and limitations of such testing.[11]

Other recommendations related to genetic testing are geared toward policymakers or genetic testing companies, and cover topics such as:

- Regulation of DTC genetic testing companies
- Marketing of DTC genetic tests
- Elements of informed consent for DTC genetic testing
- Privacy, security, and confidentiality of patients' biological samples and genetic test data
- Providing consumers with access to genetic counselors to help in interpreting results

Additional detail about recommendations from other groups is in **Appendix B Table 1**.

Appendix B Table 1. Recommendations of Other Groups

Organization Country Year	Audience for recommendation	Focus of Recommendation	Recommendation
U.S. Organizations			
American College of Medical Genetics and Genomics (ACMG) U.S. 2017[18]	Clinicians, genetic counselors, clinical diagnostic laboratories	Genetic testing (general)	• Genetic test results about known pathogenic or expected pathogenic variants in 59 specific genes should be reported back to patients, even when these are secondary findings (unrelated to the primary medical reason for testing). • Patients undergoing clinical genomic sequencing should have the option to opt out of receiving secondary findings following appropriate genetic counseling.
Centers for Disease Control and Prevention (CDC) U.S. 2014[19]	Clinicians, healthcare payers, public health programs	Genetic testing (general)	Public health programs and stakeholders should consider ways to support genetic testing for individuals at risk of three "Tier 1" genetic conditions: • Hereditary Breast and Ovarian Cancer Syndrome (HBOC), which can increase the risk of breast, ovarian, and other cancers due to mutations in *BRCA1* or *BRCA2* genes • Lynch syndrome (LS), which can increase the risk of colorectal, endometrial, ovarian, and other cancers due to mutations in mismatch-repair genes • Familial hypercholesterolemia (FH), which can increase the risk of heart disease or stroke due to mutations that can cause very high cholesterol levels. Early detection and intervention for these conditions could significantly reduce morbidity and mortality.
American College of Obstetricians and Gynecologists (ACOG) U.S. 2017[1]	Obstetrician-gynecologists, patients	DTC genetic testing	• DTC genetic testing should be discouraged because of the potential harm of a misinterpreted or inaccurate test result. • For any genetic test with medical implications, a healthcare provider with knowledge of genetics should be involved in ordering and interpreting the results. • Consumers should be apprised of risk from DTC genetic test results that can neither confirm nor eliminate disease potential, as well as potential implications for relatives. • Consumers should be aware of privacy issues before undergoing DTC genetic tests, including who will have access to the results, what systems are in place to protect confidential health information, how the sample will be handled after testing is complete, how the data might affect insurance coverage, and how genetic data will be handled if the company closes. • When a patient presents DTC genetic test results to a healthcare provider, the patient should be referred to a clinician who is skilled in risk assessment and interpretation of genetic test results in the context of the individual's medical and family history.
National Society of Genetic Counselors U.S. 2017[20]	Policymakers	Regulation of genetic testing	• DNA testing for health-related conditions and hereditary disease should be regulated. • Any decision to regulate genetic testing should be patient-focused and should consider the risk of stifling critical technological advancements. • Regulation should not impede patient access to high-quality, clinically useful information. • The goals of regulation should be to protect patients from harm by developing clinical utility and analytical validity programs, ensuing that practitioners correctly interpret results, and creating transparency in the use or intended application of a genetic test.

Appendix B Table 1. Recommendations of Other Groups

Organization Country Year	Audience for recommendation	Focus of Recommendation	Recommendation
American College of Medical Genetics and Genomics (ACMG) U.S. 2016[7]	Clinicians, genetic testing companies	DTC genetic testing	• Genetic testing laboratories should be accredited by CLIA, the state, and/or other applicable agencies and test results should indicate the specifics of the laboratory's accreditation. • A certified medical geneticist, genetic counselor, or other genetics expert should be available to help consumers understand whether a genetic test should be performed and how to interpret test results considering personal and family history. • Consumers should be fully informed about what genetic tests can/cannot say about their health. • Consumers should understand the potential for receiving unexpected results and results that neither confirm nor rule out the possibility of disease, as well as the implications of test results for family members. • The evidence base describing the validity and utility of a genetic test should be clearly stated in easy-to-understand language with scientific references available. • Privacy concerns should be addressed by informed consumers who will have access to test results, what processes are in place to protect their data, what will happen to their DNA samples, whether their data will be shared with third parties, and ownership of the sample/data.
American Society of Clinical Oncology (ASCO) U.S. 2015[10]	Clinicians, policymakers	Genetic / genomic testing for cancer risk, including DTC genetic testing	• Genetic testing laboratories should adhere to high quality standards to ensure providers and patients understand the accuracy, benefits, and limitations of genetic tests. • The FDA should follow a risk-based approach to regulating laboratory-developed or commercial genetic tests. • High-risk tests used to identify patients who are at increased risk for cancer should be subject to regulatory review. • Regulation of genetic testing should not compromise innovation or limit patient access to testing. • Oncologists and other healthcare professionals should receive continuing education in the areas of cancer risk assessment and management of individuals with an inherited predisposition to cancer.
National Society of Genetic Counselors U.S. 2015[6]	Consumers, genetic testing companies	DTC genetic testing	• People interested in at-home DNA testing, DTC genetic testing, or online genetic testing have a right to make an independent, informed decision about whether to pursue this form of testing. • Companies that offer direct access to genetic testing have a responsibility to offer consumers easy access and/or referrals to appropriate resources and qualified genetics professionals.
American Academy of Pediatrics (AAP); ACMG U.S. 2013[21]	Clinicians, parents	Genetic testing and screening of children	• AAP and ACMG strongly discourage the use of DTC genetic testing of children because of the lack of oversight on test content, accuracy, and interpretation. • AAP and ACMG do not support routine carrier testing in children when such testing does not provide health benefits in childhood. • Decisions about genetic testing and screening in children should be driven by the best interests of the child. • Genetic testing of children should be accompanied by genetic counseling. • Ideally, the assent of the child should be obtained for any predictive genetic testing for asymptomatic children.

Appendix B Table 1. Recommendations of Other Groups

Organization Country Year	Audience for recommendation	Focus of Recommendation	Recommendation
National Society of Genetic Counselors U.S. 2012[8]	Genetic counselors, patients	Genetic cancer risk assessment, counseling, and testing (including DTC genetic testing)	• Since DTC genetic testing may not allow for adequate informed consent, it is strongly encouraged that appropriately trained clinical genetics professionals be involved in the genetic testing process from the beginning. • Elements of informed consent for cancer genetic testing include: purpose of test, who to test, general information about the gene, possible test results, technical aspects and accuracy of the test, economic considerations, possibility of genetic information discrimination, psychosocial aspects of testing, confidentiality, utilization of test results, and alternatives to genetic testing. • Disclosure of genetic test results should include personalized interpretation of results, review of medical and psychological impact of results on patient and family members, an explanation of the specificity, sensitivity, and limitations of the genetic test performed, cancer risk re-assessment, referral to appropriate healthcare providers, and identification of at-risk relatives.

American College of Clinical Pharmacology
U.S.
2009[16]
	Policymakers, clinical pharmacologists	DTC genetic testing	• There is a need for government oversight of consumer-directed advertising of genetic testing.
			• In response to patients who are considering DTC genetic testing, clinical pharmacologists can:
			  ○ Verify the information presented in advertisements for DTC genetic tests
			  ○ Seek advice from a professional trained in genetics
			  ○ Identify and communicate the scientific limitations of each test
			  ○ Advise patients about the availability of genetic counseling services since many DTC genetic testing services do not provide interpretation of test results

American Society of Human Genetics U.S. 2007[11]	Policymakers, clinicians, genetic testing companies	DTC genetic testing	• DTC genetic testing companies should provide all relevant information about offered tests in a transparent, readily accessible, and understandable manner. • Professional medical organizations should educate their members about DTC genetic tests so clinicians can counsel their patients about the value and limitations of such testing. • Government agencies should take targeted regulatory action to ensure the analytical and clinical validity of DTC genetic tests and to ensure that claims about such tests are not misleading.
International Organizations			
Canadian College of Medical Geneticists Canada 2015[12]	Geneticists, genetic counselors, physicians	Genome-wide sequencing for monogenic diseases	• Clinical genome-wide sequencing is an appropriate approach for diagnosing patients suspected of having significant monogenic disease or when specific genetic tests have failed to provide a diagnosis. • Clinicians should not undertake intentional clinical analysis of secondary findings (those unrelated to the primary indication for testing) until the benefits of reporting incidental findings are established. • Clinicians should provide genetic counseling and obtain informed consent prior to undertaking clinical genome-wide sequencing. • Genetic counseling should include discussion of the limitations of testing, likelihood and implications of diagnosis and incidental findings, and the potential need for further analysis.

Appendix B Table 1. Recommendations of Other Groups

Organization Country Year	Audience for recommendation	Focus of Recommendation	Recommendation

International Society of Nurses in Genetics
International
2017[9]
	Nurses, clinicians, patients	DTC genetic testing	• Consumers should be fully informed regarding the purpose, extent, and intent of genetic testing, its scientific validity and clinical utility, and what information the tests can and cannot provide about their health.
			• Genetic test results should be delivered with the consultation of a certified clinician to avoid misinterpretation of results and potential psychosocial harm.
			• Documentation, policies, regulations, and security measures should be in place to protect the privacy of consumers' data and test samples.
			• Nurses should:
			  ○ Be receptive to open communication with patients about DTC genetic testing
			  ○ Be informed about genetic testing and associated health, ethical, legal, and social issues
			  ○ Promote public awareness by educating patients about the roles of genes and environment in health and disease, the importance of family history, genetic risk assessment, benefits and limitations of testing, disease prevention, and health promotion options
			  ○ Facilitate access to appropriate genetic counseling services for patients as needed

European Society of Human Genetics Europe 2013[13]	Policymakers, clinicians	Whole-genome sequencing	• The use of genome-wide arrays or whole-genome analysis requires a justification in terms or necessity and the balance of harms and benefits. • Clinicians who order genetic tests should use a targeted approach first to avoid unsolicited findings or findings that cannot be interpreted. • A protocol should be in place to provide guidance on reporting unsolicited findings. • Guidelines for informed consent regarding diagnostic testing should be developed, including informed consent about the use of genetic data for research purposes. • Guidelines should be established about disclosure of genetic test data that could affect minors. • Guidelines should be established for the process of re-contacting patients after the emergence of new scientific evidence relevant to the patient. • International collaboration is needed to build databases on genotypic and phenotypic data. • Genetic education should be provided to help primary care providers inform and refer patients appropriately and to help specialists counsel or refer patients and discuss and interpret results. • Genetic experts should promote public awareness of the pros and cons of genetic testing.
Austrian Bioethics Commission Austria 2010[2]	Patients, professional medical societies	DTC genetic testing	• Patients who suspect they might be at risk for a genetic condition should consult a specially trained physician, and if necessary, seek genetic or psychological counseling. • Patients should refrain from seeking DTC genetic tests to assess the risk of a multifactorial condition. • Patients who undergo DTC genetic tests should obtain information about the precise purpose of the test and what the test results will involve. • Patients who undergo DTC genetic tests should be aware that their data (including personal and genetic data) are never completely immune to unauthorized access, even when protected by a password. • Parents or legal guardians should refrain from using DTC genetic testing to analyze DNA samples taken from minors or from others without the capacity to consent. • Professional societies should educate their members about the scientific, legal, and ethical dimensions of DTC genetic testing.

Appendix B Table 1. Recommendations of Other Groups

Organization Country Year	Audience for recommendation	Focus of Recommendation	Recommendation
European Society of Human Genetics Europe 2010[22]	Policymakers, genetic testing companies	DTC genetic testing	• The clinical utility of a genetic test should be a key criterion for determining whether to offer a test to a person or a group of persons. • Laboratories providing genetic tests should comply with accepted quality standards. • Information about the purpose and appropriateness of testing should be provided. • Consumers should have access to genetic counseling about their test results, as well as psychosocial evaluation and followup for some tests. • Privacy and confidentiality of sensitive genetic data should be secured and safely guarded. • Safeguards should exist to prevent testing of minors or legally incapacitated persons. • All claims and advertisements about genetic tests should be transparent, unbiased, and fair. • Relevant ethical principles, international treaties, and recommendations related to genetic testing should be respected. • Countries should establish national guidelines about DTC genetic testing.
German National Academy of Sciences Germany 2010[3]	Policymakers	Genetic diagnostics, including DTC genetic testing	• DTC genetic tests should not be allowed because they do not fulfill the requirements of medical and ethically acceptable predictive genetic diagnostics. • DTC genetic testing companies should not be allowed to market their services directly to the public.
Human Genetics Commission United Kingdom 2010[14]	Policymakers, genetic testing companies	DTC genetic testing	• DTC genetic test providers should comply with relevant regulations related to marketing their products, laboratory analysis of biological products, and using/storing/transferring/disposing of biological samples. • Test providers should provide information about the evidence of the association between a genetic marker and a disease, condition, or trait. Test providers also should use standard statistical methodologies to calculate the risk of the disease, condition, or trait and make such methodology available for review. • Test providers should provide consumers with genetic test result information that is accurate, adequate, appropriate, and easy to understand. • When undertaking genetic tests for inherited disorders, consumers should have opportunities to obtain pre- and post-test counseling. • Test providers should obtain free and informed consent before performing any genetic tests. • Test providers should adhere to the highest levels of security and confidentiality for genetic data. • Test providers should have procedures in place for responding to consumer complaints.
Nuffield Council on Bioethics U.K. 2010[17]	Policymakers, researchers, genetic testing companies, medical educators	DTC genetic testing	• Regulators should ask DTC genetic testing companies to provide evidence for any claims about the clinical value of their tests. • Government websites should provide information about the risks and benefits of DTC genetic testing, including the relevance for insurance. • Independent research should be conducted on the impact and effects of multifactorial genetic testing. • DTC genetic testing companies should voluntarily adopt good practice. • Organizations involved in training health care professionals should provide education about best practices in advising patients about DTC genetic testing services, addressing the limitations of the tests, and determining when to refer patients to specialist services.

Appendix B Table 1. Recommendations of Other Groups

Organization Country Year	Audience for recommendation	Focus of Recommendation	Recommendation
Council of Europe Europe 2009[4]	Policymakers	Genetic testing (general)	• Genetic testing for health purposes should be performed only under individualized medical supervision because of the risk of patient misinterpretation of genetic test results and implications. • Genetic tests should meet the criteria of scientific and clinical validity • Health care providers should consider the clinical utility of a genetic test before offering it to a patient • Patients should be provided with sufficient information to make informed decisions about genetic testing. • Patients who undergo genetic tests should have access to appropriate genetic counseling.
National Council of Ethics for the Life Sciences Portugal 2008[5]	Policymakers, genetic testing companies	DTC genetic testing	• DTC genetic testing should be regulated to promote transparency and combat misleading advertising. • Health-related genetic tests for diagnostic or predictive purposes should not be available for direct marketing to the public. • Genetic tests should not be offered without medical indication and personalized supervision. • Pre-and post-test genetic counseling should be available for any genetic tests that provide predictive health-related information. • Genetic testing laboratories should provide consumers with clear, accessible information about a genetic test, including its scientific evidence, sensitivity, specificity, predictive value, and possible implications for the consumer and family members. • Genetic testing laboratories should have a quality assurance system and guarantee the privacy and confidentiality of consumers genetic data.
Belgian Advisory Committee on Bioethics Belgium 2004[15]	Policymakers, genetic testing companies	DTC genetic testing	• Patients should have adequate and comprehensive information about DTC genetic tests. • DTC genetic tests should meet high quality standards, be subject to appropriate product checks, and comply with legal requirements on the protection of personal privacy. • The storage and later use of genetic material should be prohibited. • The Committee is divided on whether to recommend a general ban on DTC genetic tests.

Abbreviations: CLIA = Clinical Laboratory Improvement Amendments; DTC = direct to consumer; FDA = Food and Drug Administration.

Appendix B Table 2. CDC Tier 1 Genomics Applications

Note: At the time this report was completed, the CDC's Office of Public Health Genomics (OPHG) provided and maintained a static table of genomic applications (i.e., clinical scenarios involving genomic testing) sorted into one of three tiers based on their system of assigning evidence for readiness for clinical implementation (where Tier 1 indicates sufficient evidence supporting implementation). This appendix contained a version of that table.

However, in 2019 the OPHG moved to a searchable database, moving from assigning tiers to individual clinical scenarios to coding guideline documents. That database can be accessed here:

https://phgkb.cdc.gov/PHGKB (last accessed September 13, 2021)

Appendix B Table 3. ACMG List of 59 Genes and Associated Phenotypes Recommended for Return of Secondary Findings in Clinical Sequencing; 2016 Update

Phenotype	Gene
Hereditary Breast and Ovarian Cancer	*BRCA1, BRCA2*
Li-Fraumeni Syndrome	*TP53*
Peutz-Jeghers Syndrome	*STK11*
Lynch Syndrome	*MLH1, MSH2, MSH6, PMS2*
Familial adenomatous polyposis	*APC*
MYH-Associated Polyposis; Adenomas, multiple colorectal, FAP type 2; Colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	*MUTYH*
Von Hippel Lindau syndrome	*VHL*
Multiple Endocrine Neoplasia Type 1	*MEN1*
Multiple Endocrine Neoplasia Type 2	*RET*
Familial Medullary Thyroid Cancer (FMTC)	*RET, NTRK1*
PTEN Hamartoma Tumor Syndrome	*PTEN*
Retinoblastoma	*RB1*
Hereditary Paraganglioma- Pheochromocytoma Syndrome	*SDHD, SDHAF2, SDHC, SDHB*
Tuberous Sclerosis Complex	*TSC1, TSC2*
WT1-related Wilms tumor	*WT1*
Neurofibromatosis type 2	*NF2*
EDS - vascular type	*COL3A1*
Marfan Syndrome, Loeys-Dietz Syndromes, and Familial Thoracic Aortic Aneurysms and Dissections	*FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11*
Hypertrophic cardiomyopathy, Dilated cardiomyopathy	*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*
Arrhythmogenic right ventricular cardiomyopathy	*PKP2, DSP, DSC2, TMEM43, DSG2*
Romano-Ward Long QT Syndromes Types 1, 2, and 3, Brugada Syndrome	*KCNQ1, KCNH2, SCN5A*
Familial hypercholesterolemia	*LDLR, APOB, PCSK9*
Malignant hyperthermia susceptibility	*RYR1, CACNA1S*

Reference: Green RC, Berg JS, Grody WW, et al; American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565-74. doi: 10.1038/gim.2013.73. Epub 2013 Jun 20. Erratum in: *Genet Med*. 2017;19(5):606. PMID: 23788249; PMCID: PMC3727274.

This Technical Brief integrates discussions with Key Informants with searches of the published literature and gray literature to inform the Guiding Questions (**Appendix C Figure 1**).

Inclusion Criteria

For all guiding questions, we prioritized research focused on genomic testing for the purposes of screening and risk prediction, as these testing indications have the most relevance for the U.S. Preventive Services Task Force (USPSTF) (**Appendix C Table 1**). We included direct-to-consumer and clinician-ordered tests for broad genomic panels, exome sequencing, or genome sequencing. We excluded testing for diagnostic purposes, cascade screening within families with a known genetic variant, as well as testing for somatic mutations (such as tumor genetics). We did not include research on carrier testing as part of preconception or prenatal counseling or on non-health–related genetic tests such as those for ancestry, paternity, or forensic purposes. We included research conducted in adult and pediatric populations, including newborns. Included settings were those relevant to primary care and conducted in countries categorized as "very high" on the 2017 U.N. Human Development Index.[23] For Guiding Question 3, included outcomes were any benefits related to health or shared decision making, as well as any harms, tradeoffs, unintended consequences, or secondary/incidental findings. We excluded reproductive decision making outcomes. While we did not exclude any specific study designs, we used a hierarchical approach to prioritize studies with lower risks of bias (starting with trials and cohort studies before exploring studies with other designs).

Gray Literature Search

Team members searched the gray literature to complement and expand on insights from Key Informants and evidence from published, peer-reviewed literature. Gray literature sources included the websites of guideline-making organizations, grants and clinical trials registries, regulatory agencies, conference proceedings, and gray literature repositories. Key Informants also were asked to suggest potential sources of information. Specific sources of literature that were examined for each Guiding Question include:

- *Guiding Question 1 (landscape)*: commercial and regulatory documents related to the current availability and regulation of genetic tests, identified through commercial testing websites as well as regulatory documents through the U.S. Food and Drug Administration (FDA)
- *Guiding Question 2 (clinical context)*: conference abstracts and position papers
- *Guiding Question 3 (benefits/harms)*: conference abstracts and clinical trial registries
- *Guiding Question 4 (issues/controversies)*: organization websites, position papers

Team members conducted internet searches to identify relevant gray literature sources for each guiding question. Ongoing clinical trials were identified through searches of clinicaltrials.gov and projectreporter.nih.gov. Gray literature was tagged according to which Guiding Question it pertained and tracked in a DistillerSR library.

Published Literature Search

For Guiding Question 3 (benefits/harms), we conducted a systematic search of English-language primary published literature. We worked with a research librarian to develop our search strategy, which was peer-reviewed by a second research librarian. Due to the large volume of genome

science discovery studies, we modified our search strategy to pursue a "best-evidence" approach to identifying the most relevant screening studies. This approach included searching the Cochrane Central Register of Controlled Trials, MEDLINE, and PubMed, publisher-supplied, for systematic reviews and clinical trials published from 2016 to January 30, 2019. The rationale for this date is based on the publication of several relevant systematic reviews in 2016 or later, as well as the publication of results from the MedSeq trial in 2017. We supplemented our database searches by reviewing reference lists from recent and relevant systematic reviews and primary studies.

We conducted hand searches of the published literature for articles relevant to all Guiding Questions. For highly relevant seminal papers, we also conducted cited-by searches using Google Scholar to further identify relevant papers. For Guiding Questions 1, 2, and 4, we reviewed results from the systematic search described above for Guiding Question 3 to identify references that were relevant to the other guiding questions (**Appendix C Table 2**).

Literature search results were managed using DistillerSR systematic literature review software (Evidence Partners, Ottawa, Canada). All titles and abstracts identified through searches were independently reviewed by two reviewers. Studies flagged for possible inclusion by at least one reviewer underwent a full-text review. Two reviewers independently reviewed each full-text article for eligibility with our prespecified inclusion criteria (**Table 1**). Discrepancies were resolved through consensus and/or consultation with a third reviewer.

Discussions With Key Informants

A list of selected Key Informants was reviewed and approved by Task Order Officers at the Agency for Healthcare Research and Quality (AHRQ). Potential Key Informants were asked to disclose conflicts of interest prior to participation. AHRQ reviewed conflicts of interests; we extended invitations to potential Key Informants who did not have conflicts of interest that precluded participation. We invited 16 Key Informants to participate in interviews via email, of which 12 participants (75%) accepted the invites. Of the invited Key Informants who did not participate, two declined, one did not respond to invitation emails, and one left their previous organization and did not have a followup email. The 12 participating Key Informants (8 nonfederal and 4 federal) represented a wide range of perspectives relevant to genomic testing, with a focus on people with experience relevant to primary care settings. The Key Informants represented the following stakeholder areas: research, clinical care, policy, ethics, patients, regulation, and industry. Key Informants were not financially compensated for participating in these interviews. Office of Management and Budget approval was not required because less than 10 non-government associated individuals were involved in the interview activities.

We conducted 30- to 60-minute semistructured telephone interviews with each Key Informant. One team member served as the interviewer and 1- to 3 additional team members took notes on a standard guide created by the research team. All interviews were audio recorded with Key Informant consent. Interview questions were grouped into "modules" covering the following topic areas: research, primary care, regulation, policy, ethics, and patients (**Appendix D**). Each Key Informant was asked questions under one or more modules according to their area of expertise. All modules included questions relevant to one or more Guiding Question, such as the potential benefits, harms, and tradeoffs of genomic testing; the challenges of genomic testing for primary care clinicians, the short-term future horizon of genomic testing; major issues or

controversies; and primary care–relevant research gaps. The predetermined questions served as a guide, and the interviewer asked subsequent or followup questions based on interviewee responses. After the interview, the interviewer sent a followup email that included a request for the Key Informant to provide publications, presentations, or other materials that might be relevant.

After each interview, team members wrote summaries and impressions of the conversation. Interview audio recordings were transcribed via a professional transcription service. One team member reviewed each transcript and categorized segments of interviewee responses by one or more Guiding Question. The team then integrated feedback from the Key Informants with evidence from the published and gray literature.

Data Management and Presentation

For articles meeting inclusion criteria, one reviewer abstracted pertinent information into summary tables. Abstracted information included study characteristics, population characteristics, setting, genomic test characteristics, context of testing, and types of outcomes measured. Data abstractions were reviewed for completeness and accuracy by a second member of the team.

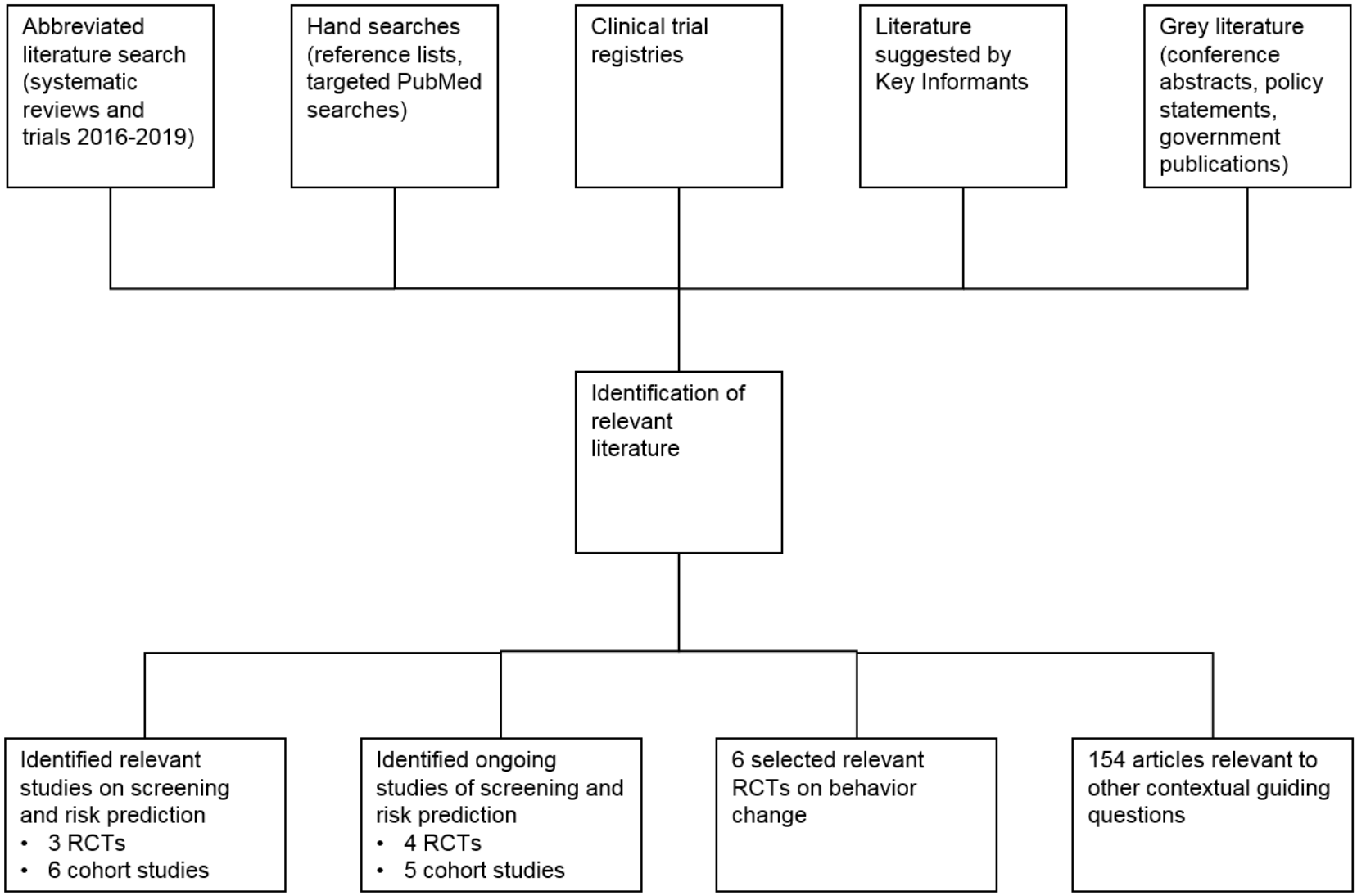
Data from the published literature was integrated with information from the gray literature and discussions with Key Informants. Following the standard procedures for technical briefs, quality assessment (i.e., critical appraisal) of identified studies was not conducted. The evidence for each Guiding Question was synthesized in a narrative format, with supporting summary tables appropriate to the identified evidence.

For Guiding Question 3, we audited outcomes reported in relevant studies to outline for the USPSTF the types of evidence available related to the use of genomic testing. We prioritized outcomes that are most relevant to the USPSTF portfolio and also added nontraditional outcomes after team discussion. We narratively summarized the findings and conclusions of these articles as reported by the study authors, but did not abstract particular data from the studies or evaluate the quality or accuracy of the author-generated conclusions.

Expert Reviewers

Expert reviewers were invited to provide written comments on the draft Technical Brief. Reviewer comments on the preliminary draft of the Technical Brief were considered by the Evidence-based Practice Center in preparation of the final draft of the Technical Brief.

Appendix C Figure 1. Literature Flow



Appendix C Table 1. Inclusion and Exclusion Criteria for Guiding Questions

	Include	Exclude
Testing indication* all GQs	Screening Risk prediction Pharmacogenomic§	Diagnostic Carrier testing (as part of preconception or prenatal counseling) Non-health–related tests (ancestry, paternity, kinship, forensic)
Populations all GQs	Pediatric†, adult	
Diseases/genetic conditions all GQs	Germline variants	Somatic mutations (e.g., tumor genetics)
Genetic/genomic tests all GQs	Clinician-ordered or DTC tests, including: • Broad genomic panel testing • Exome/genome sequencing	Targeted testing (e.g., single gene testing in an individual suspected of having a specific variant) Tumor tests Family history assessment
Settings all GQs	Primary care–relevant or referable (including DTC results brought to primary care)	
Countries all GQs	Countries categorized as "very high" on the 2017 U.N. Human Development Index	
Outcomes GQ3	Any identified or potential benefits, including: • Health-related benefits • Informed / shared decision making Any harms/tradeoffs, including: harms, false-positive results, false-negative results, unintended consequences, liability issues, privacy issues, ethical issues, implications for family members, exacerbation of health disparities Secondary/incidental findings, regardless of indication	Reproductive decision making outcomes
Study designs GQ3	Hierarchical approach: starting with trials and cohort studies; looking to other study designs (e.g., survey, qualitative, case-control) as needed.	
Publication date GQ3	2010‡	

* Secondary/incidental findings will be included in this technical brief regardless of indication for testing.
† Pediatric populations include newborns.
‡ We will use a staged approach, starting with reviewing literature published in the last 5 years (2013 and later) and expanding to earlier literature (2010 and later) as needed.
§ The vast majority of evidence related to pharmacogenomics is related to the underlying effect of single variants on drug response and adverse effects, and thus most of these tests fell outside of the scope of this technical brief.

Abbreviations: DTC = direct-to-consumer; GQ = guiding question; UN = United Nations.

Appendix C Table 2. Methods by Guiding Question

	Key informant interviews	Gray literature and / or hand searching of published literature	Systematic literature search
Guiding Question 1: Landscape of genomic testing			
a - Available tests and panels	X	X	
b - Regulatory environment	X	X	
c - Short-term (3–5 years) future horizon	X	X	
Guiding Question 2: Clinical context and use of genomic testing			
a - Patient use of DTC genomic tests; clinical ordering of broad genomic panels		X	
b - Patients sharing DTC results with primary care clinicians	X	X	
c - Challenges for primary care clinicians	X	X	
d - Care models/clinical resources: primary care and genomics	X	X	
Guiding Question 3: Available evidence about the benefits and harms of genomic testing			
a - Nontraditional outcomes related to genomic testing	X	X	X
b - Results reported on the benefits or harms of genomic testing		X	X
Guiding Question 4: Important issues and controversies			
a - Issues and controversies	X	X	
b - Primary care–relevant research gaps	X	X	

Abbreviation: DTC = direct to consumer.

RESEARCH

1. Could you start by telling us a little about the research you have done related to clinical genomic testing or direct-to-consumer testing?
2. What are the potential benefits to patients do you feel are most important outcomes within research of genomic screening in patients?
3. What about harms, unintended consequences, or tradeoffs?
4. How are these benefits or harms specific to genomic screening, and don't appear in other areas of primary care research?
5. Part of our work will involve highlighting gaps in the existing research on genomic testing and direct-to-consumer testing in primary care. What would you prioritize as the key gaps in this area?
6. What kind of research do you think is needed to fill these gaps? And are there any studies underway that you feel will be particularly important in this area?

PRIMARY CARE

1. What is your clinical experience with genomic testing and direct-to-consumer testing?
2. What is your experience with genomic testing in the areas of screening and risk prediction in these populations?
3. What is your experience with patients sharing direct-to-consumer genomic test results with their primary care clinicians?
4. What challenges do direct-to-consumer genomic tests pose for primary care clinicians?
5. We are interested in learning about organizations or care models that have had success with workflow or staffing designs that help primary care clinicians talk with patients about genomic screening results. Can you tell me about any you have heard of?
6. What resources have you used to help you address genomic screening and direct-to-consumer testing in clinical care? [Prompts: decision aids, written resources, websites, organizations...]
7. What are the potential benefits of genomic screening to patients?
8. What about harms, unintended consequences, or tradeoffs?
9. How are these benefits or harms specific to genomic testing, and don't appear in other areas of primary care practice?
10. What do you think genomic screening in primary care practice will look like in the next 3 to 5 years? How is that different from what you see today?
11. What do you see as the major issues or controversies related to genomic screening in clinical care? [Prompts if needed: test accuracy (false positives, false negatives); liability; privacy; ethics; familial implications; health disparities/access; discrimination; regulatory issues]

REGULATION

1. Tell us about your background and your experience with genomic testing.
2. Tell us about how genomic screening tests are regulated, and how that is different than how other tests or devices are regulated?
3. How does this regulation differ between clinical genomic testing and direct-to-consumer testing?

4. How do you expect regulations to change, if at all, in the next 3 to 5 years?
5. Who are the stakeholders in determining regulations? How have various stakeholders influenced the process?
6. What impacts does the regulatory environment have for primary care practice? For patients?

POLICY

1. Tell us about your background and your experience with genomic testing.
2. What do you see as the major issues or controversies related to genomic screening? [Prompts if needed: test accuracy (false positives, false negatives); liability; privacy; ethics; familial implications; health disparities/access; discrimination; regulatory issues]
3. What do you think health system and public polices around genomic screening in primary care will look like in the next 3 to 5 years? How is that different from what you see today?
4. What are the important research gaps regarding policies in genomic testing in primary care?

ETHICS

1. What ethical and legal implications are most important when considering the use of genomic screening in primary care settings? [Prompt: reminder of scope, non-diagnostic]
2. What about for direct-to-consumer testing?
3. What do you view as the most important potential tradeoffs of benefits and harms in primary care when policies around genomic testing are being determined?
4. What do you see as the main unanswered questions in terms of the ethical implications of genomic screening and primary care?

PATIENTS

1. What organization do you represent? How did you get involved in genetic testing?
2. What has your experience been with genomic screening? What kinds of tests have you (or the other patients you represent) encountered?
3. What is your (or patients' you represent) experience with sharing direct-to-consumer test results with primary care physicians?
4. What do you see as the main benefits for individuals of genomic screening?
5. What about any harms, or negative aspects?
6. What do you see as the major issues or controversies related to genomic screening? [Prompts if needed: test accuracy (false positives, false negatives); liability; privacy; ethics; familial implications; health disparities/access; discrimination; regulatory issues]
7. How do you think patients' experience of genomic screening will change in the next 3 to 5 years?
8. What research do you think is needed in the areas of clinical genomic testing and direct-to-consumer testing?

Appendix D Table 1. Audit of Published and Planned Outcomes for Studies of Genomic Testing

Study	Test Accuracy	Intermediate Outcomes	Health Outcomes	Beliefs and intentions	Harms
BabySeq[24-29]	Detection of disease predisposition Feasibility	*Healthcare utilization*		Personal utility *Behavioral intentions* *Self-efficacy* *Information seeking/sharing* *Participant understanding*	*Psychosocial distress*
CHARM[30]	*Detection of disease* *Detection of disease predisposition*				
ClinSeq[31-33]	Test accuracy Detection of disease predisposition	Change in disease surveillance Healthcare utilization		*Behavioral intentions*	Psychosocial distress
GeneScreen[34-36]	Detection of disease predisposition	Healthcare utilization Change in disease surveillance Lifestyle changes		Behavioral intentions Participant understanding	Psychosocial distress Family level distress
MedSeq[37-43]	Detection of disease Detection of disease predisposition	Lifestyle changes* Change in treatment/dose Healthcare utilization		Personal utility Information seeking/sharing Participant understanding	Psychosocial distress
MilSeq[44]	*Detection of disease predisposition*	*Physiologic†* *Healthcare utilization*	*Quality of life*	*Participant understanding*	
MyCode[45-50]	Genome sequencing findings Detection of disease Detection of disease predisposition	Early treatment Change in treatment/dose Change in disease surveillance Healthcare utilization		*Attitudes*	
MyPeBS[51]		*Disease incidence*	*Morbidity* *Mortality* *Stage at detection* *Quality of life*	*Information seeking/sharing*	*Harms from workup* *Psychosocial distress* *False reassurance* *False positives*
MVP-ROAR[52]	*Cascade Screening*	*Physiologic†* *Change in treatment/dose* *Medication adherence* *Healthcare utilization* *Lifestyle changes**	*Quality of life*		

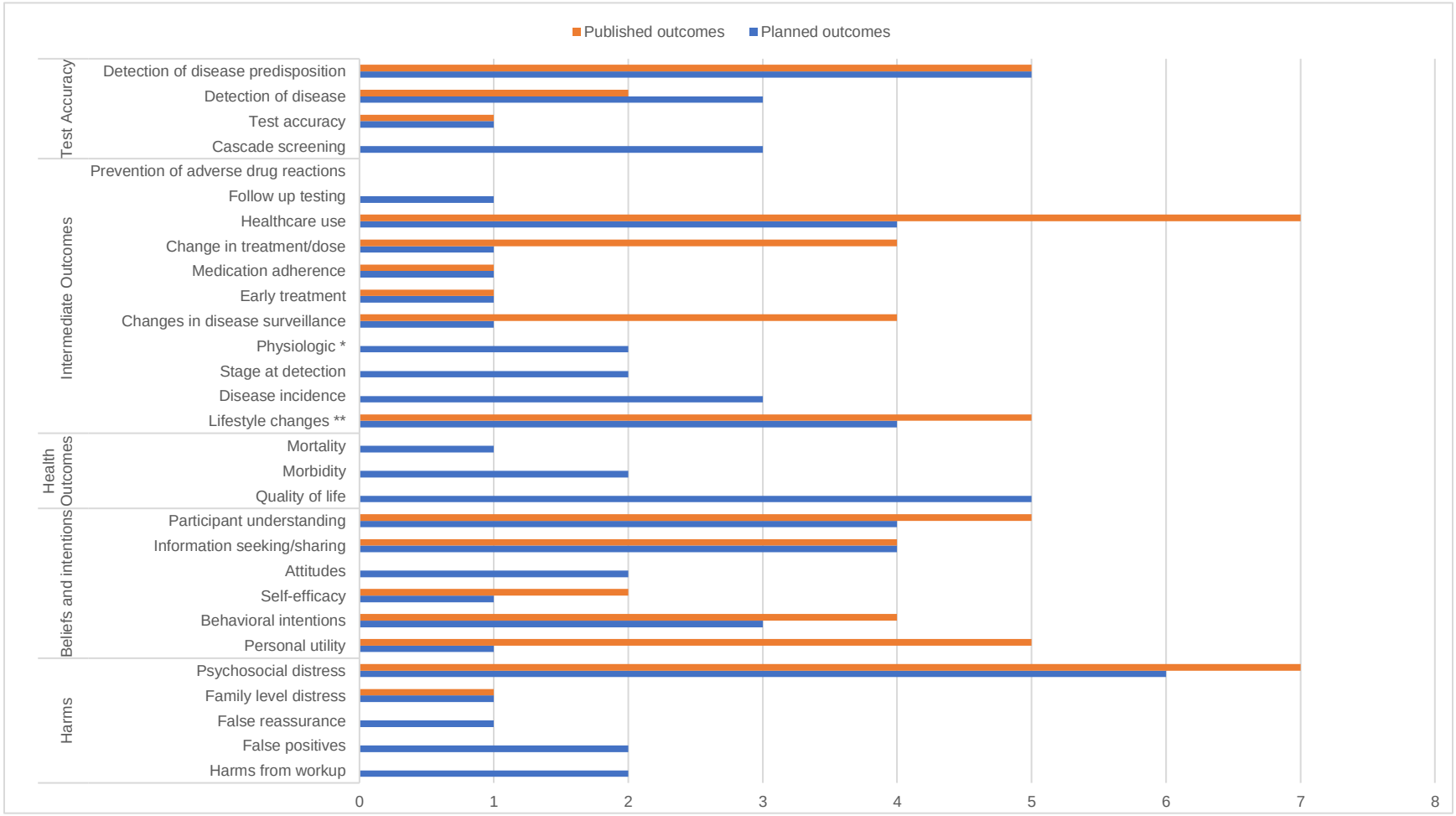
Appendix D Table 1. Audit of Published and Planned Outcomes for Studies of Genomic Testing

Study	Test Accuracy	Intermediate Outcomes	Health Outcomes	Beliefs and intentions	Harms
NC_Nexus[53-55]	*Test accuracy* *Detection of disease* *Detection of disease predisposition* *Feasibility*			*Information seeking/sharing* *Participant understanding* *Attitudes*	*Psychosocial distress* *Family level distress*
PRoGRESS[56]	*Cascade screening*	*Lifestyle changes**	*Quality of life*	*Personal utility* *Behavioral intentions* *Information seeking/sharing* *Participant understanding*	*Psychosocial distress*
PeopleSeq[57,58]		Lifestyle changes* Change in treatment/dose Healthcare utilization		Personal utility Behavioral intentions Self-efficacy Information seeking/sharing Participant understanding	Psychosocial distress
PGen[59-68]		Lifestyle changes* Change in treatment/dose Medication adherence Healthcare utilization		Personal utility Behavioral intentions Self-efficacy Information seeking/sharing Participant understanding	Psychosocial distress
PGT[69,70]	*Feasibility*	*Lifestyle changes**			Psychosocial distress
PopSeq[71]	*Detection of disease* *Cascade screening*	*Lifestyle change* *Healthcare utilization*	*Quality of life*		*Psychosocial distress*
Risk-Based Breast Cancer Prevention[72]	*Detection of disease predisposition*	*Disease incidence*			
Scripps[73-81]		Lifestyle changes* Healthcare utilization Change in disease surveillance		Personal utility Behavioral intentions Information seeking/sharing Participant understanding	Psychosocial distress
WISDOM[82,83]	*Detection of disease predisposition*	*Disease incidence* *Change in disease surveillance* *Followup testing* *Early treatment*	*Morbidity* *Stage at detection*		*Harms from workup* *Psychosocial distress* *False positives*

Notes: Published outcomes are in regular font; planned outcomes are in italics.

* "Lifestyle changes" include changes in diet, smoking behaviors, and physical activity.
† "Physiologic" outcomes include changes in body mass index, blood pressure, glucose, and cholesterol.

Appendix D Figure 1. Outcomes of Published and Planned Genomic Testing Studies



* "Physiologic" outcomes include changes in body mass index, blood pressure, glucose, and cholesterol.
** "Lifestyle changes" include changes in diet, smoking behaviors, and physical activity.

Appendix D Table 2. Characteristics of Trials on Polygenic Risk Scores for Behavior Change

Study	N	Aim	Population	Intervention	Relevant outcomes
Genetic Counseling/Lifestyle Change for Diabetes Prevention (GC/LC)[84-87]	180	Examine whether diabetes genetic risk testing and counseling can improve diabetes prevention behaviors	Primary care patients with BMI >29.1 (men) or 27.2 (women); with one other criteria for metabolic syndrome	Intervention: Polygenic T2D risk score + 12-week DPP Comparison: DPP only	Diabetes Prevention Program attendance* Diabetes incidence Weight/BMI
Genetic Test to Stop Smoking (GeTSS)[88,89]	67	Evaluate the risk score as a motivator in a primary care smoking cessation clinic alongside the usual counseling and prescribing protocol	Smokers ages 20-70 years	Intervention: Lung cancer risk score incorporating genetic-based risk plus smoking cessation intervention. Comparison: smoking cessation intervention only	Smoking cessation*
Personal Genomics for Preventive Cardiology[90,91]	94	Whether providing a genetic risk score for coronary artery disease would serve as a motivator to improve adherence to risk-reducing strategies	Individuals at intermediate or high CAD risk	Intervention: Standard of care plus a genetic risk score Comparison: Standard of care	LDL* HDL Blood pressure Weight Diet Physical activity Anxiety Medication adherence
Myocardial Infarction Genes (MI-GENES)[92-99]	216	Assess whether disclosing a genetic risk score for coronary heart disease leads to lowering of low-density lipoprotein cholesterol levels	White Mayo clinic biobank participants ages 45-65 years with intermediate CHD risk (5%-20% in next 10 years)	Intervention: Framingham risk score plus and genetic risk information Comparison: Framingham risk score only	LDL* Diet Physical activity Statin use Anxiety
Clinical Validity and Utility of Genomic-targeted chemoprevention of Prostate cancer[100,101]	700	To test whether counseling based on family history versus a genetic risk score plus family history differentially affects PSA screening rates at 3 months	Men ages 40-49 years with no prior PSA screening	Intervention: Risk based on family history plus genetic risk score Comparison: Family history risk only	PSA screening uptake* Anxiety
Effect of Type 2 Diabetes Genetic Risk Information on Health Behaviors and Outcomes (TDE)[102,103]	450	Evaluate the utility of a genetic test for type 2 diabetes risk in combination with standardized risk assessment on perceived risk and behavior change	Outpatients without diabetes ages 18-80 years	Intervention: Risk assessment plus genetic risk Comparison: Standard risk assessment only	Weight/BMI* Fasting blood glucose* Physical activity*

* Indicates study's primary outcome.

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CHD = congestive heart disease; DPP = Diabetes Prevention Program; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PSA = prostate screening antigen; T2D = type 2 diabetes.

Appendix D Table 3. Results of Trials on Polygenic Risk Scores for Behavior Change

Relevant Outcomes	Study	Conclusion	Direction of effect
Health outcomes	GC/LC	After 6 years, time to diabetes did not differ between groups, but the results suggested lower diabetes incidence among control (no genetic testing) vs. intervention (genetic risk score) participants.[84]	↓
Medication initiation/changes	MI-GENES	Initiation of statin use was significantly higher in the +GRS group than in the CRS group (P<0.01).[95]	↑
	Personal Genomics for Preventive Cardiology	No difference in the proportion of participants on statins or antihypertensive drugs at the 3- or 6-month visit.[91]	↔
Changes in disease surveillance	Clinical Validity and Utility of Genomic-targeted chemoprevention of Prostate cancer	Overall, no significant differences were observed in the rate of PSA screening at 3 months or 3 years by the type of feedback. The participants who were told they had increased lifetime prostate cancer risks (based on genetics and family history) were significantly more likely to engage in PSA screening; this was not observed in the family history–only arm.[101]	↔, ↑
Lifestyle changes	GC/LC	Receipt of personal genetic risk information and counseling had no statistically significant effect on measured behaviors.[86]	↔
	GeTSS	The 6-month smoking quit rates were not significant between the two groups; however, the subjects with the "very high risk" had a significantly higher quit rate.[88]	↔, ↑
	Personal Genomics for Preventive Cardiology	No significant difference in physical activity or diet between the two groups. Among participants with a higher GRS, we observed modest effects on physical activity.[91]	↔, ↑
	MI-GENES	No significant differences in dietary fat intake or physical activity levels 6 months after CHD risk disclosure were observed between CRS and +GRS participants.[95]	↔
	TDE	There were no significant changes in physical activity from baseline to 12 months. Neither family history nor genetic risk levels affected changes.[102]	↔
Physiologic	GC/LC	Receipt of personal genetic risk information and counseling had no statistically significant effect on weight loss.[86]	↔
	Personal Genomics for Preventive Cardiology	No significant difference in LDL-C reduction, HDL-C, blood pressure, or weight between the two groups. Among participants with a higher GRS, we observed modest effects on weight loss.[91]	↔, ↑
	MI-GENES	The overall downward longitudinal trend in LDL-C was significantly greater in +GRS participants than in CRS participants (P=0.04). After adjustment for statin initiation, group randomization was not significantly associated with the end of study LDL-C levels.[95]	↑
	TDE	There were no significant changes in BMI, weight, or fasting blood glucose from baseline to 12 months. Neither family history nor genetic risk levels affected changes.[102]	↔

Appendix D Table 3. Results of Trials on Polygenic Risk Scores for Behavior Change

Relevant Outcomes	Study	Conclusion	Direction of effect
Psychosocial distress	Personal Genomics for Preventive Cardiology	No significant difference in anxiety between the two groups.[91]	↔
	MI-GENES	No significant differences in anxiety levels 6 months after CHD risk disclosure were observed between CRS and +GRS participants.[95]	↔
	Clinical Validity and Utility of Genomic-targeted Chemoprevention of Prostate cancer	Immediate post-result anxiety did not significantly differ by randomization group.[101]	↔

Abbreviations: BMI = body mass index; CHD = coronary heart disease; CRS = conventional risk score: GC/LC = Genetic Counseling/Lifestyle Change for Diabetes Prevention; GeTSS = Genetic Test to Stop Smoking; GRS = genetic risk score; HDL-C + high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI-GENES = Myocardial Infarction Genes.

Pharmacogenomics describes the effects that variants across the genome may have on an individual's drug response. The use of these test results can help predict whether a medication may be effective for an individual and to help prevent adverse drug reactions.[104] Pharmacokinetics describes the variability in the ability to process a drug including absorption, distribution, metabolism, and elimination. Pharmacodynamics describes the variability that is not attributable to the drugs concentration.[105] The first U.S. Food and Drug Administration (FDA)–approved drug to receive pharmacogenomic specific labeling was warfarin in 2006. Since that time, many new drugs have contained genomic information in labeling at their time of initial approval. The FDA maintains a list of the over 100 therapeutic agents with pharmacogenomic information including in labeling.[106]

The Clinical Pharmacogenetics Implementation Consortium (CPIC) publishes genotype-based drug guidelines. These guidelines provide clinicians with information to translate patient-specific genetic information into clinical phenotypes and drug dosing groups. These guidelines are based upon a systematic grading of the evidence, are peer reviewed, and freely available online.[107] In addition to providing guidance on actionable pharmacogenetic variants, CPIC plans to begin offering guidance on gene-disease pairs, which has a weak evidence base and are not currently actionable, despite heavy marketing to providers and the public.[108] Non-pharmacogenomic indications backed by guidelines from organizations such as CPIC are currently included in FDA labeling.

In addition to the research programs, pharmacogenomic information is being included in large genome sequencing programs worldwide, including the National Institutes of Health's All of Us research program,[109] which aims to build a database of more than 1 million diverse participants throughout the United States. The All of Us program will utilize the pre-emptive model and return drug-gene interaction data back to participants to assist with clinical decision support for future prescriptions. A similar pharmacogenomic implementation programs using this pre-emptive model is being developed in Estonia. Estonian health officials have researched and identified links between certain gene variants associated with adverse drug reactions. Those officials are currently determining how best to followup on these pharmacogenomic findings with participants and providers.[110,111]

Several U.S.-based healthcare systems also provide or will provide similar pharmacogenomic information within their genome sequencing programs, including the Colorado Center of Personalized Medicine[112] and Northshore's Genomic Health Initiative.[113] The Electronic Medical Records and Genomics Network and the Pharmacogenomics Research Network (eMERGE-PGx) project, a U.S.-based multisite collaboration, has conducted implementation research on how best to integrate pharmacogenomic data into electronic health record (EHR) data.[114-116] Within the eMERGE-PGx project, the Northwestern Medical Group, for a select number of patients, has integrated genomic variant data into its EHR system and will study any change in physician actions. Geisinger's MyCode program,[117] also in collaboration with the eMERGE-PGx project, is piloting a program that gives patients a written report of their pharmacogenomic results to use in any healthcare setting. Separately, Vanderbilt has created a research-oriented resource that links de-identified EHR data to a genetic biobank. Researchers there aim to use this resource to supplement traditional drug development research to identify predicted drug effects more rapidly.

Appendix F Table 1. Exemplar Quotes From Key Informant Interviews

Topic	Quote
Clinical utility	Well, obviously someone's at risk for something and they find out about it and do something about it, then that's good. Everybody's for that.
	You can't always prevent an outcome, but you can certainly change the course of the disease is one of the, I'd say the biggest health benefits. I think in some cases there are some psychological benefits to knowing that you haven't inherited something. Sometimes when there is a family history of something and you know what it is – some people get screening and they find out that they have not inherited what could exist in the family, but that's just because even when you're doing genomic screening and presumably healthy, there is often a hidden family history. So yeah, I think it's just the ability with that knowledge to guide early and more frequent screening, kind of enhanced in early screening.
	A lot of primary care providers think about clinical genomic testing or genomic screening and DTC testing as one more tool in their toolkit, something else they can use to persuade patients to take steps to improve their overall health.
	I imagine what would be of interest to the USPSTF would be the average patient population, should they all undergo sequencing … entire gene sequencing with high validity and high reliability, people are proposing that that should be done. That to me is a very pressing research gap and important question that should be answered. And then it compounds, because while you're at it, you could also look for Lynch syndrome and you could also look for any other number of conditions. So what's the right number of conditions? In theory the benefit kind of compounds, maybe, and I think the risk in false negatives, as long as you're doing sequencing and you're weeding out the patients that otherwise wouldn't meet clinical criteria for testing. I think that's a very tantalizing prospect, to be able to meaningfully improve screening for certain conditions like that.
Harms	Sadly, I think there may be more cases cropping up of people that have misinterpreted or over interpreted test results and then did prophylactic surgery or implantable devices in people that didn't need them.
	I do think one harm that I heard about actually a lot at ACMG, a lot of people seemed to be talking about this, is this idea of harms that can come from overaggressive workup and I think those are helpful to consider for some variants in particular, that's why I think investigations into penetrance of these disorders in unselected families is really very important.
	We're assessing psychological distress, because I think a hot topic is still this idea if you dump these unanticipated or unintended findings on people, they're going to have very bad outcomes. I don't know that we found any evidence of that, and when I reviewed the literature, I don't see a lot of evidence of that.
	In order to give someone the treatment that they need, you need to be able to predict to what treatment they will respond best, so the core of precision medicine is prediction. But then we start making personalized health care based on bad predictions, it becomes a mess. So that is really my biggest concern - that people start introducing it not understanding the limitations of it all and introducing a lot of unnecessary care.
Primary care clinician role	Primary care providers are not going to be deeply engaged in returning results until or unless it becomes a common part of their practice. And so insisting that they somehow learn what I want them to learn as a geneticist or what I think they need to know in order to return results is not a good use of anybody's time. If it gets to the point where a couple times a week or a couple times a day they're being confronted with questions, they're going to learn the answers to them and learn how to navigate it and start doing it themselves with less referral to the specialist.
	To me that's the $60 million ethical question right there – how do we move from these esoteric contexts in which we've been doing genetic testing through counselors and with medical genetic specialists of various sorts, to something that could be scaled for a primary care setting?

Appendix F Table 1. Exemplar Quotes From Key Informant Interviews

Topic	Quote
	For years genetic testing has been done with the sort of unique type of pretest counseling provided by a genetic counselor, where they'll sit and they'll take a family history and they'll talk with the patient about what the goals of pursuing the test are, the pros and cons of different kinds of results and get them prepared to cope with the finding that will come back. And that is extraordinarily exceptional compared to other areas of medicine. We don't do that kind of preparatory work for almost any other type of diagnostic evaluation. We just assume that patients will want to know.
Equity	I think the direct-to-consumer testing is a great option. It's just as a clinician, I don't know how it's validated. It's a great option for people—it's very affordable, it's very easy, very accessible, but again as a clinician, I'm not quite sure what to do. So it would be awesome if we're going to use direct-to-consumer testing if it would come with a lot more information about—if you're a clinician and you're dealing with this, what would you do?
	A lot of the baseline reference genomes that we're basing a lot of our research findings on are basically from eastern European white people, or people of eastern European descent, and so getting more diverse representation of participants I think will help us better understand for different populations what the genetic variants mean for their health.
	I think we are not thinking enough about the population at large. When people start thinking about next gen sequencing, nobody says—shall we spend the money on sequencing or shall we give better care to people from lower socioeconomic status that have bad health outcomes? It's not that question. It is genomics, yes or no. And I think that's the wrong question. Because healthcare, the finances, the budgets are limited. So we should not spend it on things we don't need.
USPSTF portfolio	I do think it is outdated for the USPSTF to have guidelines just on BRCA. We have to move to panel testing, there's so much overlap now. We have families with Lynch that end up being *BRCA2*. We have families that look like *BRCA2* that end up being Lynch. We have families that look like BRCA that end up being *PALB2*. I mean, there's just so much overlap, and it's confusing to patients and providers, I'm sure, that only one test out of what is now panel testing is covered or even mentioned, and it makes it really hard to require health plans to cover it if what they're required to cover is only a partial test of what they actually provide.
Future horizon	It's a little hard for me to predict where it's all going to be. I mean, if you didn't say 3 to 5 years, if you said 35 years, I would say everyone will have their genome done and will have powerful ways of using that information. But between here and there, I'm not sure of the stops along the road.
	I think the incidence of people getting a DTC test and then taking it to their clinician is going to increase, particularly as we continue to authorize more and more types of genetic testing. I think doctors, primary care in particular, are going to have to figure out how they want to address those types of test results. Do they want to order a confirmatory test? Do they want to trust the test results that their patient is providing them with, since they didn't order them? My guess is that's likely to increase over time. The medical professional societies, the adoption of these technologies is really going to depend on their efforts in terms of educating their members about the utility of these types of tests, and when it is and is not appropriate to order them.

Abbreviations: ACMG = American College of Medical Genetics and Genomics; DTC = direct-to-consumer; USPSTF = U.S. Preventive Services Task Force.

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