Four Actionable Bottlenecks and Potential Solutions to Translating Psychiatric Genetics Research: An Expert Review

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Abstract

Background: Psychiatric genetics has had limited success in translational efforts. A thorough understanding of the present state of translation in this field will be useful in the facilitation and assessment of future translational progress. **Purpose:** A narrative literature review was conducted. Combinations of 3 groups of terms were searched in EBSCOhost, Google Scholar, and PubMed. The review occurred in multiple steps, including abstract collection, inclusion/exclusion criteria review, coding, and analysis of included papers. **Results:** One hundred and fourteen articles were analyzed for the narrative review. Across those, 4 bottlenecks were noted that, if addressed, may provide insights and help improve and increase translation in the field of psychiatric genetics. These 4 bottlenecks are emphasizing linear translational frameworks, relying on molecular genomic findings, prioritizing certain psychiatric disorders, and publishing more reviews than experiments. **Conclusions:** These entwined bottlenecks are examined with one another. Awareness of these bottlenecks can inform stakeholders who work to translate and/or utilize psychiatric genetic information. Potential so-

lutions include utilizing nonlinear translational frameworks as well as a wider array of psychiatric genetic information (e.g., family history and gene-environment interplay) in this area of research, expanding which psychiatric disorders are considered for translation, and when possible, conducting original research. Researchers are urged to consider how their research is translational in the context of the frameworks, genetic information, and psychiatric disorders discussed in this review. At a broader level, these efforts should be supported with translational efforts in funding and policy shifts.

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Introduction

Psychiatric disorders are a major burden in the USA, resulting in over USD 300 billion annually in cost from health care expenses, loss of wages, and disability benefits [1]. Among adults, over a quarter of the population will meet criteria for 1 or more psychiatric disorders in a given year [2]. Costs will only continue to increase without effective prevention, detection, treatment, and support for these conditions [3]. The translation of genetic information to the clinic has improved prevention

and treatment of several chronic physical disorders (i.e., nonpsychiatric) [4]. It is possible that the mental health field could similarly benefit from the translation of psychiatric genetics research via the reduction of subsequent morbidity and mortality. Psychiatric genetic information, such as individual-level information (e.g., family history and polygenic risk scores) and population-level information (e.g., gene-environment interplay and the etiology of disorders), can be powerful in genetic counseling by improving self-efficacy and reducing stigma [5–9]. However, a research-to-practice gap exists, whereby psychiatric genetic information about psychiatric disorders is not being integrated into clinical care [10–16].

Historically, the application of genetic information – whether it be nonmolecular epidemiological information (e.g., family heritability estimates from twin studies, gene-environment interplay data) or molecular information (e.g., genome-wide association data, polygenic risk scores, epigenetics) – is lacking in the development of psychiatric disorder prevention and treatment as compared to nonpsychiatric medical conditions such as breast cancer [17–21], cardiovascular disease [4, 22–25], type 2 diabetes [26], and macular degeneration [27]. For example, the incorporation of molecular genomic testing for *BRCA* variants in clinical settings has led to applications for the diagnosis of breast cancer and more effective treatment [21] as well as effective prevention efforts above and beyond nonmolecular family history information [28]. Scientific understanding of breast cancer patient, researcher, and clinician attitudes toward complex topics, such as the return of incidental molecular genetic findings and the biobanking of DNA samples, has additionally progressed the field [29, 30]. A comparable level of applicable research knowledge (e.g., molecular genomic findings and insights into stakeholders' attitudes) is not yet available for psychiatric disorders, leaving many to conclude that the application of genetic information to mental health is years away [4, 31, 32]. This supposition is ascribable to the higher polygenicity and complex genetic structure of psychiatric disorders.

Contrasting with the prevailing skepticism toward its near future prospects for translation, the basic science of psychiatric genetics continues to evolve in an innovative, multidisciplinary way. The insistence that this knowledge be similar to that used in translating nonpsychiatric disorders before being useful for translation, however, may undermine the value of psychiatric genetic information that is known. We argue that instead of waiting for more

knowledge, the field of psychiatric genetics should consider working toward translation of the knowledge it is rapidly generating. With an intentional re-examination, rebuilding, and informed application of appropriate translational frameworks, psychiatric genetic translational breakthroughs might no longer be relegated to decades away. The first step in this process is to review the state of translating psychiatric genetic research via a narrative literature review.

Strategy

Search Methods

A thorough, non-systematic, narrative literature review was conducted in multiple steps (see online suppl. Text 1 for a more thorough explanation of each step; see www.karger.com/doi/10.1159/000510832 for all online suppl. material). Given that the scope of this paper was to summarize a broad area (the translation of psychiatric genetic information) and a specific question was not posited, a narrative literature review was conducted instead of a systematic review [33]. First, all combinations of terms about translation, psychiatric disorders, and genetics were searched. The abstracts from all potentially relevant articles were downloaded and reviewed for inclusion/exclusion criteria (see online suppl. Table 1 and suppl. Text 2).

Search Results

The first step of the review process ended with 372 abstracts that were loosely related to the aims of this paper. After reviewers completed the inclusion/exclusion checklist and coding form and the lead author confirmed the articles, 157 abstracts met criteria for inclusion. Eleven of these were duplicates and 32 were not peer-reviewed articles (e.g., conference proceedings, commentaries, and poster presentations) or did not meet inclusion criteria after a full read, resulting in 114 articles for analysis. Online suppl. Table 2 contains a list of the final articles included in the review. Limitations of the search and the review can be found in online suppl. Text 4.

Review Findings

The current narrative literature review examined the state of the science of translating psychiatric genetic information into clinical care. Evidence was found for 4 areas of this research that, if thoroughly examined, may

help to propel translation in this area further. Specifically, there are 4 bottlenecks that contribute to the hindrance of nuanced, innovative, and progressive thinking in this area. These will be discussed in turn and are as follows: emphasizing linear translational frameworks, relying on (and waiting for) molecular genomic findings, prioritizing certain psychiatric disorders, and publishing more reviews than experiments.

Part 1: Emphasizing Linear Translational Frameworks

Differences between the relationship of genetics to disease in psychiatric and nonpsychiatric contexts raise questions about using the same type of translational frameworks for both types of disorders. Admittedly, non-Mendelian, chronic physical conditions and psychiatric disorders are all “complex” traits with an interplay of genetic and environmental etiological factors. Yet, the genetic structure of psychiatric disorders consists of a greater number of alleles with smaller penetrance, meaning that each gene contributes little to the overall variation of the trait [34, 35]. There is also evidence for nonadditive genetic factors that contribute to psychiatric disorders, reducing the chances of successful molecular genetic studies [34]. These key differences between nonpsychiatric and psychiatric disorders could limit the generalizability of the translational frameworks used for nonpsychiatric disorders to psychiatric ones.

Specifically, 2 frameworks that are highly prevalent across all health-related research fields follow a linear structure [36] and have historically spearheaded advancements in medicine and other fields with a biological focus [37, 38]. These linear frameworks are bench-to-bedside (i.e., research that begins at the biological level and can eventually lead to clinical trials or randomized controlled trials) [39, 40] and precision medicine (i.e., the use of biological information to improve patient health that may be acquired from the bench or beyond and is specific to particular treatment contexts and individual patient needs) [41, 42]. Success in these frameworks is predicated on the ability to uncover the underlying biological basis of disease (e.g., genetics and neurobiology) and convert it to innovation at the level of patient care. Accordingly, such frameworks have been successful in nonpsychiatric fields but have had little effect when applied to the genetics of psychiatric disorders [4, 31, 32]. Each framework will be discussed in turn below.

Bench-to-Bedside Research

It is common for bench-to-bedside research to utilize animal models and biomarker development, which are consistent approaches to psychiatric genetic translation. Animal models are regularly used to investigate complex traits (e.g., depression) without questioning or justifying the translational framework. The assumption that genetic research at the animal level will eventually translate to psychiatric precision medicine because a bench-to-bedside framework has been successful in translating and utilizing the genetic information for other complex but nonpsychiatric disorders is often implicit in such discussions [43–55]. It has seemingly become common for studies to explicitly use the term “precision” or “personalized” medicine when reviewing literature that is strictly at the bench-to-bedside level (e.g., animal models and drug development preclinical trials) and/or make it clear that precision medicine is the end goal of current bench-to-bedside efforts [55–61]. Occasionally, there is a call for the need to translate genetic findings from animal models into patient-specific treatment while simultaneously acknowledging that the biological roots of psychiatric disorders are still being uncovered [45, 62], a paradox that arguably feeds the assumption that linear translational frameworks should be used to translate psychiatric genetic information. Biomarker development suffers from the same assumption as animal models. It is common to discuss past successes with nonpsychiatric chronic or Mendelian disorders and how future psychiatric treatment will likewise be enhanced by biomarker development for psychiatric disorders [63–66]. That is not to say that such claims are not true, but that they do not rely on strong evidence.

Thus, the field might benefit from critical reflection on the time and place to rely on bench-to-bedside translation. For example, Hariri and Holmes [67] argue that translational efforts should also emphasize investigations of non-pharmaceutical treatment processes, supporting their argument with the compelling results of neural circuit manipulation for stress-related disorders in rodent models. Others have argued that new methods (i.e., an integrative research domain criteria approach [RDoC], an established matrix of inter-related domains, and constructs proposed by NIH) need to be taken to be able to effectively use information from the “bench” [68, 69], especially as epigenetics becomes more common [70].

Precision Medicine Research

Similar to research using a bench-to-bedside framework, research that uses a precision medicine frame-

work makes explicit [16, 71–83] and implicit [84–101] comparisons between the translation of genetic information to psychiatric and nonpsychiatric care. These comparisons give way to the assumption that linear frameworks will undoubtedly work, albeit in the future. Notably, several researchers have taken care to acknowledge that it will take more time to translate psychiatric genetic information to patient care due to the non-Mendelian nature and heterogeneity of such disorders [102–112]. There has also been a recent increase in the discussion of pharmacogenetic treatment for psychiatric disorders, specifically, examining metabolism rates of currently approved psychiatric medications, response to treatment, gene-drug interactions, or other genetic biomarker differences among individuals [94, 113, 114], or reviewing the literature on such treatments [82, 110, 115–118].

Moving Linear Translation Forward

There are ways to expand linear frameworks to allow for more reflection. First, bench-to-bedside research often leads into precision medicine; discussing both lenses within a research study could offer a more thorough discussion about the translation of psychiatric genetic research. For example, Damianco and colleagues [119] discussed genetics in terms of biomarkers and preclinical models from a bench-to-bedside approach and then the precision medicine application of those biomarkers for early identification and treatment for psychiatric disorders from an RDoC perspective. Foley and colleagues [120] followed a similar structure, discussing the need for gene and drug discovery (bench-to-bedside framework) that will help us to understand molecular mechanisms and eventually improve treatment (precision medicine), possibly with the use of clustered regularly interspaced short palindromic repeats (CRISPR). Other papers that also discussed bench-to-bedside research within the lens of future precision medicine include Siegel and colleagues [121], Stern and colleagues [122], Tomasi and colleagues [117], and Zayats and Neale [123]. While a justification for these translational frameworks is not provided, such research highlights the potential benefits of combining linear translational frameworks more fully than research that solely works from one framework or the other.

Second, several researchers acknowledge the inherent genetic differences between psychiatric and nonpsychiatric disorders and that precision medicine based on psychiatric genetic information is unlikely [105, 124, 125] or at least will take longer than anticipated [126]. Precision

medicine will likely have to integrate several biological mechanisms into several possible treatments [124] or take another yet-to-be-determined approach in order to be successful for psychiatric genetics [125]. Psychiatric disorders are too complicated genetically as well as phenotypically for the successful application of the same version of precision medicine that has worked for chronic physical disorders [125]. In the meantime, it has been recommended that patients' other biological, social, and clinical information be considered when prescribing psychiatric medication.

Third, many researchers have posited their own translational models that overcome flaws in linear frameworks. Amare and colleagues [127] discussed predictive, preventive, and personalized medicine, an extension of traditional precision medicine. Their predictive, preventive, and personalized medicine framework offers 3 alternative/complementary strategies to pharmacogenomics (the primary way to translate psychiatric genetic information in precision medicine): (1) diagnostic, therapeutic, or prognostic genetic testing based on candidate genes; (2) combine “-omics” data; and (3) combine genomics information with other predictors (-omics, neurological information, and clinical characteristics). Bickman and colleagues' [128] framework, precision mental health, is also an extension of precision medicine and specifically calls NIH to move beyond genetic factors as the sole focus of precision medicine in psychiatry and embrace an RDoC perspective. Wittchen and colleagues [129] also offered a framework, an integrative translational model that explicitly does assume that what worked in the past will work in the future. Their framework specifically contrasts itself with precision medicine. However, genetics made up a small component of this discussion. While working from a precision medicine perspective, Hutchison [124] noted the flaws of precision medicine (sample size, lack of clinical translation, lack of replication, and emphasis on univariate approaches) and offers a model that uniquely combines 2 networks, neural and genetic, that should be targeted when treating substance use disorders. Herbert and colleagues [130] presented the IMPACT model for psychiatric treatment that includes pharmacogenetic testing across a range of psychiatric disorders. Relatedly, several studies [59, 114, 126, 131] offer roadmaps for how to navigate translation in their review.

Fourth, 3 studies pointed out ways that genetic studies are biased and exclusive toward individuals who are not of European descent [59, 108, 109]. Peterson and colleagues [59] noted flaws in current molecular genomic methods and offered suggestions for improving genetic

ancestral analyses. While such a method-focused study is at the bench-to-bedside level, implications will undoubtedly have an impact on precision medicine in the future. Similarly, Martin and colleagues [108, 109] highlighted ways that molecular genomic methods only benefit European descendants and that ancestral diversity needs to be prioritized in future studies.

Moving beyond Linear Frameworks

An option to effectively translate psychiatric genetic information is to utilize nonlinear frameworks such as dissemination and implementation (D&I). D&I requires simultaneous integration of information from many stakeholders and focuses on the ecology of the service delivery system [36, 132–134]. Such a framework offers novel, systematic, and comprehensive ways to address the translational gap within psychiatric genetics [135]. It can integrate psychiatric genetic information into care quickly and effectively because it is designed to close research-to-practice gaps as each side of the gap informs the other [136, 137].

Unfortunately, to our knowledge, there are no translational psychiatric genetic articles that solely utilize a D&I framework. However, there are many articles that incorporate aspects of D&I (e.g., include stakeholders, ecological theory, and focus on implementation) [5, 109, 121, 131, 138–145]. For example, Finn and Smoller [139] were early proponents of using psychiatric genetic counseling in clinical care (after more evidence and empirical support). Costain and colleagues [5] took this a step further by showing that psychiatric genetic counseling (which relies on genetic epidemiological information) improves disorder knowledge and decreases stigma for patients with schizophrenia. Such a study clearly overlaps with D&I by disseminating information to patients (a key stakeholder group) via an implementation strategy and evaluating the effectiveness of that strategy. Drury and Cuthbert [138] continued the discussion of RDoC, beginning from a precision medicine perspective and expanding in a nonlinear, D&I-esque direction by specifically calling for an inclusion of clinicians and other transdisciplinary collaborators to progress translation. Harold and colleagues [140] offered clear suggestions for clinicians on how to incorporate psychiatric genetic information (genetic epidemiological and molecular) information into care with the help of families. This clear pathway from research to practice is at the heart of D&I via the inclusion of multiple stakeholders (parents, children patients, and clinicians). Similarly, Roos [142] discussed the role of genomics, recurrent

risk, and family history in clinical care for schizophrenia, as did Vortsman and colleagues [143] when discussing the implementation of pharmacotherapy into the clinical care of autism spectrum disorder. Finally, Hendershot [141] offered a rare discussion of when and how to implement genomic information (i.e., pharmacogenomics) into evidence-based practice guidelines for alcohol use disorder and that there is a need for efficient, not just effective, translation.

Summary: Part 1

Overall, the vast majority of research on the translation of psychiatric genetic information occurs from linear bench-to-bedside and precision medicine frameworks and make implicit and explicit assumptions that these frameworks will lead to clinical and pharmacological improvements in patient care. These assumptions leave little room for discussion of treatment impact or an objective evaluation of whether linear frameworks are the right path forward when translating psychiatric genetic information. One contributing factor is that funding agencies and programs have long supported a linear translational framework, making it difficult for researchers to move beyond it. Thus, funding and policy shifts need to occur supporting a diversity of translational frameworks if nonlinear approaches are to be efficiently adopted.

Fortunately, studies in the last few years have seen a slight increase in studies that discuss the genetic differences between psychiatric and nonpsychiatric disorders, calling into question how precision medicine will function in psychiatry. As will be discussed in Part 2 below, these assumptions likely limit the type of genetic information that is attempted to be translated. Molecular genomic information, which is still being actively researched for psychiatric disorders, is inherently the information of choice within bench-to-bedside and precision medicine frameworks. Two key options have presented themselves that may move the field of psychiatric genetics forward. First, we can continue the push to move linear frameworks forward. Several articles were outlined that question the use of precision medicine, offer new frameworks, and reflect upon the fact that relatively little genetic information is known about psychiatric disorders. Second, we can simultaneously embrace nonlinear, ecological-based frameworks such as D&I that value partnerships with stakeholders. These frameworks might immediately impact patient care by identifying innovative ideas about what translation can look like for psychiatric genetics and what type of information is translated.

Part 2: Relying on Molecular Genomic Information

The second bottleneck that has dominated the translation of psychiatric genetic information is the disproportionate reliance on molecular genomic information over nonmolecular epidemiological forms of genetic information (e.g., heritability estimates, family history, and gene-environment interplay data). This is intrinsically linked to the first bottleneck of emphasizing linear frameworks, because linear frameworks rely on biological (e.g., molecular genomic) information. The exclusion of nonmolecular genetic information is worrisome because such information may be more accessible to patients and other stakeholders and has been shown to be efficacious in treatment settings [9]. Recent public health efforts have started to shift the narrative around the translation of genetic information broadly [13, 17, 146] and psychiatric genetics specifically [12, 147] to include this type of genetic information. This shift involves turning some attention away from molecular genomic and epigenetic information and opening up the possibility of utilizing family history, heritability, and other genetic epidemiological sources of information either singularly or in tandem with molecular genetic information [12, 13]. Nonmolecular information is still relevant, even in a “genomics” era, as it may present genetic information in a more readily accessible form. This improves the likelihood of stakeholder understanding [12, 148], thereby reducing a significant barrier to the translation of genetic information for psychiatric disorders. For example, nonmolecular genetic information like family history could be used to identify at-risk persons (similar to Meiser et al. [149]) who are then targeted for behavioral interventions. Such a translational pipeline would be a natural extension of work done by psychiatric genetic counselors who provide patients and family members with genetic information about schizophrenia [5, 6].

Molecular Genomic Information

Research that discuss the translation of molecular psychiatric genetic information is typically done via a review [16, 43, 44, 46–48, 50–52, 62–64, 66, 69, 71, 73, 74, 76–82, 84–89, 93, 96, 97, 99, 101, 102, 104–107, 120, 127, 138]; few experimental articles exist (see Part 4 below). Reviews often include potential ways that molecular genomic information could help the field. Topics of interest range from summarizing different aspects of precision medicine, such as the pharmacogenetics of alcohol use disorder [101] and genetic testing for autism spectrum disorder (ASD) [89], to outlining clinical barriers to precision

medicine in psychiatry such as lack of evidence and training [81, 143] (see Part 3 for a discussion of specific psychiatric disorders studied).

Such research often discusses molecular genomics in a broad context with few or no specific examples of copy number variants, genome-wide association findings, or polygenic risk scores [45, 54, 55, 59, 72, 90, 100, 103, 108–111, 116, 119, 123–125, 128, 129, 150–153], but there is a recent trend of reviewing specific biomarkers and potentially actionable molecular variants (e.g., for gene-drug interactions) in-depth [53, 56–58, 61, 82, 83, 112, 114, 115, 117, 118, 121, 122, 131, 144, 154]. For example, Bousman, et al. [115] provided a review of the gene-drug interactions of 91 psychotropic drugs and 16 genetic variants across 5 genes, giving rationale for listing those 16 variants as the minimum panel for pharmacogenetics testing. There is also a growing trend of including or focusing on epigenetics (the study of gene expression) [53, 56, 61, 65, 70, 80, 101, 116, 118, 153]. Luoni and Riva [65], for example, provided a nice overview of the mechanisms that regulate miRNA biogenesis and the possibility of using that as a biological target in pharmacological interventions for psychiatric disorders.

Nonmolecular Genetic Information

The research on translating the genetic epidemiology of psychiatric disorders [5, 6, 126, 139, 140, 142, 155] is scarce. Occasionally, the translation of both genetic epidemiology and molecular genomics are discussed together [75, 153, 156, 157]. Rende and Slomkowski [155] stand out for providing a rare behavioral genetic perspective by discussing the rationale for using a family design for studying the translation of genetic risk for disorders. Such a design can offer a fuller picture of a disorder and subsequent translation to clinical care by incorporating both genetic and environmental information. Bulik et al. [158] further discussed the importance of psychiatric genetic counseling for eating disorders, a field that focuses on family history and other genetic epidemiological information because molecular information is not yet actionable. However, if non-genomic information is mentioned in the context of translating psychiatric genetic information, it is typically done so in passing, such as mentioning heritability or family history in the introduction but not how that information can also be used in clinical care (e.g., Foley et al. [120] and Gandal et al. [76]). On the one hand, this is a missed opportunity because genetic epidemiological information can be more quickly and easily translated. On the other hand, rigorous research is needed to show that inclusion of information such as family

history in prevention or intervention efforts is useful. Such research is underway in psychiatric genetic counseling centers [9, 158]. However, the field would benefit from more widespread examination of translating non-molecular genetic information.

Summary: Part 2

There is a need to investigate how and when to translate all psychiatric genetic information. To date, there is a demonstrable bottleneck in the literature, where researchers rely on molecular genomic information when reflecting on psychiatric genetics translation. While important, this ignores other genetic information that could improve patient care and prevention efforts. Given that the future of uncovering the molecular genomic basis of psychiatric disorders is unclear, it is urgent to include genetic epidemiological information in translational efforts.

Part 3: Prioritizing Certain Psychiatric Disorders

So far, each bottleneck has been subsumed by and entwined with the previous one. That trend continues with these last 2 bottlenecks. The third one noted among translational psychiatric genetic research is that certain psychiatric disorders are prioritized over others. This likely stems from the emphasis on linear translational frameworks and reliance on molecular genomic information, because the psychiatric disorders that are most often studied are those for which researchers have uncovered the most genetic markers. Overall, a wide range of psychiatric disorders are represented in the literature – some are individually discussed and others are discussed in combination with other disorders. Comorbidity is sometimes mentioned [69, 76, 90, 130, 156], and there are also broad discussions of psychopathology [44, 58, 59, 67, 77, 108–112, 130, 144, 153, 159]. Yet, there is a higher representation of disorders for which the most known genetic variants have been discovered to date. These include schizophrenia, ASD, and mood disorders [45, 51, 53–56, 60, 64, 69, 71, 73, 75–80, 89, 94–97, 100, 102, 103, 107, 113, 114, 116, 118, 119, 122, 126, 127, 143, 156, 157, 160]. This comes as no surprise, but it must be noted that even for disorders such as schizophrenia and bipolar disorder, the genetic variants known are not clinically actionable due to how little genetic variance they account for [34]. This tendency to primarily discuss disorders such as schizophrenia and mood disorders (i.e., the disorders for which the most genetic information is available) may serve to

perpetuate the assumption about the generalizability of linear views of translation as well as the disproportionate emphasis toward molecular genetic information, as discussed above (Parts 1 and 2). Often such articles are reviews, which align with the bottleneck discussed in Part 4 below. For example, Ozomaro and colleagues [80] provided a review of the genetics, epigenetics, and endophenotypes of major depressive disorder, bipolar disorder, and schizophrenia, stating that the groundwork is being laid for precision medicine in psychiatry and that such precision medicine will have an emphasis on biomarkers and imaging.

Other disorders for which the translational applicability of their genetic information has been studied include alcohol use/substance use disorder and other addictions [46, 48, 49, 57, 61, 77, 82, 84–86, 91, 99, 101, 121, 124, 131, 141, 145, 151, 152], anxiety [52, 113, 117, 118, 156, 161], suicide [98], post-traumatic stress disorder [66, 156], stress [50, 67], attention deficit hyperactivity disorder [55, 118, 123], and eating disorders [158]. Even though these disorders have fewer known genetic markers than schizophrenia, ASD, or mood disorders, most of this research discusses how the few known markers can make a difference. Malter and colleagues [50] discussed the role of the *BDNF* gene in anxiety and stress and how it can aid in bench-to-bedside translation by bridging human behavioral and imaging genetics with animal models. Similarly, Chen and colleagues [82] reviewed how identifying biomarkers that affect treatment response to smoking cessation can aid in precision medicine of nicotine addiction.

Summary: Part 3

Psychiatric disorders for which the most genomic information is known, specifically schizophrenia, ASD, and mood disorders, dominate the discussion of translating psychiatric genetic information. This is disproportionate to which disorders are most common in the population. Other internalizing disorders such as anxiety and stress are highly prevalent, and thus, psychiatric genetic translational efforts should actively strive to include a wider range of disorders so that more patients can benefit from this research.

Part 4: Publishing More Reviews than Experiments

The final bottleneck that is enmeshed with the other 3 is that published articles focus more on reviews than on experiments. This might be expected given the long delay

between research and practice in linear frameworks such as bench-to-bedside; reviews are easier and faster to generate. To our knowledge, only 14 experimental articles address the translation of psychiatric genetic information [5, 6, 49, 60, 91, 92, 94, 98, 113, 114, 130, 145, 151, 162]. There is heterogeneity among these articles. For example, Costain and colleagues [5] provided genetic counseling to individuals who had previously been diagnosed with schizophrenia as well as their family members [6]. They noted that perception of recurrent risk improved along with knowledge and etiological attribution about schizophrenia while stigma reduced. Lee and colleagues [94] developed a person-centered algorithm to identify individual patients with schizophrenia who will respond to antipsychotic medications based on molecular markers. Niculescu and colleagues [98] found biomarkers associated with suicide as well as subtypes of suicide (high anxiety, low mood, both, non-affective) that will hopefully improve precision medicine for suicide. Finally, Bradley and colleagues [113] addressed drug metabolism of psychiatric drugs from a pharmacogenomic perspective, offering actionable precision medicine insights.

Summary: Part 4

Many published articles discuss the potential of translating psychiatric genetic information. Few articles conduct novel experimental research that seeks to move the field of translating psychiatric genetics forward. Specifically, ~12% of articles included in this review were experimental. This is more than Holmes and colleagues' [163] critique of personalized medicine where they found that the ratio of reviews/commentaries to experimental articles is 25:1 (4%), but ~12% is still a low percentage. While it is important to thoroughly discuss translation, it is also necessary to test theories, models, frameworks, and approaches. Only through experimental research we will truly understand the optimal translational framework for each type of psychiatric genetic information and each psychiatric disorder.

Conclusions

The current narrative review examined the state of translating psychiatric genetic information into clinical care. This was done by dissecting 4 bottlenecks among translational psychiatric genetic research. These bottlenecks were emphasizing linear translational frameworks, relying on molecular genomic findings, prioritizing certain psychiatric disorders, and publishing more reviews than

experiments. They are closely entwined, with each subsequent bottleneck subsumed by the previous one. The purpose of this review was not to condemn these bottlenecks but to highlight them and encourage that a balance be struck in the field. Linear translational frameworks (bench-to-bedside and precision medicine) are not inherently inappropriate for translating psychiatric genetic information, but given that they have had little success to date, it is worth exploring nonlinear, ecological frameworks such as D&I. The same is true for relying on molecular genomic findings. For example, it is possible that polygenic risk scores will have clinical implications but likely not for many years [164]. Translating nonmolecular, epidemiological genetic information such as family history, heritability, and etiological attribution would be relatively simpler than translating genomic information due to the fact that this information is already known for all psychiatric disorders. If both of these bottlenecks are overcome, then this will likely lead to more breadth and depth in the types of psychiatric disorders that are studied. Conversely, it is possible that an initial focus on translating psychiatric genetic information on a wider range of disorders (e.g., anxiety, eating disorders, suicide, and alcohol use) will help to break the first 2 bottlenecks. It also cannot be emphasized enough that original experimental research needs to be done in this area. Both quantitative and qualitative research is needed, ideally after partnerships with community members and local clinics are established. This will ensure that the clinical utility of psychiatric genetics is thoroughly assessed. Finally, it bears repeating that funding and policy shifts need to occur to allow these bottlenecks to be fully fixed at the research level.

Hopefully, this review can help stakeholders to reflect upon the framework(s) that they utilize when translating psychiatric genetic information and, when appropriate, seek out less-studied frameworks, less-utilized genetic information, and less-examined psychiatric disorders in an experimental project. Thus, this review has direct implications for all stakeholders involved in psychiatric disorder research and/or clinical care, most immediately for researchers and clinicians. Such future research will help the field to outline which frameworks are best for which psychiatric disorders and for which types of genetic information. This will require increasing knowledge and competence of these 4 interrelated topics (translational frameworks, genetic information, psychiatric disorders, and study design) among stakeholders as well as continued open discussion about this topic. The time is right for such a shift; it is our obligation to determine the best ways to translate psychiatric genetic information.

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Statement of Ethics

This study is in compliance with ethical standards; no human or animal subjects were part of this study. The authors followed all ethical guidelines, such as but not limited to disclosing all funding and conflicts of interest, avoiding plagiarism, and following guidelines for authorship.

Conflict of Interest Statement

None of the authors have any conflicts of interest to disclose.

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Public Significance Statement

Translation of psychiatric genetic information has been limited, but thorough reflection and balance of 4 key bottlenecks may bring progress. Stakeholders should note the translational framework that they utilize, the type of genetic information and psychiatric disorder that they study, and whether they publish experimental studies or reviews.

Author Contributions

J.L.B. gathered articles for the review. J.L.B., R.A.D., and E.C.L. reviewed the articles. J.L.B. wrote the first draft. R.A.D. and E.C.L. provided editorial feedback and guidance. All authors have seen and approved the final version of the manuscript being submitted.

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