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Applying Genetic and Genomic Tools to Psychiatric Disorders: A Scoping Review

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Abstract

Introduction The bioethics literature reflects significant interest in and concern with the use of genetic and genomic information in various settings. Because psychiatric treatment and research raises unique ethical, legal, and social issues, we conducted a scoping review of the biomedical, bioethics, and psychology literature regarding the application of genetic and genomic tools to psychiatric disorders (as listed in the DSM-5) and two associated behaviors or symptoms to provide a more detailed overview of the state of the field.

Objectives The primary objective was to examine the available bioethics, biomedical, and psychology literature on applying genetic and genomic tools to psychiatric disorders (other than neurodevelopmental disorders) and two behaviors or symptoms sometimes associated with them (aggression or violence and suicidality) to identify the disorders to which these tools have been applied, the contexts in or purposes for which they have been applied, the ethical, legal, or social concerns associated with those uses, and proposed recommendations for mitigating those concerns.

Methods We used Arksey and O'Malley's scoping review framework: (1) identify the research question; (2) identify relevant studies; (3) select studies; (4) chart the data; and (5) collate, summarize, and report results (2005). We relied on Levac et al. to inform our application of the framework (2010). The PRISMA extension for scoping reviews checklist informed our reporting (2018). We searched three electronic databases MEDLINE (PubMed), Embase, and PsycInfo (EbscoHost) for peer-reviewed journal articles in English to identify relevant literature. One author screened the initial results and additional screening was done in consultation with other authors. A data extraction form using DSM-5 diagnostic categories (excluding neurodevelopmental disorders) was developed and two authors independently each reviewed approximately half of the articles. Inter-rater reliability was ensured by double-coding approximately 10% of the papers. An additional author independently coded 10% of the articles to audit the data.

Results In 365 coded publications, we identified 15 DSM-5 diagnostic categories in addition to the two pre-selected behaviors or symptoms (aggression or violence and

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suicidality) to which genetic or genomic tools have been applied. We identified 11 settings in or purposes for which these tools were applied. Twenty-two types of ethical, legal, or social concerns associated with the application of genetic or genomic tools to these disorders or behaviors/symptoms were identified along with 13 practices or policies that could mitigate these concerns.

Conclusion Genetic and genomic tools have been applied to a wide range of psychiatric disorders. These raise a range of ethical, legal, and social concerns. Additional research is warranted to better understand the concerns and effective ways to address them. Advancing the literature to identify relevant ethical, legal, or social concerns and solutions to those problems likely requires greater attention to specific applications of genetic or genomic tools to particular psychiatric disorders and associated behaviors/symptoms as well as broad stakeholder engagement.

Keywords Genetics · Genomics · Psychiatry · Psychiatric disorders · Mental health

Introduction

The bioethics literature reflects significant interest in and concern with the use of genetic and genomic information in various settings. These include privacy, confidentiality, discrimination, the interests of biological relatives in genetic information, the interests individuals might have in obtaining as well as not obtaining genetic information, and stigmatization, among others. Psychiatric treatment and research also raise special concerns. In the research setting, these include worries about participants' decision-making capacity, informed consent, and research-related risks (Dunn & Holtzheimer, 2019; Iltis et al., 2013; Lauriello and Lyketsos, 2002; Roberts et al., 2006; Roberts et al., 2003). The view that potential participants with psychiatric disorders are less likely than participants in medical studies to have decision-making capacity or that research risks in psychiatry are particularly high might be unjustified or exaggerated in some cases (Luebbert et al., 2008; Tait et al., 2011; Carpenter et al., 2000; Jeste et al., 2006; Yanos et al., 2009). Nevertheless, they may result in exclusion from research or limitations on research, both of which raise additional ethical concerns about the generalizability of results and denying populations access to the benefits of research findings (Handong & Weng, 2016; Humphreys et al., 2015; Iltis et al., 2020; Michels, 1999). Concerns regarding psychiatric care sometimes result in unique ethical and legal requirements. For instance, in some jurisdictions, a person who holds a durable power of attorney for health care (DPAHC) may be able to make a wide range of healthcare decisions for an incapacitated patient but be unable to authorize psychiatric care or certain types of psychiatric treatment in the absence of a special DPAHC for mental health care (Fleischner, 1998; Henderson et al., 2008). Thus, applying genetic and genomic tools, such as pedigree studies, genetic testing and screening, whole genome sequencing, whole exome sequencing, and genome wide association studies, to psychiatric disorders and stigmatized behaviors or symptoms often associated with such disorders raises special concerns (Adriaens & De Block, 2013; Appelbaum, 2004; Harris &

Schaffner, 1992; Rostami et al., 2019; Rudnick, 2002).[1] Some of this work has led to concerns about eugenics and charges of racism (Sfera, 2013; Thomson, 2010; Berryesa and Cho, 2013; Hudson, 2009; Rembis, 2009; Pilgrim, 2008; Levitt, 2012).

Currently, there is no overview of the range of psychiatric disorders to which genetic and genomic tools have been applied, the purposes for which they have been applied, the ethical, legal, and social concerns they raise, or the possible approaches to mitigating those concerns. The literature offers snapshots of what has been done, the concerns raised, and possible solutions. This makes it difficult to appreciate the scope and breadth of the topic. This scoping review of the bioethics, biomedical, and psychology literature was prepared to provide greater awareness of the range of psychiatric disorders and two associated behaviors or symptoms to which genetic or genomic tools have been applied, the settings in or purposes for which those tools have been applied, the ethical, legal, and social concerns raised in the literature, and the suggestions for addressing or mitigating those concerns. It can facilitate a more comprehensive and informed exploration of and response to the ethical, legal, or social concerns associated with applying genetic and genomic tools to psychiatric disorders and associated behaviors or symptoms.

Methods

Scoping reviews allow for a broad overview of available literature (Munn et al., 2018). We used Arksey and O'Malley's scoping review framework: (1) identify the research question; (2) identify relevant studies; (3) select studies; (4) chart the data; and (5) collate, summarize, and report results (2005). We relied on Levac et al. to inform our application of the framework (2010). The PRISMA extension for scoping reviews checklist informed our reporting (Tricco et al., 2018). The protocol for this scoping review was registered on February 13, 2021 on the Open Science Framework and registration approved on February 16, 2021. The final protocol was registered on March 8, 2021 through the Center for Open Science (https://osf.io/3jzsm/).

Step 1: Identifying the Research question

Objectives

Our primary objective was to examine the available bioethics, biomedical, and psychology literature on applying genetic and genomic tools to psychiatric disorders and two behaviors or symptoms often associated with them to answer 4 questions:

1. To which psychiatric disorders have genetic or genomic tools been applied? We were also interested in examining the application of genetic and genomic tools

[1] Lay explanations and definitions of these and other terms can be found in a glossary of genetic terms published online by the National Human Genome Research Institute at https://www.genome.gov/genetics-glossary.

to two symptoms or behaviors sometimes associated with psychiatric disorders, aggression or violence and suicidality, and thus we included those as well.

2. In what settings or for what purposes does the literature report application of genetic or genomic tools to psychiatric disorders or the two pre-selected associated symptoms or behaviors?

3. What ethical, legal, or social concerns associated with applying genetic or genomic tools to these disorders or associated behaviors or symptoms are identified in the literature?

4. What practices or policies have been proposed to mitigate or address the ethical, legal, or social concerns identified in the literature?

The answers to these four questions yield a more comprehensive account of the appropriate scope of inquiry on this topic than previously available in the bioethics literature.

Step 2: Identifying the Relevant Studies

ASI developed a systematic literature search strategy in consultation with a research librarian (SHJ). Three electronic bibliographic databases, MEDLINE (PubMed), Embase, and PsycINFO (EbscoHost), were selected, and only peer-reviewed journal articles in English were included. No publication date restrictions were applied. Keywords were defined broadly to capture as many relevant publications as possible. The search strategy used a combination of controlled vocabulary and keywords and was customized for each database. Each strategy with search dates is described in Appendix 1 (Online Supplementary Material). Disorders classified in the DSM-5 under Neurodevelopmental Disorders, such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) were excluded because more genetic research on these has been done compared to other psychiatric diagnoses, to the point that they are often factored into genetic counseling risk assessments (Peay, 2020). This led to a decision that the sheer volume of research on neurodevelopmental disorders warrants a separate study.

Step 3: Selecting Studies to be Included

Eligibility: To be eligible for inclusion, a publication had to meet the following criteria:

-be identified using the search strategy described in Appendix 1 (Online Supplementary Material)

-appear in a peer-reviewed publication, and

-mention one or more types of genetic or genomic tools applied to a psychiatric disorder that is not a neurodevelopmental disorder or one of the following behaviors/symptoms sometimes associated with psychiatric disorders: aggression or violence, or suicidality. These two symptoms/behaviors were chosen because of particular author interest and will be used to determine if other behaviors/symptoms should be assessed separately.

Papers for inclusion were selected in two stages. First, ASI screened the abstracts and titles of the initial 3369 papers against the eligibility criteria. For any papers whose eligibility was unclear, ASI read the full text and consulted with SWS when necessary. This left us with 716 papers (258 from Embase, 85 from PubMed, and 373 from PsycInfo). We identified duplicates and triplicates, i.e., papers that appeared in more than one database, and counted only the first instance of the paper, excluding an additional 243 papers.

We identified papers that were not available electronically to us through the Wake Forest University Z. Smith Reynolds Library or through Interlibrary Loan. Because this research was conducted during the COVID-19 pandemic, access to stacks and off-site storage was limited, making it impossible to access 44 papers, which we excluded. All remaining references were put into a group library in the reference management system, Zotero.

Next, two authors (AL and SN) were trained on assessing eligibility and data extraction so that, during the data extraction process, they could identify papers that passed the initial screen but were ineligible. These papers were brought to the attention of ASI and, if necessary, to SWS for evaluation. During data extraction, an additional 64 papers were deemed ineligible and were excluded. The total number of papers included in the final review is 365. These are listed in Appendix 2 (Online Supplementary Material). See Figure 1 for an overview of this process.

Step 4: Charting the Data

Data Charting Process: A data charting form created in GoogleSheets was used during data extraction. It included the bibliographic information for each paper and four groups of lists: psychiatric disorders and associated behaviors/symptoms to which genetic or genomic tools were applied; purposes for or settings in which those tools were applied; ethical, legal, or social concerns mentioned; and approaches to addressing or mitigating those concerns mentioned. Each group included a list of options as well as an "Other" column. The authors extracting data (AL and SN) were instructed to enter notes under "Other" describing any relevant information that did not fit into one of the predetermined selections, such as a psychiatric condition that was not listed on the form. Later, all entries in the "Other" columns were reviewed by ASI and SWS to determine whether they fit into one of the previously defined categories or represented a new category. All findings are reported here by name because our goal was to provide a comprehensive overview of all answers to our four questions. No relevant findings were left as "Other" for the purpose of final reporting.

To ensure inter-rater reliability, after the initial eligibility assessment, all team members (with the exception of SHJ), reviewed and extracted data from the same 10 papers and compared results. This allowed us to refine the data extraction form and to develop a shared understanding of the data to be extracted. ASI assigned roughly an even number of articles from each database to the two coders (SN and AL). ASI also assigned two papers out of every 20 (10%) to both readers. Coders compared their results on those duplicates to ensure consistency

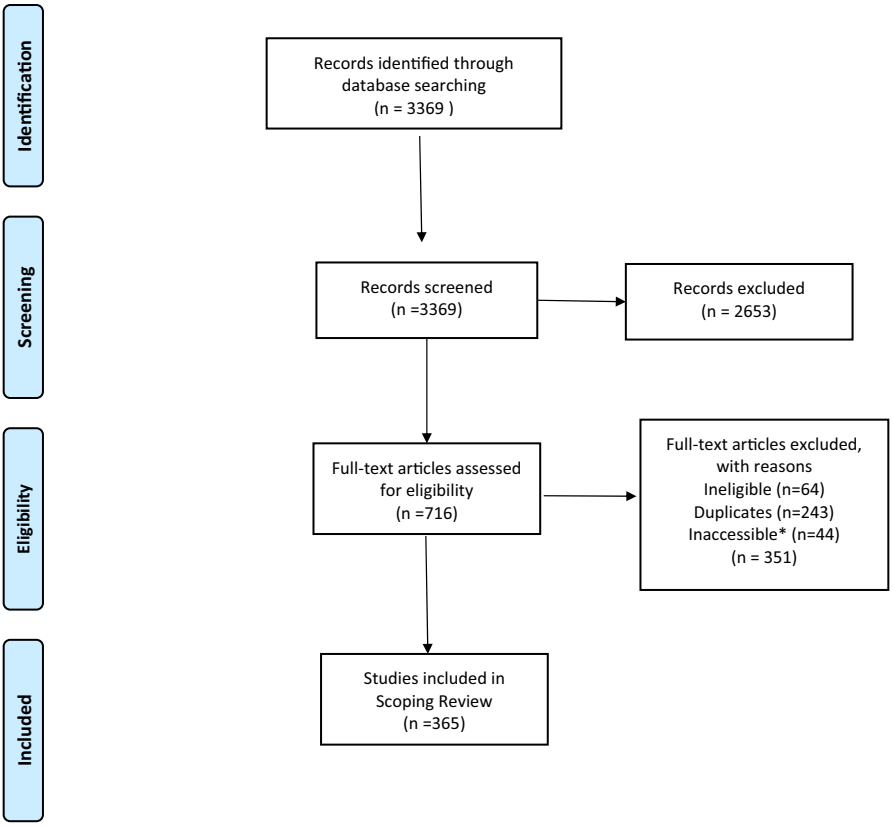

Figure 1 Flow diagram of literature search (based on Moher et al., 2009; modified to reflect our process)

throughout the process. In total, 45 papers (12%) were coded by both Coders. This is higher than the planned 10% because some papers were excluded during data extraction, leaving us with a smaller total number of papers than we had when the assignments were made.

Any questions that arose regarding eligibility or data extraction were resolved in consultation with input from ASI and SWS. To ensure data integrity, ASI audited the data by independently coding 10% of the papers and comparing her responses to AL and SN's data extraction forms.

Step 5: Collating, Summarizing, and Reporting Results

Data were extracted from all included articles to generate the complete list reported here of psychiatric disorders and two associated behaviors/symptoms, the purposes for or settings in which genetic or genomic tools were applied, the ethical, legal and

Table 1 Psychiatric disorders and two associated behaviors or symptoms to which genetic or genomic tools have been applied

Behavior or symptom	Number (N)
Aggression or violence	44
Suicidality	7
Disorder based on DSM-5 category	
Problems related to other psychosocial, personal, and environmental circumstances	73
Substance-related and addictive disorders	71
Depressive disorders	60
Problems related to crime or interaction with the legal system	60
Disruptive, impulse-control, and conduct disorders	53
Neurocognitive disorders	46
Bipolar and related disorders	24
Trauma and stressor-related disorders	21
Anxiety disorders	15
Personality disorders	7
Obsessive compulsive and related disorders	5
Sleep wake disorders	4
Feeding and eating disorders	2
Sexual dysfunctions	1

Table 2 Purposes for which or settings in which genetic or genomic tools were applied to psychiatric disorders or two associated symptoms/behaviors (aggression or violence and suicidality)

Context or purpose	Number (N)
Research	299
Criminal proceedings	28
Clinical: treatment decision-making	23
Clinical: prediction	33
Clinical: diagnosis	10
Clinical: screening	8
Clinical: reproductive planning	3
Direct-to-consumer genetic testing	2
Adoption proceedings	2
Child custody decisions	1
Education	1

social concerns identified, and the possible mechanism to address or mitigate those concerns mentioned in the literature.

Table 3 Ethical, legal, or social concerns associated with applying genetic or genomic tools to psychiatric disorders or two associated behaviors/symptoms (aggression or violence and suicidality)

Ethical, legal, or social concern	Number (N)
Privacy or confidentiality	44
Stereotyping or stigma	30
Psychological harm	23
Insurance discrimination	22
Employment discrimination	20
Use in criminal proceedings to reduce responsibility or punishment	14
Poor cost–benefit ratio/limited value	9
Rights and interests of third parties affected by information	8
Misunderstanding what genetic information means	8
Use in criminal proceedings to attribute greater responsibility or punishment	6
Poorly informed decisions to undergo genetic testing or screening	6
Clinicians' interpretations of results may be unreliable	6
Contribute to eugenic practices or beliefs	6
Potential use in family law matters (adoption, divorce, custody)	4
Could be used to require pre-emptive supervision/surveillance or treatment	3
The right not to know is in jeopardy	3
Results might be unreliable	3
Connecting race or ancestry to genetic information may be stigmatizing and harmful	2
Nursing home discrimination	2
Return of research results could be problematic as could refusal to return results	2
Banking discrimination	1
Education discrimination	1

Results

The number of articles that mention each condition, setting/purpose, concern, or solution was totaled. These are reported in Tables 1, 2, 3, and 4. As reported in Table 1, we identified 15 groups of psychiatric disorders and the 2 pre-selected associated behaviors or symptoms to which genetic or genomic tools were applied. The list of settings in or purposes for which the tools were applied is reported in Table 2. Not surprisingly, the vast majority of applications were for research purposes since much of this remains under investigation and much of the published literature in these fields consists of reporting research results. Over time, some of those applications might be used in other settings or for other purposes, including some of the settings or purposes identified in this review.

While many of the non-research applications were for health-related purposes, such as testing to choose a medication for a patient, others were not. Most noted among the non-health-related applications was use in criminal cases.

As reported in Table 3, we identified 22 types of ethical, legal, or social concerns associated with the application of genetic or genomic tools to psychiatric disorders

Table 4 Policies or practices recommended to mitigate or address ethical, legal, or social concerns associated with applying genetic or genomic tools to psychiatric disorders or two associated behaviors/symptoms (aggression or violence and suicidality)

Policy or practice	Number (N)
Improve informed consent practices	41
Implement legal protections against discrimination	9
Expand use of genetic counseling	9
Give patients and research participants more control over their information and biospecimens	9
Improve and expand future research	8
Exclude from legal proceedings	8
Include in legal proceedings	8
Develop guidelines for use and educate clinicians	7
Expand access and follow-up care	6
Protect the interests of third parties	5
Improve public understanding of genetics and genomics	4
Withhold research results	4
Strengthen regulation of direct-to-consumer genetic testing	2

and associated behaviors/symptoms. In Table 4, we report the 13 types of practices or policies mentioned in the literature to address or mitigate ethical, legal, or social concerns.

Discussion

Through this scoping review, we sought to provide a descriptive overview of the bioethics, biomedical, and psychology literature regarding the types of psychiatric disorders and two associated symptoms/behaviors to which genetic or genomic tools have been applied and the settings in or purposes for which they have been applied. We also sought to document the ethical, legal, or social concerns associated with those applications and possible solutions to those concerns mentioned in the literature. One motivation for this scoping review was that, without an awareness of the range of disorders to and purposes for which genetic and genomic tools are applied, the literature remains fragmented, discussion might occur primarily at a general level without sufficient specificity to inform practice, and differences among the ethical concerns associated with various applications might be missed.

This review reveals a wide range of psychiatric disorders to which genetic or genomic tools have been applied in clinical and research settings as well as non-health related contexts, such as the criminal justice system. There are important differences among many of the disorders we found and the two associated symptoms or behaviors we studied in terms of who is affected, how they affect people, and the stigma associated with them (Preti et al., 2009; Bernal et al., 2007; ESEMeD/MHEDEA 2000 Investigators, 2004; Fleury et al., 2011; Krendl & Freeman, 2019;

Hinshaw & Stier, 2008; Schomerus et al., 2011; Mannarini & Rossi, 2019). For instance, consider the impact of and stigma associated with having a mild depressive disorder versus a substance use disorder or antisocial personality disorder. Thus, generic references to applying genetic or genomics tools to psychiatric disorders are unlikely to advance our understanding of the ethical issues they raise or possible solutions to those concerns.

The list of ethical, legal, and social concerns identified included a series of concerns regarding discrimination, which are common in literature regarding genetics and genomics. Some concerns, however, likely are unique to psychiatric disorders or conditions, most notably those involving the criminal justice system or forced preventive interventions or preemptive surveillance for people with particular genotypes. For instance, it is difficult to imagine that literature on genetic testing for a predisposition to a medical condition such as cardiovascular disease or breast cancer would include discussion of possibly forcing individuals to undergo preventive interventions or surveillance. Yet, this concern arose in the literature we reviewed (see, for example, Glick & Soreq, 2003). Application of genetic or genomic tools in the criminal justice system might have a disparate impact on minorities who are over-represented in the criminal justice system (see, for example, Mallett, 2018 and Walker, 2020). Additionally, applications of these tools to a wide range of disorders or conditions, particularly prenatally, have raised concerns about eugenics (Iltis, 2016; Mehlman, 2011). These may be amplified where mental health is concerned given the history of mental illness or perceived mental illness and eugenics.

The proposals for addressing the ethical, legal, or social concerns identified were not surprising. Typically, they were general rather than specific (e.g., a law prohibiting discrimination) and similar to what we find in the bioethics literature on genetics more broadly (see Kious, 2010 for arguments against some such legal protections). While our review was not intended to assess the quality of proposed solutions to ethical concerns, we noticed that in addition to being fairly general, authors typically did not mention evidence that their suggestions would be effective. The importance of evidence-based solutions to ethical concerns has been discussed in other contexts and applies here as well (Anderson & DuBois, 2007, 2012; Halpern, 2005). This is an area for further investigation.

In the bioethics literature, ethical, legal, or social concerns associated with technologies or interventions often lead to recommendations to limit the use of that technology, a view captured by the precautionary principle. Introduced with a focus on environmental considerations and health, the principle has been applied to other contexts, including innovative surgery and human research (Kopelman et al., 2004; Kopelman, 2004; Meyerson, 2013; Resnik, 2004; Weed, 2004; Soule, 2004; Cranor, 2004; Engelhardt and Jotterand 2004). Certainly, some authors reject the precautionary principle, including recently in the context of selecting for particular future persons or editing the human genome (Gyngell et al., 2019; Savulescu, 2014). Nevertheless, a precautionary approach is common, perhaps due partly to the omission bias. Many people perceive the risks associated with acting as worse than or less justified than those incurred through inaction (Baron and Hershey, 1998; Connolly & Reb, 2003). We found this to be the case in the literature we reviewed. Most of the proposed approaches to addressing ethical, legal, or social concerns involved

limiting the application of genetic or genomic tools or restricting access to and use of the information obtained. However, we found that some authors focused on the possibility that particular technologies would *not* be used or accessible, leading them to recommend expanding rather than restricting use (Shields, 2011; Kahn, 1997; Connolly & Beavers, 2016; Fishbein, 1996).

Another area calling for additional research is stakeholder engagement to identify both ethical, legal, or social concerns associated with applying genetic and genomic tools to psychiatric disorders and associated behaviors/symptoms as well as possible solutions to those concerns. Community engagement has become central in many areas of biomedical research (Goodman et al., 2020; Sanders Thompson et al., 2020). In research involving genetic and genomic tools, engagement with members of the public, research participants, and families has informed practices and recommendations, and new areas for engagement are emerging (see, for example, Bollinger et al., 2012, 2014; Wolf et al., 2012, 2015; Gordon et al., 2018; Umeukeje et al., 2019; Kaplan et al., 2017; Young et al., 2019; Tuttle et al. 2020). We were not looking specifically for evidence of stakeholder or community engagement, but we noted little evidence of it. Such engagement may be essential with respect to psychiatric disorders because of long-standing biases and stigma associated with many psychiatric disorders. This includes the reality that persons with psychiatric disorders may mistakenly be assumed to lack decision-making capacity, to be unreliable research participants, or to face higher-than-acceptable risk levels if they are included in research (Iltis et al., 2013; Luebbert et al., 2008; Tait et al., 2011).

This scoping review has three limitations. First, the scoping review methodology is meant only to generate a broad overview of the literature. We did not assess the quality of the publications reviewed nor was our data extraction approach designed to measure the intensity or significance of the concerns raised. Second, we did not include all possible publications nor did we review the gray literature, which refers to material such as dissertations, conference abstracts and presentations, and other material not published in commercial publications, and which some scoping reviews include. We only reviewed publications written in English and we omitted 44 articles because they were inaccessible due to the pandemic. Not all bioethics journals are indexed in any of the three databases, though we note that many are indexed in PubMed or Embase. Third, we excluded neurodevelopmental disorders and included only two behaviors/symptoms often associated with psychiatric disorders.

Conclusion

We undertook a scoping review of the biomedical, bioethics, and psychology literature regarding the application of genetic or genomic tools to psychiatric disorders and two associated behaviors or symptoms, aggression or violence and suicidality. Our descriptive results reveal a wide range of disorders to which genetic or genomic tools have been applied in various health and non-health related settings. Depending on the disorders in question and the purpose for or setting in which these tools are applied, various ethical, legal, or social concerns likely will arise, requiring different evidence-based solutions.

Advancing the literature to identify relevant ethical, legal, or social concerns and effective solutions to those problems likely requires greater attention to specific applications of genetic or genomic tools to particular psychiatric disorders and associated behaviors/symptoms as well as broad stakeholder engagement.

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