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COMMENTARY/POSITION PAPER

A primer in genomics for social and behavioral investigators

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Abstract

Genomics is being increasingly utilized in medical research and health care. Countless opportunities exist for social and behavioral scientists to answer novel and important research questions. Evidence that will be produced from such enquiries can help ensure appropriate use of genomic information and realize the potential of genomics to improve patient care and medical outcomes. Here, we provide an accessible overview of different types of genetic and genomic tests and the resulting information produced. There are important nuances that distinguish genetic from genomic tests and different information that each yield. We outline key examples where social and behavioral scientists have made an impact in this field, and opportunities for future research. The intention of this primer is to introduce or clarify genomics concepts to social and behavioral scientists, summarize prior research and outline future research directions. The time is ripe for social and behavioral scientists to engage in genomics and make important contributions to improve clinical and community translation of genomic discoveries.

Keywords:

Genomics, Social sciences, Behavioral sciences, Translational research

Implications

Practice: To improve clinical and community translation of genomic discoveries.

Policy: To realize the importance of engaging social and behavioral scientists in genomics translation and related research.

Research: To outline key social and behavioral research in genomics and opportunities for future work.

Medicine is becoming increasingly personalized and raising novel research questions [1]. Social and behavioral scientists contribute to this tailored approach to health care with investigation into how individual variation (e.g., demographics, personality, beliefs, attitudes) predicts health outcomes. Genomic underpinnings also explain variance in disease risk, disease expression, and response to treatment. As such, there is a burgeoning contribution of genomics to health outcomes research [2]. Further, as genomic technologies become more mainstream in health care, research focusing on how people interpret, understand and respond to genomic information is a growing area of inquiry that offers promising opportunities for social and behavioral researchers.

Contemporary research enterprises such as the All of Us Research Program (https://allofus.nih.gov/), NSIGHT (Newborn sequencing in genomic medicine and public health; https://www.genome.gov/27558493/newborn-sequencing-in-genomic-medicine-and-public-health-nsight/), IGNITE (Innovation Grants to Nurture Initial Translational Efforts) and the CSER (Clinical sequencing exploratory research; https://cser-consortium.org/) cohort studies foreshadow widespread integration of genomics into health care. These National Institutes of Health initiatives have facilitated the integration of social and behavioral research into genomic science, resulting in clinical studies that included psychological and behavioral outcomes [3]. For example, within the CSER consortium, social and behavioral scientists collaborated to develop a conceptual model, identifying opportunities for offering genome sequencing and identified research questions that assess decision making to undergo sequencing and to act on actionable findings that promote design quality [3]. Further, a meta-analysis of psychological wellbeing outcomes across CSER studies was conducted by social and behavioral scientists, demonstrating that changes in anxiety, depressive symptoms, and test-related distress were infrequently elevated following receipt of results from genome sequencing, offering suggestions for innovation in assessing psychological wellbeing (J.O. Robinson et al., unpublished data). Opportunities for studying population genome sequencing are likely to become available with funding from the All of Us Research Program, offering an opportunity for social and behavioral scientists to enhance the quality of the research and implications of the outcomes. These research endeavors model the essential roles of social and behavioral researchers in translational genomics research. Other endeavors, such as the Early Check Newborn Screening Research Program in North Carolina (https://www.rti.org/news/new-rti-international-program-offer-free-elective-genetic-testing-north-carolina-newborns), exemplify

the integration of single gene testing into a research program that assesses the clinical and psychological outcomes of early identification of rare disease conducted by social and behavioral scientists.

Aspects of genetic testing have been part of routine medical care since 1970 [4]. Since then, many pregnant women with access to health care services have undergone genetic screening to learn about risks of chromosomal conditions in their fetus. In pediatrics, genetic testing is commonly used to identify the cause of developmental delays and birth anomalies [5]. Perhaps best known to social and behavioral scientists is the use of genomics to predict cancer and cardiovascular disease risk in adults [6]. As technologies improve and become more accessible, the contribution of genetics to disease risk will be more fully realized and testing more broadly applied in mainstream medicine.

In parallel to these advances, the public is increasingly aware of genetics and genomics. While the Food and Drug Administration (FDA) has limited the offering of direct to consumer genomic testing, genomic testing for health purpose is gradually being re-introduced by some companies, and ancestry testing has remained popular [7]. The direct to consumer (DTC) genomic testing company "23andme," introduced new advertising campaigns for a wide variety of potential consumers, with slogans targeting sports fans, "Root for your roots" and Mother's Day gift buyers, "We love Mom genes!" [8]; thus activating interest in personal genetic information broadly.

Social and behavioral investigators have made significant contributions in genetics; we highlight key examples:

(1) In the context of genetic testing and behavior change, Aspinwall et al. [9] reported that 2 years after receipt of genetic testing and counseling for inherited melanoma risk, individuals at high risk continued to adhere to improved sun protection behaviors.
(2) Initially, as genetic testing among healthy populations was gaining traction, there was fear that patients would be alarmed by test results conferring small increases in risks, leading to inappropriate health service use. However, Kaphingst et al. [10] found that adults receiving genetic test result information for common disease risks did not interpret their health risks in an overly deterministic way.
(3) Researchers have contributed to understanding predictors and correlates surrounding uptake of testing, with important implications for interventions to enhance genetic testing outcomes [11]. For example, Sanderson et al. [12] found that in a study offering genetic testing for lung cancer risk through an online platform, daily Internet access and prior awareness of genetic tests for cancer risk predicted uptake of testing. Interestingly, the association between intentions to uptake testing and actual rates of testing were only moderately associated, with different factors predicting intentions as compared to actual uptake.

For investigators with a cursory familiarity with genetics who may be considering the pursuit of similar types of inquiries to the examples given here, we review the application of genomics to health.

This primer aims to promote genomic health-related concepts among social and behavioral investigators, in parallel with efforts from the Genomics Working Group of the Society of Behavioral Medicine (SBM), spearheaded by Dr. Colleen McBride, and charged with assessing the membership's views on whether and how SBM should be engaging in genomics (C.M. McBride, personal communication). The working group has conducted member focus groups to assess interest in embracing genomics as a field of interest to SBM members and has plans to report the findings.

GENETICS OR GENOMICS?

Genetics is the study of single genes and their effect within an organism [13]. Traditionally, the study of genetics was limited by the technological capability to the investigation of one gene at a time. With advances in technology, it has become possible to study many genes simultaneously, and the term "genomics" was adopted [14]. Below, we outline the nuances that distinguish genetic from genomic tests and the different information that each yield.

SINGLE GENE TESTS AND APPLICATIONS

Humans have about 19,000 genes housed in 46 chromosomes found in nearly all cells in the body [15]. We have two copies of every gene. At conception, one copy of each gene is passed on from one's mother, one copy is passed on from one's father. Single gene inheritance has been understood for about a century by recognizing family patterns of disease. The term "variant" is a change in the usual gene make up (previously referred to as a "mutation").

Traits that are *dominantly* inherited result from a variant in one gene copy that can be inherited from either parent. The trait or condition is dominantly inherited because it will manifest regardless of the variant in the other gene copy. Well known genetic conditions that are dominantly inherited include Huntington disease (a very rare degenerative condition) and several hereditary cancer syndromes. The gene variant that leads to Huntington disease is fully penetrant. That is, if one lives long enough s/he will become affected with the condition, assuming s/he does not die of other causes first. In contrast, most cancer gene variants increase cancer risk but are not fully penetrant. An individual with a variant in the *BRCA1* or *BRCA2* gene, for example, may never develop breast cancer, yet the risk for developing cancer is substantially higher than for those who do not have a variant in one of these genes. Traits that are *recessively* inherited require gene variants in both copies for it to manifest. Well known examples of

autosomal recessive conditions are cystic fibrosis and sickle cell anemia. For these conditions to emerge, both parents must carry a variant in the same gene.

With the invention of techniques such as polymerase chain reaction (PCR) and Sanger sequencing, single-gene tests were one of the first type of genetic tests to be used in health care [16]. Single gene tests can be used to help diagnose an individual's condition or predict the development of a disease. Genetic tests are offered to learn what variants we all carry that could lead to having an affected child. Such "carrier" testing is offered to couples contemplating pregnancy to learn what variants may increase their risks, as everyone carries variants in genes, but most are not adversely affected [17].

SINGLE GENE TESTS: KEY SOCIAL AND BEHAVIORAL RESEARCH EXAMPLES

Researchers have studied how behaviors change in response to learning genetic information in the context of single gene disorders. One example is in the context of individuals at high risk of melanoma due to mutations in the *CDKN2A* gene, which affects the tumor suppressor protein p16. This type of inherited melanoma has an autosomal dominant inheritance pattern. Evidence suggests that there is the added benefit of providing genetic information to patients at high risk of melanoma which may lead to changes in sun protection behavior [18]. Other examples include recommendations that women increase the number of mammograms after positive *BRCA1/2* genetic testing [19], and that individuals found to be at high risk for colorectal cancer through genetic testing have high compliance with recommended screening [20].

Further evidence that individuals change their behavior in response to receiving genetic information is in the context of Alzheimer's disease [21]. The REVEAL (Risk Evaluation and Education for Alzheimer's disease) study investigated whether giving individuals specific information about a gene variant that incurs a higher risk for Alzheimer's disease influenced health behavior. Those identified to be at increased risk were more likely to report having engaged in Alzheimer's disease-specific behavior changes one year after learning the information, compared to those at lower risk based on their gene variant. While this is an important first look at behavior change in response to learning genetic information, opportunities for social and behavioral researchers to offer theoretical and evidence-based approaches remain; for example, such studies may be enhanced by more robust outcomes than self-report.

SNP PROFILE AND MULTIGENE PANEL TESTS AND APPLICATIONS

While the discovery of thousands of single gene disorders has affected health decision making in rare or less common disorders as described above, there have not been parallel examples of benefits resulting from genetic discoveries in common, complex conditions [22]. The most common type of genetic variation in the human genome is the single nucleotide polymorphism (SNP; pronounced "snip"). SNPs occur everywhere in the genome; both within genes and outside. Along with environmental factors, SNPs contribute toward the etiology of common cancers and diseases such as heart disease and diabetes [23]. In comparison to rare gene variants, a SNP (often in combination with other SNPs) conveys much smaller risks among a much larger number of individuals.

To predict these risks, the combination of many SNPs can be used to create a "profile," wherein an individual with a specific combination of SNPs has a higher risk profile for developing a certain disease compared to other members of the population. Aside from research applications, testing for common disease risk using SNPs is not widely available. DTC testing companies previously offered risk prediction based on SNP data, though public access has decreased following more stringent FDA regulation in recent years [24]. While it remains unknown whether SNP profiling will be used routinely, large cohort studies recently have been more successful at identifying families with multiple SNPs to predict risks for diabetes, autism, and schizophrenia [25].

While SNP profiling generates information from a limited number of prespecified genomic locations, it has recently become possible to generate vastly increased amounts of genomic information through improved sequencing technologies. Technological advances have led to dramatically decreased costs associated with sequencing the genome, propelling these technologies into research and to a limited degree, the clinic [26]. Advanced sequencing technologies can be applied to three broad categories of tests that differ based on the type and amount of information produced; whole genome, whole exome, and multigene panel testing. Genome sequencing produces a read of the entire genetic code while exome sequencing selects out only the exons (regions that code for proteins) of genes. Multigene panel testing involves first selecting for genes of interest, so that only information about select regions of the genome is produced, for example, cancer-specific gene panels.

It is useful to understand the difference between SNP profiling and multigene panel tests as, while they may seem like similar tests, the type of information produced, and the implications may be very different. SNP profiling generates information from a limited number of prespecified genomic locations to generate health risk estimates, whereas multigene panel tests assess genes known to contribute to hereditary forms of various conditions and more often identify variants associated with significant health risks. Over time, however, an increasing number of genes have been added to panel tests, complicating interpretation of novel variants in less well-understood genes.

SNP PROFILE AND MULTIGENE PANEL TESTS: KEY SOCIAL AND BEHAVIORAL RESEARCH EXAMPLES

SNP profile tests have been most widely utilized by the aforementioned DTC companies such as 23andme. While DTC companies have been limited in their ability to provide meaningful health risk results, some patients choose to download their raw DNA data and access third-party interpretation services. Social and behavioral researchers have investigated this process from the consumer perspective and found that they face many challenges in understanding these results [27]. Thirty percent of participants consulted medical professionals to help with interpretation. Assessing consumers' understanding and use of genomic data remains a fruitful area of research to inform development and assessment of interventions to be made available to consumers.

A recent systematic review concluded a lack of evidence to support the added value of communicating genetic risk information (most commonly SNP profiles) for common, complex disease and behavior change [22]. While this may seem to many as an indication that additional inquiry on this topic is futile, it is important to consider that many studies included in the analysis were methodologically flawed [28], suggesting the need for a new generation of studies that incorporate relevant theory and high-quality, carefully designed interventions [29]. For example, as Hay and McBride point out, many studies did not account for participants' preexisting motivation to change, small study samples which were not diverse, and that many studies offered genetic information unaccompanied by education or support [30].

As the risk perception and decision-making literature grows, so does our understanding about how individuals make sense of genetic risk information. There is much to learn about factors such as how the information is framed and communicated and how individuals' attitudes, beliefs, and affect interact with how people make sense of genetic risk profiles. Scholars have used health behavior theories to frame such studies, for example, Cameron et al. [31] promote the use of self-regulation theory and Horne et al. [32] (among others) recommend the theory of planned behavior. We urge social and behavioral scientists to continue to contribute their knowledge of theory in this area, as many atheoretical clinical studies continue to appear in the literature, suggesting opportunities for collaboration remain.

While the capability to sequence the entire genome is available to researchers and clinicians, interpretation of the data remains a challenge, currently limiting the usefulness of the data to inform patient management. Although there exists scientific evidence about the function of some genetic variants detected through genome sequencing many of the variants that will be detected lack such evidence. There are considerable discussion and debate about how to handle "variants of uncertain significance" (VUS). Research participants indicate interest in receiving these results, despite their uncertainty [33]. Some fear that the return of these variants to patients will have negative consequences [34], and there is evidence that many clinicians feel unprepared to communicate VUS results to patients [35]. Another challenge of VUS relates to the re-classification of variants in light of scientific evidence [36]. While ideally, patients should be informed of any new information that could impact their health management, the limit in resources to systematically manage this may be prohibitive. With these challenges relating to VUS come opportunities for social and behavioral research to help understand the consequences of learning such information and inform policy and guidelines for laboratories and clinicians handling VUS.

GENOMIC SEQUENCE TESTS AND APPLICATIONS

The development of genomic sequencing technologies has enabled many known genes to be investigated through multigene panel testing, genomic sequence tests that are untargeted (either the whole genome or whole exome) are also used, more often in a research setting for gene discovery. The use of sequencing technologies in an untargeted approach may detect variants in genes that are unrelated to the original indication for testing, termed secondary findings (SF) [37]. With the increasing use of sequencing technologies, the debate has centered on how to practically and ethically manage SFs. While prior evidence about the impact of single gene test results can inform the management of SFs, additional considerations may occur given the unexpected nature of SFs.

Recommendations from the American College of Clinical Genetics and Genomics (ACMG) about SFs list 59 medically actionable genes to disclose to patients undergoing clinical genomic testing for any purpose [37]. The guidelines state that informed consent to undergo genome sequencing is necessary, and patients should be able to opt-out of receiving these findings. The list of genes will change over time, as the genomic knowledge base grows, and guidelines will likely evolve as further evidence is gathered. As more individuals are sequenced and those receiving SFs increases, the opportunities for behavior change research also are increased.

Although evidence about the impact of SFs on patients is scarce, investigators have suggested reasons to not disclose SFs to patients including the possibility for psychological harms, costs associated with follow-up and impinging on the patient's "right not to know" the information [38,39]. The central opposing reason which supports disclosure of SFs is the benefit through treatment or prevention for conditions where such efforts exist.

Two exploratory studies of return of SFs suggest minimal to no evidence of harms from returning results to research participants [40,41]. While most participants followed up on their results with an appropriate specialist and communicated results to relatives,

there was little follow up pursued by at-risk relatives. These results emerged from short-term follow-up studies and need to be assessed over longer periods of time and replicated in other populations. Nonetheless, they are sufficient to raise the hypothesis that while patients may reap health benefits from SFs, the benefit to at-risk relatives may not be realized as intended.

GENOMIC SEQUENCE TESTS: KEY SOCIAL AND BEHAVIORAL RESEARCH EXAMPLES

Similar to other types of genetic testing, exome and genome sequencing have been predominantly more clinically useful in rare as compared with common disease. For example, exome sequencing can be used in the clinic to help diagnose cases of developmental delay in children [42,43]. Exome sequencing in this instance is useful when other more common diagnostic methods such as biochemical and radiological testing have not yielded answers.

While sequencing has contributed to diagnosing rare disease, the benefits of the technology for common disease, or among healthy individuals are less clear. Social and behavioral investigators have begun to explore the potential impact of genome sequencing for patients and research participants, including health, psychosocial and personal outcomes, as well as strategies for delivering the technology in a way that could be scalable to the population level. There remain countless opportunities for social and behavioral investigators to explore the impact of genome sequencing; we describe two examples below.

Biesecker et al. [44] conducted a randomized non-inferiority trial with primarily healthy adults to compare educating about exome sequencing results via a web-based platform with in-person. A specific category of results (carrier results) was selected to be returned to patients which do not have health implications for the patients themselves who are post-reproductive age, though may inform reproductive planning for their adult children. This study assessed knowledge of recessive inheritance, test-specific distress and decisional conflict about choosing to learn results and found a lack of significant difference in arms. The authors conclude that some types of results from exome sequencing can be disclosed to patients online, removing the need to visit a health professional in-person, although replication in more diverse populations is needed. With a shortage of qualified professionals to return genomic results to patients, this work suggests that alternative modes of delivery may be appropriate in some circumstances. Similarly, others have concluded that genetic risk information, from single gene testing, about Alzheimer's disease can be safely delivered via telephone [45].

Women diagnosed with breast or ovarian cancer at age 40 or younger are more likely to have a gene variant in the *BRCA* genes and may benefit from learning genomic information. Among a sample from this population of women, Kaphingst et al. [46] found that preference to learn genomic information varies widely. Three psychological factors were found to be associated with preferences to learn genomic information: knowledge about sequencing benefits, worry about genetic risks and importance placed on health information. This research suggests that a general-purpose policy for all regarding the return of genomic results may not be appropriate. Rather, decision support material should be developed to help patients make informed choices about receiving genomic results. Future research and development of such decision support material is needed and should be guided by those familiar with decision-making scientific theory as well as genomic expertise.

FUTURE DIRECTIONS

For clinical translational genomics to be realized, social and behavioral research is an essential piece. Herein, we highlighted examples of studies that contribute to genomics, which broadly includes an investigation into how people interpret and respond to genomic information, and the design and development of decision support materials for patients and providers interacting with genomics and novel systems, along with effective interventions, to communicate genomic information. There are expansive opportunities for social and behavioral researchers to apply their expertise in novel ways to translational genomics. For example, Ferrer et al. [47] developed the evidence-based TRIRISK model to conceptualize and assess three domains of risk perceptions in common conditions such as diabetes and cancer. The premise of the TRIRISK model is that deliberative, affective and experiential domains of risk perception can be distinguished as they explain unique variance in predicting health behaviors. Future research opportunities include an assessment of how receipt of genomic information may be associated with risk perceptions in these domains. The TRIRISK model also has implications for how genomic information is communicated, and behavioral interventions are developed. We encourage social and behavioral scientists to think broadly and creatively about how theories and methodologies in their own specialties may be applied to genomics research.

CONCLUDING REMARKS

Within SBM and beyond, social and behavioral scientists should be integrated into research teams and contributing to identifying key research questions, designing innovative studies to address those questions and contributing evidence toward translating genomics into clinical care. Now is the time for social and behavioral scientists to make their mark in this exciting new area of clinical science.

Compliance with Ethical Standards

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