Barriers and facilitators for population genetic screening in healthy populations: a systematic review

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Abstract

Studies suggest that 1-3% of the general population in the United States unknowingly carry a genetic risk factor for a common hereditary disease. Knowing this information could help guide improved disease risk management and preventive care. Population-based genetic screening is the process of offering otherwise healthy patients screening for genetic variants that predispose them to certain diseases that are “clinically actionable”, meaning that they can be prevented or mitigated if they are detected early in asymptomatic individuals. Optimizing population genetic screening may significantly reduce morbidity and mortality from these diseases by informing risk-specific prevention or mitigation strategies and facilitating appropriate participation in early detection and screening. To better understand current barriers, facilitators, perceptions, and outcomes related to the implementation of population screening, we conducted a systematic review and searched PubMed, Embase, and Scopus for articles published from date of database inception to May 2020. We included articles that (1) detailed the perspectives of participants in population screening programs and (2) described the barriers, facilitators, perceptions, and outcomes related to population genetic screening programs among patients, healthcare providers, and the public. We excluded articles that (1) focused on direct-to-consumer or risk-based genetic testing and (2) collected data before January 2000. Twenty-nine articles met these criteria. Barriers and facilitators to population genetic screening were organized by the Social Ecological Model and further categorized by themes. We found that research in population genetic screening has focused on stakeholder attitudes about screening with all included studies designed to elucidate individuals’ perceptions. Additionally, inadequate knowledge and perceived limited clinical utility presented a barrier for healthcare provider uptake. There were very few studies that conducted long-term follow-up and analysis of population genetic screening. Our findings suggest that these and other factors, such as prescreen counseling and education, may play a role in the acceptance and implementation of population-based genetic screening. Future studies to investigate macro-level determinants, provider buy-in and education, prescreen counseling, and long-term outcomes of population genetic screening are needed for the effective design and implementation of such programs.

1 Introduction

Population genetic screening can identify otherwise healthy individuals carrying genetic variants that confer a higher-than-average risk of developing hereditary conditions. For example, an estimated 2 million people in the United States (US) have genetic variants that predispose them to Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Lynch Syndrome (LS), and familial hypercholesterolemia (FH) and increase their risk for adverse health outcomes. The Centers for Disease Control and Prevention Office of Genomics and Precision Health has prioritized screening for these conditions as Tier 1 applications for genomics (Tier 1 Genomics Applications and their Importance to Public Health | CDC, 2021) and additional clinical guidelines in the US recommend genetic testing for patients with a family or personal history of one of these conditions (Goldberg et al., 2011; Gupta et al., 2019). Although the eleven genes associated with the Tier 1 applications are well-understood, highly penetrant, and the conditions are clinically actionable, clinical evidence is currently insufficient to recommend widespread screening in healthy populations (Hampel and de la Chapelle, 2011; Representatives of the Global Familial Hypercholesterolemia Community, 2020). However, clinical pilot offerings for population genetic screening are on the rise and offer promising opportunities to build the necessary knowledge base for expanding DNA-based population screening.

Understanding the barriers, facilitators, perceptions, and outcomes to DNA-based screening of healthy populations is critical for implementing screening programs in US healthcare settings. No systematic reviews have studied this topic to our knowledge. To address this need, we conducted a systematic review of current research literature to identify factors that may affect the clinical implementation of population genetic screening.

2 Methods

We adhered to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) reporting guidelines (Moher et al., 2009) for this review (Supplemental Material, Appendix A). Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020198198 (Shen et al.). We worked with a medical librarian (RC) to develop search strategies for the concept of population genetic screening in unknown and average risk populations, which were used to search PubMed, Embase, and Scopus from date of database inception to May 22, 2020, when all searches were completed. Search filters were used to limit the results to original research articles written in English and to exclude preconception, prenatal, and carrier testing. The complete strategy for each of the searches can be found in Supplemental Material, Appendix B. We also manually examined the references of relevant literature reviews to identify additional studies that may have been missed by the database searches. All references were uploaded to Covidence Systematic Review software (Veritas Health Innovation), a systematic review management system for study selection.

Two of nine reviewers (ES, SS, LP, CA, MD, KF, BH, LM, AS) independently reviewed each title and abstract for eligibility and thematic issues were resolved by discussion. MR oversaw the process and formally resolved specific conflicts. Two of eight reviewers (ES, SS, LP, CA, MD, BH, LM, AS) assessed the full texts and thematic issues were resolved by discussion. KF oversaw this process and formally resolved specific conflicts. We included articles that detailed the perspectives of participants of population screening programs and individuals asked about population screening to capture all possible barriers, facilitators, perceptions, and outcomes from the position of patients, healthcare providers, and the public. Conference abstracts, meeting reports, literature reviews, guidelines, and simulation modeling studies were excluded. Articles focusing on genetic literacy and research, hypothetical gene correlations, and those that lacked a methods section or relevant outcomes were also excluded. Finally, we excluded

articles that focused on direct-to-consumer or high-risk genetic testing and articles that collected data before January 1, 2000 to understand views of population genetic screening in a clinical context with the use of contemporary technology.

Data extraction forms were developed in Covidence using the PICOS framework (Schardt et al., 2007) to collect information about each study's population (patients, healthcare providers, and the public), intervention (disease area(s), whether population genetic screening was offered, and whether participants met with providers before or after screening), comparator group if applicable, outcomes (barriers, facilitators, perceptions, effectiveness measures such as change in health behavior), and setting (e.g., scale, country, type) (see Supplemental Material, Appendix C). We defined patients as healthy individuals with no known risk status who were seen in the healthcare system and the public as individuals who were selected from and represented the broader community. The extraction forms were developed based on a previous review (Srinivasan et al., 2020) and four sets of two reviewers independently piloted them on a subset of five articles to agree on a final version. ES, SS, and LP resolved disagreements in data extractions and discussed specific articles as needed. We separately examined articles that had implemented population screening and those that had not implemented population screening to account for contextual differences before analyzing these article types together. Barriers and facilitators were arranged according to the Social Ecological Model (Golden and Earp, 2012), which views health as affected by the interaction between individual, community, and physical, social, and political environments (Table 2 and Table 3). Perceptions were categorized into favorable, unfavorable, and in-between. Perceptions are summarized in Supplemental Material, Appendix D and effectiveness measures are summarized in Supplemental Material, Appendix E.

Reviewers independently assessed the methodological quality of each study following the Mixed Method Appraisal Tool, version 2018 (Hong et al.) for each study type (RCT, descriptive, observation, qualitative, or mixed methods). Meta-analysis was not conducted due to the high variation in study design, population, setting, and outcomes.

3 Results

Of the 4,821 unique studies that were identified through database searching, 323 articles were assessed for full-text eligibility. Twenty-nine articles (Shaw III and Bassi, 2001; Laskey S.L. et al., 2003; Sanderson et al., 2004, 2017; Allen K.J. et al., 2008; Borry et al., 2008; Neghina A.M. and Anghel A., 2010; Haga et al., 2011; Hardie, 2011; Henneman L. et al., 2011; Nielsen and El-Sohemy, 2012; Nusbaum R. et al., 2013; Haga S.B. et al., 2014; Vassy J.L. et al., 2014; Hietaranta-Luoma H.-L. et al., 2015; O'Neill S.C. et al., 2015; Shiloh S. et al., 2015; Godino J.G. et al., 2016; Nicholls S.G. et al., 2016; Sanderson S.C. et al., 2016; Vassy et al., 2017; Fenton G.L. et al., 2018; Hay J.L. et al., 2018; East et al., 2019; Rego S. et al., 2019; Rubinsak et al., 2019; Zoltick E.S. et al., 2019; Joshi E. et al., 2020; Smit et al., 2020) were included in our analysis after assessing the articles according to the inclusion and exclusion criteria, and their characteristics are available in Table 1 (see Figure 1 for PRISMA diagram).

Six studies investigated the perspective of patients (Allen K.J. et al., 2008; Neghina A.M. and Anghel A., 2010; Nusbaum R. et al., 2013; Hietaranta-Luoma H.-L. et al., 2015; East et al., 2019; Rubinsak et al., 2019), four investigated the perspective of providers (Borry et al., 2008; Haga et al., 2011; Vassy J.L. et al., 2014; Joshi E. et al., 2020), one study investigated the perspectives of both patients and providers (Vassy et al., 2017), and eighteen studies investigated the perspective of the public (Shaw III and Bassi, 2001; Laskey S.L. et al., 2003; Sanderson et al., 2004, 2017; Hardie, 2011; Henneman L. et al., 2011; Nielsen and El-Sohemy, 2012; Haga S.B. et al., 2014; O'Neill S.C. et al., 2015; Shiloh S. et al., 2015; Godino J.G. et al., 2016; Nicholls S.G. et al., 2016; Sanderson S.C. et al., 2016; Fenton G.L. et al., 2018; Hay J.L. et al., 2018; Rego S. et al., 2019; Zoltick E.S. et al., 2019; Smit et al., 2020). Ten studies did not record race or ethnicity information (Allen K.J. et al., 2008; Borry et al., 2008; Neghina A.M. and Anghel A., 2010; Hardie, 2011; Hietaranta-Luoma H.-L. et al., 2015; Godino J.G. et al., 2016; Fenton G.L. et al., 2018; East et al., 2019; Joshi E. et al., 2020; Smit et al., 2020). Two studies were conducted solely with female participants (Henneman L. et al., 2011; Rubinsak et al., 2019) and one did not record information about gender (Joshi E. et al., 2020). Seven studies did not record the mean age of participants (Laskey S.L. et al., 2003; Borry et al., 2008; Haga et al., 2011; Haga S.B. et al., 2014; Fenton G.L. et al., 2018; Rego S. et al., 2019; Joshi E. et al., 2020).

Eighteen studies implemented population screening programs of some kind (Allen K.J. et al., 2008; Neghina A.M. and Anghel A., 2010; Nielsen and El-Sohemy, 2012; Nusbaum R. et al., 2013; Haga S.B. et al., 2014; Hietaranta-Luoma H.-L. et al., 2015; O'Neill S.C. et al., 2015; Shiloh S. et al., 2015; Godino J.G. et al., 2016; Sanderson S.C. et al., 2016; Sanderson et al., 2017; Vassy et al., 2017; Fenton G.L. et al., 2018; Hay J.L. et al., 2018; East et al., 2019; Rego S. et al., 2019; Zoltick E.S. et al., 2019; Smit et al., 2020) and the remaining eleven investigated individuals' opinions on population genetic screening (Shaw III and Bassi, 2001; Laskey S.L. et al., 2003; Sanderson et al., 2004; Borry et al., 2008; Haga et al., 2011; Hardie, 2011; Henneman L. et al., 2011; Vassy J.L. et al., 2014; Nicholls S.G. et al., 2016; Rubinsak et al., 2019; Joshi E. et al., 2020). Of those that implemented screening programs, five provided counseling before screening (Neghina A.M. and Anghel A., 2010; Sanderson S.C. et al., 2016; Sanderson et al., 2017; East et al., 2019; Smit et al., 2020), four provided counseling after screening (Allen K.J. et al., 2008; Haga S.B. et al., 2014; Shiloh S. et al., 2015; Rego S. et al., 2019), five provided counseling at both timepoints (Nusbaum R. et al., 2013; Hietaranta-Luoma H.-L. et al., 2015; Vassy et al., 2017; Fenton G.L. et al., 2018; Zoltick E.S. et al., 2019), and four did not record counseling availability (Nielsen and El-Sohemy, 2012; O'Neill S.C. et al., 2015; Godino J.G. et al., 2016; Hay J.L. et al., 2018).

The majority of studies (n=16) were conducted in the US (Shaw III and Bassi, 2001; Laskey S.L. et al., 2003; Haga et al., 2011; Nusbaum R. et al., 2013; Haga S.B. et al., 2014; Vassy J.L. et al., 2014; O'Neill S.C. et al., 2015; Shiloh S. et al., 2015; Sanderson S.C. et al., 2016; Sanderson et al., 2017; Vassy et al., 2017; Hay J.L. et al., 2018; East et al., 2019; Rego S. et al., 2019; Rubinsak et al., 2019; Zoltick E.S. et al., 2019), while the rest were

conducted in Europe (UK (Sanderson et al., 2004; Godino J.G. et al., 2016), The Netherlands (Henneman L. et al., 2011), Romania (Neghina A.M. and Anghel A., 2010), Finland (Hietaranta-Luoma H.-L. et al., 2015), European Union (Borry et al., 2008)), Canada (Nielsen and El-Sohemy, 2012; Nicholls S.G. et al., 2016; Joshi E. et al., 2020), and Australia (Allen K.J. et al., 2008; Hardie, 2011; Fenton G.L. et al., 2018; Smit et al., 2020). Sixteen studies were conducted in a clinical setting (Neghina A.M. and Anghel A., 2010; Haga et al., 2011; Nusbaum R. et al., 2013; Haga S.B. et al., 2014; Vassy J.L. et al., 2014; Hietaranta-Luoma H.-L. et al., 2015; Shiloh S. et al., 2015; Sanderson S.C. et al., 2016; Sanderson et al., 2017; Vassy et al., 2017; Hay J.L. et al., 2018; East et al., 2019; Rego S. et al., 2019; Rubinsak et al., 2019; Zoltick E.S. et al., 2019; Joshi E. et al., 2020), nine were conducted in a community setting (Shaw III and Bassi, 2001; Sanderson et al., 2004; Allen K.J. et al., 2008; Henneman L. et al., 2011; Nielsen and El-Sohemy, 2012; Godino J.G. et al., 2016; Nicholls S.G. et al., 2016; Fenton G.L. et al., 2018; Smit et al., 2020), and four did not report the setting type (Laskey S.L. et al., 2003; Borry et al., 2008; Hardie, 2011; O'Neill S.C. et al., 2015). One study was conducted on an international scale (Borry et al., 2008), ten were conducted nationally (Sanderson et al., 2004; Haga et al., 2011; Hardie, 2011; Nielsen and El-Sohemy, 2012; O'Neill S.C. et al., 2015; Shiloh S. et al., 2015; Godino J.G. et al., 2016; Nicholls S.G. et al., 2016; Zoltick E.S. et al., 2019; Joshi E. et al., 2020), three on a state scale (Fenton G.L. et al., 2018; Hay J.L. et al., 2018; Smit et al., 2020), two regionally (Hietaranta-Luoma H.-L. et al., 2015), five in a city/town (Shaw III and Bassi, 2001; Allen K.J. et al., 2008; Henneman L. et al., 2011; Vassy J.L. et al., 2014; Vassy et al., 2017), and nine at a single center (Laskey S.L. et al., 2003; Neghina A.M. and Anghel A., 2010; Nusbaum R. et al., 2013; Haga S.B. et al., 2014; Sanderson S.C. et al., 2016; Sanderson et al., 2017; East et al., 2019; Rego S. et al., 2019; Rubinsak et al., 2019).

Ten articles conducted descriptive studies using survey and questionnaire data (Shaw III and Bassi, 2001; Laskey S.L. et al., 2003; Sanderson et al., 2004; Allen K.J. et al., 2008; Borry et al., 2008; Neghina A.M. and Anghel A., 2010; Haga et al., 2011; East et al., 2019; Rubinsak et al., 2019; Zoltick E.S. et al., 2019), six conducted qualitative studies using interview and focus group data (Henneman L. et al., 2011; Nusbaum R. et al., 2013; O'Neill S.C. et al., 2015; Rego S. et al., 2019; Joshi E. et al., 2020; Smit et al., 2020), six conducted mixed-method studies (Hardie, 2011; Vassy J.L. et al., 2014; Nicholls S.G. et al., 2016; Sanderson S.C. et al., 2016; Sanderson et al., 2017; Fenton G.L. et al., 2018), six conducted randomized controlled trials (Nielsen and El-Sohemy, 2012; Haga S.B. et al., 2014; Hietaranta-Luoma H.-L. et al., 2015; Godino J.G. et al., 2016; Vassy et al., 2017; Hay J.L. et al., 2018), and one conducted non-randomized controlled trials (Shiloh S. et al., 2015).

3.1.1.1 Intrapersonal Barriers

Psychosocial Factors, Knowledge, Attitudes, and Beliefs

Psychosocial factors such as anxiety, fear, and worry about screening (Hardie, 2011; Nusbaum R. et al., 2013; Rubinsak et al., 2019), dislike of blood (Neghina A.M. and Anghel A., 2010), potential negative psychological and emotional impacts (Henneman L. et al., 2011; Sanderson S.C. et al., 2016; Joshi E. et al., 2020), mistrust (Hardie, 2011), disinterest (Neghina A.M. and Anghel A., 2010; Hardie, 2011), the possibility of receiving unwanted information (Zoltick E.S. et al., 2019), and the belief that a low-risk result may not give reassurance (Henneman L. et al., 2011) were reported as reasons to reject screening. Two studies reported moral and ethical reasons as barriers (Shaw III and Bassi, 2001; Hardie, 2011). Providers cited inadequate knowledge (Haga et al., 2011; Joshi E. et al., 2020), not having ordered a genetic test for themselves (Haga et al., 2011), their belief that it would not provide useful information (Haga et al., 2011), and their belief that it would lead to unnecessary future testing (Vassy J.L. et al., 2014) as barriers to participating in population genetic screening programs. Additionally, patients reported a lack of information (Neghina A.M. and Anghel A., 2010; Nusbaum R. et al., 2013; Rubinsak et al., 2019) a barrier.

Clinical Factors

Providers (Vassy J.L. et al., 2014; Joshi E. et al., 2020) and the public (Zoltick E.S. et al., 2019) cited the uncertainty of results as a barrier. Providers additionally reported limited clinical utility as a barrier (Borry et al., 2008; Vassy J.L. et al., 2014; Joshi E. et al., 2020).

Other

Perceived cost of genetic screening (Hardie, 2011; Rubinsak et al., 2019; Zoltick E.S. et al., 2019), religious reasons (Hardie, 2011), and higher education (Sanderson et al., 2004) were reported as barriers. Patients additionally reported a lack of time as a barrier to receipt of genetic screening (Neghina A.M. and Anghel A., 2010).

3.1.1.2 Interpersonal Barriers

Family

A perceived potential for a negative impact on children (Sanderson S.C. et al., 2016) and a lack of family history (Hardie, 2011; Rubinsak et al., 2019) were negatively correlated with interest and/or receipt of genetic screening.

3.1.1.3 Community Barriers

Data

Concerns related to confidentiality and privacy (Haga et al., 2011; Nusbaum R. et al., 2013; Sanderson S.C. et al., 2016; Zoltick E.S. et al., 2019) and data security (Joshi E. et al., 2020) were reported as barriers.

Healthcare System

Providers and the public reported that the potential impact of results on insurance (Haga et al., 2011; Henneman L. et al., 2011; Zoltick E.S. et al., 2019; Joshi E. et al., 2020) and the potential increased cost to the health system (Henneman L. et al., 2011; Joshi E. et al., 2020; Smit et al., 2020) would hinder their participation of genetic screening at a population level.

Other

The possibility for discrimination by employers was reported by providers and the public as a barrier (Henneman L. et al., 2011; Joshi E. et al., 2020).

3.1.1.4 Intrapersonal Facilitators

Demographics and Socio-Economic Status

One study (Sanderson et al., 2004) reported that male gender ($p = 0.029$) and later middle age were positively correlated with interest in screening. On the other hand, another study (Neghina A.M. and Anghel A., 2010) reported that younger age was a facilitator to uptake of screening. Higher socioeconomic status was additionally cited as a facilitator (Neghina A.M. and Anghel A., 2010; Hay J.L. et al., 2018).

Psychosocial Factors, Knowledge, Attitudes, and Beliefs

Interest-related facilitators include interest about ancestry (Sanderson S.C. et al., 2016; Zoltick E.S. et al., 2019), professional interest (Sanderson S.C. et al., 2016; Zoltick E.S. et al., 2019), interest in genetics and/or science (Sanderson S.C. et al., 2016; Rego S. et al., 2019; Zoltick E.S. et al., 2019), and general curiosity (Hardie, 2011; Nusbaum R. et al., 2013; Sanderson S.C. et al., 2016; East et al., 2019; Zoltick E.S. et al., 2019). Altruism (Nusbaum R. et al., 2013; Sanderson S.C. et al., 2016; Rego S. et al., 2019) and the chance for participants to learn about themselves (Nielsen and El-Sohemy, 2012; Sanderson S.C. et al., 2016; Rubinsak et al., 2019) were reported as facilitators as well. Trust in provider (Hardie, 2011) and trust in medicine (Hardie, 2011) were both significantly correlated with interest in population screening. Additional facilitators include knowledge (Borry et al., 2008; Haga et al., 2011) and the belief that screening will provide helpful information (Shaw III and Bassi, 2001).

Clinical Factors

All stakeholders viewed the potential for medical intervention and/or monitoring (Borry et al., 2008; Nielsen and El-Sohemy, 2012; Sanderson S.C. et al., 2016; East et al., 2019; Joshi E. et al., 2020) as a facilitator to population genetic screening. The public reported that curability ($p < 0.001$) (Shaw III and Bassi, 2001), non-fatalness of a condition ($p < 0.01$) (Shaw III and Bassi, 2001), a more certain outcome (Shaw III and Bassi, 2001), a known or suspected personal history (Sanderson S.C. et al., 2016; Hay J.L. et al., 2018), the potential to encourage health improvements through means such as behavioral changes (Hardie, 2011; Nielsen and El-Sohemy, 2012; Sanderson S.C. et al., 2016; Zoltick E.S. et al., 2019), and the use of results for future diagnostic purposes (Sanderson S.C. et al., 2016) were positively associated with interest and/or receipt of genetic screening through a population-based context. Additionally, patients reported their seeking medical information as a reason for receiving screening (Neghina A.M. and Anghel A., 2010; Nusbaum R. et al., 2013; East et al., 2019). Patients and the public reported that the ability to prepare for future health (Nicholls S.G. et al., 2016; Sanderson S.C. et al., 2016; East et al., 2019; Rego S. et al., 2019; Zoltick E.S. et al., 2019) and the use of results for pharmacogenomics (Sanderson S.C. et al., 2016; East et al., 2019; Zoltick E.S. et al., 2019) were facilitators to genetic screening.

Other

Patients reported that the chance to have a free screen (Neghina A.M. and Anghel A., 2010) and a ‘nothing to lose’ attitude (Nusbaum R. et al., 2013) were facilitators for their receipt of genetic screening. Viewing genetic screening as a novel opportunity (Sanderson S.C. et al., 2016) and a fun and entertaining activity (Zoltick E.S. et al., 2019) was reported by the public as a facilitator for undergoing screening.

3.1.1.5 Interpersonal Facilitators

Family

All interpersonal facilitators were related to participants’ family. Seven studies reported that the ability to provide information to family members was important to participants (Nusbaum R. et al., 2013; Nicholls S.G. et al., 2016; Sanderson S.C. et al., 2016; East et al., 2019; Rego S. et al., 2019; Rubinsak et al., 2019; Zoltick E.S. et al., 2019). One study reported that having family who have had their genomes sequenced facilitated uptake (Zoltick E.S. et al., 2019). Family history was reported in six studies (Hardie, 2011; Sanderson S.C. et al., 2016; Hay J.L. et al., 2018; Rego S. et al., 2019; Rubinsak et al., 2019; Zoltick E.S. et al., 2019) and labeled as a statistically significant factor in one (Sanderson et al., 2004). On the other hand, a lack of family health history was also reported as a facilitator in four studies (Sanderson et al., 2004; Sanderson S.C. et al., 2016; Rego S. et al., 2019; Zoltick E.S. et al., 2019).

4 Discussion

The current state of research in population-based genetic screening focuses on individuals, with most studies revealing barriers and facilitators to interest and/or participation in population genetic screening at an individual level. We identified few interpersonal facilitators and barriers and no community-level facilitators. All our included studies were designed to elucidate stakeholders' views and attitudes. The studies which revealed interpersonal and community factors conducted surveys or semi-structured interviews, suggesting a need for additional rigorous studies to explicitly investigate macro-level determinants for population screening.

Additionally, studies reported potential ethical issues, concerns relating to data management, and potential discrimination as barriers to interest in genetic screening. These factors are especially important in the age of 'big data' (Price and Cohen, 2019), and previous literature has called for the consideration of ethical questions in implementing population screening (Murray et al., 2018). The BabySeq Project is assessing ethical, legal, and social implications (ELSI) relating to the ethical issues of result return (Friedman et al., 2017) and the medical, behavioral, and economic impacts (Holm et al., 2018) of newborn screening (the largest population-level screening programs in the United States). These studies, along with essential ELSI questions raised by newborn screening (Goldenberg et al., 2019), provide a framework for adapting ELSI considerations in evaluating general population genetic screening.

Most studies investigated the general public's perspective of population genetic screening. While the public will likely play an important role in the acceptance of population screening in the overall community, there are other stakeholders — particularly healthcare providers — to consider. Primary care providers, who will likely be the touchpoint for many interested in genetic screening, reported inadequate knowledge as a barrier to ordering screening. In one study (Haga et al., 2011), roughly half of providers reported that they felt prepared to order genetic screening. Previous literature has noted the limited evidence regarding the views and roles of healthcare providers in genomic medicine (Hann et al., 2017a; Hauser et al., 2018; Crellin et al., 2019) and identified the importance of educational resources for provider preparedness to order and interpret results (Rohrer Vitek et al., 2017; Hauser et al., 2018; Smit et al., 2019). With few provider-based studies (most of which studied primary care providers), we see a need for increased studies to investigate the viewpoints of providers and develop the necessary educational interventions.

Skeptical providers cited a perceived lack of clinical utility as a barrier, reporting that although they believe genetic screening technology is valuable in genomics research, they do not believe that it is ready for clinical use (Joshi E. et al., 2020). On the other hand, providers who supported screening reported the potential for results to inform medical intervention and/or monitoring as a reason for their support. Our findings are consistent with previous literature indicating that obtaining provider buy-in is needed for the implementation of large-scale screening (Peterson et al., 2016). Additionally, the current perception of clinical utility places value on genomic medicine in relation to informing treatment, and excludes other important applications of genomics for screening such as risk prediction and prognosis (Joseph et al., 2016). The Association for Molecular Pathology (Joseph et al., 2016) recommends expanding the definition of clinical utility for molecular tools through approaches such as utilizing a modified ACCE model (ACCE Model List of 44 Targeted Questions | CDC, 2019) and promoting patient-centered definitions of clinical utility. Our data suggests the need for interventions directed toward obtaining buy-in and expanding the definition of clinical utility.

Psychosocial and attitudinal barriers, such as anxiety and worry toward screening and the possibility for negative psychological and emotional impacts, were the most reported individual-level barriers across stakeholders, even though studies to date have demonstrated limited impacts on psychological and emotional outcomes with any adverse responses dissipating over time (Hietaranta-Luoma H.-L. et al., 2015; Hollands et al., 2016; Frieser et al., 2018; Smit et al., 2020). Of the studies that implemented screening programs, all screened for different disease states and half provided prescreen counseling mediated by a healthcare provider. They had varying forms of preintervention information content and delivery and only a few assessed the efficacy of different delivery methods. Most (except two) were conducted in racially/ethnically diverse countries (Australia, Canada, United States, and United Kingdom), however roughly one third did not include information on the race or ethnicity of individuals receiving genetic screening. Although the best method for prescreen education has not yet been determined, there is some evidence showing that different contexts will likely have different requirements (Evans and Manchanda, 2020). This is of particular importance as studies have found ethnic minorities to be generally more apprehensive toward genetic testing than white individuals (Hann et al., 2017b). This suggests a need for additional studies designed to investigate the best manner of prescreen education and counseling specific to the delivery context.

Finally, out of the studies that implemented population-based genetic screening and collected post-intervention data, only one followed participants for more than twelve months (Allen K.J. et al., 2008). Without sufficient long-term data, it is difficult to assess the efficacy of the screening programs at the population level. There is a need for prospective cohort studies to evaluate any long-term benefits, such as clinical and economic outcomes, to population-level genetic screening implementation (Murray et al., 2018, 2020). The BabySeq project provides a model for identifying these long-term outcomes (Holm et al., 2018), which may be adapted to the context of population genetic screening. Such studies will likely address our previous points of determining ELSI factors to population screening and assessing the effects of prescreen education methods as well.

5 Limitations

Our included studies did not assess effect sizes of barriers and facilitators on interest and/or uptake of genetic screening in population-based programs, which prevented us from conducting a meta-analysis. Additionally, the heterogeneity in disease states and reported effectiveness measures prevented us from fully synthesizing the data. With all systematic reviews, there is the possibility that we missed relevant literature.

6 Conclusions

We found that (1) research in population genetic screening has focused on stakeholder attitudes, (2) there is a need for additional studies investigating healthcare provider roles and education, (3) perceived limited clinical utility presents a barrier for provider uptake, (4) psychosocial, attitudinal, and belief-related factors present a barrier for stakeholders to participate in screening, and (5) there is a need for long-term follow-up studies of population genetic screening. Future research should (1) investigate macro-level determinants of and address ELSI questions toward population genetic screening, (2) investigate the views of providers and develop educational resources, (3) examine provider buy-in and clinical utility expansion, (4) evaluate the best manner for prescreen education and counseling for specific contexts, and (5) assess the long-term outcomes of population genetic screening. Taken together this data can inform future interventions to improve the development and implementation of population genetic screening.

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

ES, SS, and MR conceived of the study and designed the protocol. RC conducted database searches. ES, SS, LP, MD, KF, BH, and LM participated in the screening, full-text review, and data abstraction processes. AS and CA participated in the screening and full-text review. MR participated in the screening and data abstraction processes. ES synthesized the data and prepared the first draft of the manuscript. All authors read and approved the final manuscript.

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Table 1

Table 1 is available in the Supplementary Files section.

Tables 2-3

Table 2. Barriers to interest and participation in population genetic screening

	Patient				Provider				Public			
Reasons	N	%	Significance	Study	N	%	Significance	Study	N	%	Significance	Study
Intrapersonal												
Psychosocial Factors, Knowledge, Attitudes, and Beliefs												
Anxiety, fear, and worry toward screening				(Nusbaum R. et al., 2013; Rubinsak et al., 2019)								(Hardie, 2011)
Potential negative psychological and emotional impacts								(Joshi E. et al., 2020)	18	50		(Sanderson S.C. et al., 2016)
												(Henneman L. et al., 2011)
Mistrust												(Hardie, 2011)
Possibility of unwanted information												(Zoltick E.S. et al., 2019)
Belief that low risk result may not give reassurance												(Henneman L. et al., 2011)
Inadequate knowledge						41		(Haga et al., 2011)				
								(Joshi E. et al., 2020)				
Not having ordered a genetic test for themselves								(Haga et al., 2011)				
Belief that it would not provide useful information						36		(Haga et al., 2011)				
Dislike of blood		11		(Neghina A.M. and Anghel A., 2010)								
Moral and ethical reasons												(Shaw III and Bassi, 2001; Hardie, 2011)
Disinterest		18.5		(Neghina A.M. and Anghel A., 2010)								(Hardie, 2011)
Belief that it would lead unnecessary testing								(Vassy J.L. et al., 2014)				
Lack of information		41		(Neghina A.M. and Anghel A., 2010)								
				(Nusbaum R. et al., 2013; Rubinsak								

		et al., 2019)					
Clinical Factors							
Uncertainty of results				(Vassy J.L. et al., 2014; Joshi E. et al., 2020)			(Zoltick E.S. et al., 2019)
Limited clinical utility				(Borry et al., 2008; Vassy J.L. et al., 2014; Joshi E. et al., 2020)			
Other							
Cost		(Rubinsak et al., 2019)					(Hardie, 2011; Zoltick E.S. et al., 2019)
Lack of time	32.5	(Neghina A.M. and Anghel A., 2010, 201)					
Higher education							(Sanderson et al., 2004)
Religious reasons							(Hardie, 2011)
Interpersonal Barriers							
Family							
Impact on children							(Sanderson S.C. et al., 2016)
Lack of family history		(Rubinsak et al., 2019)					(Hardie, 2011)
Community							
Data							
Confidentiality/privacy		(Nusbaum R. et al., 2013)	43	(Haga et al., 2011)	20	57	(Sanderson S.C. et al., 2016)
							(Zoltick E.S. et al., 2019)
Data security				(Joshi E. et al., 2020)			
Healthcare System							
Potential impact on insurance			50	(Haga et al., 2011)			(Henneman L. et al., 2011; Zoltick E.S. et al., 2019)

		(Joshi E. et al., 2020)	
Cost to health system		(Joshi E. et al., 2020)	(Henneman L. et al., 2011; Smit et al., 2020)
Other			
Possibility for discrimination by employers		(Joshi E. et al., 2020)	(Henneman L. et al., 2011)

Table 3. Facilitators to interest and participation in population genetic screening

	Patient				Provider				Public			
Reasons	**N**	**%**	**Significance**	**Study**	**N**	**%**	**Significance**	**Study**	**N**	**%**	**Significance**	**Study**
Intrapersonal												
Demographics and Socio-Economic Status												
Male gender										72	p = 0.029	(Sanderson et al., 2004)
Later middle age										78		(Sanderson et al., 2004)
Younger age				(Neghina A.M. and Anghel A., 2010)								
Higher socio-economic status				(Neghina A.M. and Anghel A., 2010)								(Hay J.L. et al., 2018)
Psychosocial Factors, Knowledge, Attitudes, and Beliefs												
Interest about ancestry									13			(Sanderson S.C. et al., 2016)
												(Zoltick E.S. et al., 2019)
Professional interest/utility									1			(Sanderson S.C. et al., 2016)
												(Zoltick E.S. et al., 2019)
Interest in genetics/science												(Sanderson S.C. et al., 2016; Rego S. et al., 2019; Zoltick E.S. et al., 2019)
General curiosity				(Nusbaum R. et al., 2013; East et al., 2019)								(Hardie, 2011; Zoltick E.S. et al., 2019)
										66		Sanderson S.C. et al., 2016)
Chance to learn about themselves				(Rubinsak et al., 2019)						86		(Nielsen and El-Sohemy, 2012)
									7			Sanderson S.C. et al., 2016)
Altruism				(Nusbaum R. et al., 2013)								(Rego S. et al., 2019)
									15			Sanderson S.C. et al., 2016)
Trust in provider											p < 0.001	(Hardie, 2011)

Trust in medicine					p < 0.001	(Hardie, 2011)
Belief that screening will yield helpful information						(Shaw III and Bassi, 2001)
Knowledge			(Borry et al., 2008; Haga et al., 2011)			
Clinical Factors						
Known or suspected personal history						(Sanderson S.C. et al., 2016; Hay J.L. et al., 2018)
Curability of condition					p < 0.001	(Shaw III and Bassi, 2001)
More certain outcome						(Shaw III and Bassi, 2001)
Non-fatalness of condition					p < 0.01	(Shaw III and Bassi, 2001)
Prepare for future health	57	(East et al., 2019)				(Nicholls S.G. et al., 2016; Sanderson S.C. et al., 2016; Rego S. et al., 2019; Zoltick E.S. et al., 2019)
Potential for medical intervention/monitoring		(East et al., 2019)	(Borry et al., 2008; Joshi E. et al., 2020)	73		(Nielsen and El-Sohemy, 2012)
						(Sanderson S.C. et al., 2016)
Potential to encourage health improvements						(Hardie, 2011; Sanderson S.C. et al., 2016; Zoltick E.S. et al., 2019)
				83		(Nielsen and El-Sohemy, 2012)
Seeking medical information	37	(East et al., 2019)				
	85.7	(Neghina A.M. and Anghel A., 2010)				
		(Nusbaum R. et al., 2013)				

Diagnostic purposes			1			(Sanderson S.C. et al., 2016)
Pharmacogenomics		(East et al., 2019)				(Sanderson S.C. et al., 2016; Zoltick E.S. et al., 2019)
Other						
Nothing to lose		(Nusbaum R. et al., 2013)				
Chance to have a free screen	71.4	(Neghina A.M. and Anghel A., 2010)				
Novel opportunity						(Sanderson S.C. et al., 2016)
Fun and entertaining						(Zoltick E.S. et al., 2019)
Interpersonal						
Family						
Provide information for family members	40	(East et al., 2019)				(Nicholls S.G. et al., 2016; Rego S. et al., 2019; Zoltick E.S. et al., 2019)
		(Nusbaum R. et al., 2013; Rubinsak et al., 2019)	11			(Sanderson S.C. et al., 2016)
Having family who have had their genomes sequenced						(Zoltick E.S. et al., 2019)
Family history		(Rubinsak et al., 2019)				(Hardie, 2011; Hay J.L. et al., 2018; Rego S. et al., 2019; Zoltick E.S. et al., 2019)
				74	p = 0.005	(Sanderson et al., 2004)
				33		(Sanderson S.C. et al., 2016)
Lack of family health history			1			(Rego S. et al., 2019)
				70		(Sanderson et al., 2004)
						(Sanderson S.C. et al., 2016; Zoltick E.S.

et al., 2019)

Figures

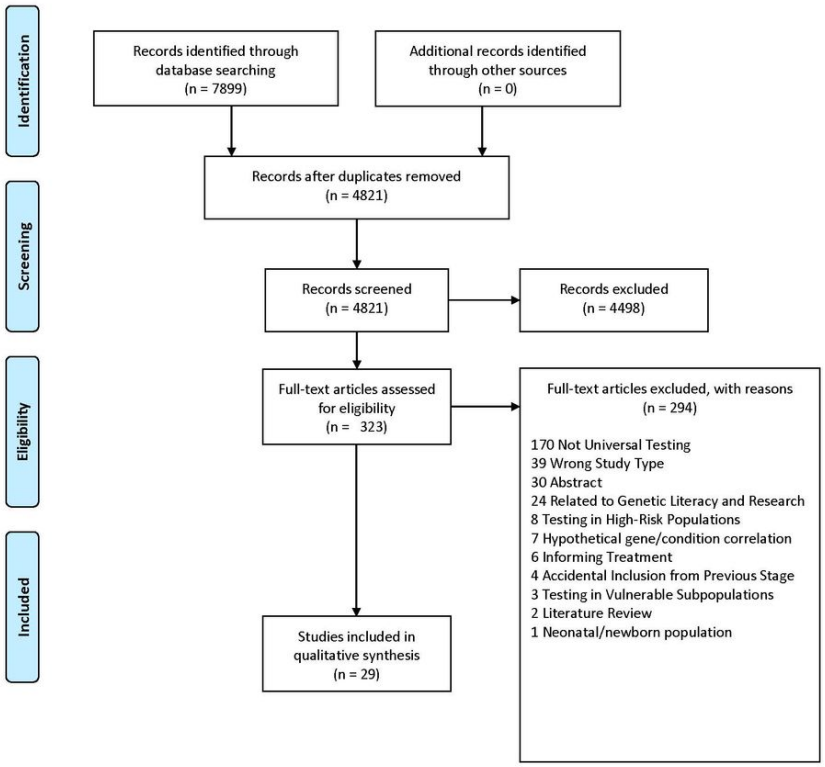

Figure 1

PRISMA diagram

Supplementary Files

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