Polygenic risk scores for genetic counseling in psychiatry: Lessons learned from other fields of medicine

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ARTICLE INFO

Keywords:
- Polygenic risk score
- Genetic counseling
- Genetic testing
- Psychiatry
- Breast cancer
- Cardiovascular disease
- Alzheimer’s disease

ABSTRACT

Polygenic risk scores (PRS) may aid in the identification of individuals at-risk for psychiatric disorders, treatment optimization, and increase in prognostic accuracy. PRS may also add significant value to genetic counseling. Thus far, integration of PRSs in genetic counseling sessions remains problematic because of uncertainties in risk prediction and other concerns. Here, we review the current utility of PRSs in the context of clinical psychiatry. By comprehensively appraising the literature in other fields of medicine including breast cancer, Alzheimer’s Disease, and cardiovascular disease, we outline several lessons learned that could be applied to future studies and may thus benefit the incorporation of PRS in psychiatric genetic counseling. These include integrating PRS with environmental factors (e.g. lifestyle), setting up large-scale studies, and applying reproducible methods allowing for cross-validation between cohorts. We conclude that psychiatry may benefit from experiences in these fields. PRS may in future have a role in genetic counseling in clinical psychiatric practice, by advancing prevention strategies and treatment decision-making, thus promoting quality of life for (potentially) affected individuals.

1. Introduction

Psychiatric disorders are highly prevalent across the globe. In the United States (US) alone, psychiatric disorders affect 11 million adults (Booke et al., 2020). For example, 1 % of the general population is affected by schizophrenia, 1 % by bipolar disorder, and 10 % of men and 25 % of women suffer from major depression at least once in their lifetime (Inglis et al., 2015). Psychiatric disorders are complex and polygenic disorders, with genetic and environmental factors contributing to their susceptibility. It is currently hypothesized that common variants with small effects as well as some rare variants with larger effects underlie mental illness at a population level (Inglis et al., 2015). This complex etiology often results in misunderstanding the cause of the disorder by patients and family members and in overestimations of the genetic contribution to the disorder (Booke et al., 2020; Austin et al., 2006). Gaps in understanding the etiology of their mental illness may cause people to come up with their own explanatory model, which can result in unnecessary senses of guilt and shame (Booke et al., 2020; Inglis et al., 2015). These feelings may impact negatively on treatment motivation and increase risk behavior, and may needlessly deter people from having offspring (Booke et al., 2020). There is evidence that people with a mental illness are able to adapt to more positive health behaviors when accurate information is provided (Leventhal et al., 1997). Genetic counseling is especially designed to help people understand the origin and genetics of their psychiatric disorder. In counseling sessions possible misconceptions are explored, health-enhancing behavior is encouraged, a patient’s sense of control over their disorder is strengthened, and feelings of guilt and shame are discussed and when possible reduced (Amir et al., 2010). The definition of genetic counseling according to The National Society of Genetic Counselors from the US declares: “Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources and research; counseling to promote informed choices and adaptation to the risk or condition.”

Previously, genetic counseling was only provided to families

https://doi.org/10.1016/j.neubiorev.2020.11.021
Received 27 August 2020; Received in revised form 17 November 2020; Accepted 27 November 2020
Available online 7 December 2020
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suffering from Mendelian disorders or other complex illnesses, such as heritable breast cancer, for which genetic susceptibility testing is available (Austin and Honer, 2008). Psychiatric disorders do not generally display a Mendelian inheritance pattern (Inglis et al., 2015; Austin and Honer, 2008). Nevertheless, nowadays genetic counseling in psychiatry is available in the clinic and can be used to estimate recurrence risks in patients and family members, as well as to inform about the origins of the disorder, and how to treat the disorder and improve prognosis (Hoehe and Morris-Rosendahl, 2018; Skirton and Eiser, 2003). Here, we review the current utility of polygenic risk scores (PRSs) in the context of clinical psychiatry. By comprehensively collecting and then appraising literature on PRS in psychiatry and in other fields of medicine, we outline several lessons learned that may benefit the incorporation of PRS in psychiatric genetic counseling.

### Research into context

#### Evidence before this study

We reviewed the literature on the use of polygenic risk scores (PRSs) in genetic counseling for psychiatric disorders. PubMed was used to search for all articles published using the following terms: “PRS OR “polygenic risk score” AND psychiatry” and “(PRS OR “polygenic risk score”) AND (schizophreni* OR MDD OR bipolar)”. Only a few articles were relevant and explained how PRSs have been investigated in psychiatry and what the clinical utility of PRs could be. We found that genetic counseling is beneficial for affected individuals and their family members in terms of outcomes such as improved understanding of their disease and risk perception as well as reduced guilt and stigma associated with psychiatric disorders. In addition, genomic tests may be available in some clinics for particularly autism spectrum disorders and intellectual disability, but for mental disorders the accuracy of risk prediction and PRSs is not as high as needed in genetic counseling. Previous work on the use of PRSs in other specialties, such as breast cancer, Alzheimer’s Disease (AD), and cardiovascular disease (CVD), was then reviewed. PubMed was used to search for relevant articles using the following terms: “PRS OR “polygenic risk score” AND breast cancer” and “(PRS OR “polygenic risk score”) AND Alzheimer” and “(PRS OR “polygenic risk score”) AND cardiovascular disease”. In the articles we reviewed it became apparent that PRS is better implemented in these specialties than in psychiatry and that PRS risk prediction accuracy is higher for these diseases than for psychiatric disorders.

#### Added value of this study

This study examines how psychiatry could benefit from lessons learned in other specialties, to optimize the use of PRS for genetic counseling in psychiatry. For the first time, this review combines information and research from psychiatry and other specialties to study the clinical potential of PRSs in genetic counseling in psychiatry. Knowledge from other specialties is used to understand how the use of PRSs could be improved in psychiatry.

### Implications of all the available evidence

This review summarizes existing evidence reporting on the use of PRSs in psychiatry and other specialties. The findings currently do no support the use of PRSs for risk prediction in psychiatry. PRS risk prediction in psychiatry is less accurate than in other fields of medicine, e.g., breast cancer, AD, and CVD. Lessons to be learned from those three fields of medicine include the importance of environmental factors, of large-scale studies and of reproducible methods allowing for cross-validation between cohorts. Ultimately, the use of PRSs in genetic counseling for psychiatric disorders may facilitate personalized prevention and treatment strategies.

### 2. Process of genetic counseling in psychiatry

The process of genetic counseling in psychiatry has been described extensively (Austin, 2020; Austin and Honer, 2007). Genetic counseling is a dynamic process and consists of two wide-ranging phases: information gathering and information provision and support (Fig. 1) (Austin, 2020; Austin and Honer, 2007). Information gathering is divided into three steps: identification of needs, identification of the disease construct, and family history. In the first step the counselor should identify the needs of the individual. There are many reasons why people seek genetic counseling, such as to receive information about recurrence risks or to obtain explanations for why one developed the disease (Austin and Honer, 2007). Family members may also seek counseling, for example because of concerns about their own risk of developing mental illness. In the second step the disease construct is identified. This knowledge needs to be obtained to provide information about the origin of the disease (Austin, 2020; Austin and Honer, 2007). The third step is obtaining the family history. Information regarding substance abuse, medication use, hospitalization, learning difficulties, and death causes of family members should also be obtained (Austin and Honer, 2007). The acquired information can be used for risk assessment and may reveal the presence of a genetic syndrome underlying the psychiatric disorder (Estrov et al., 2000; Bassett and Chow, 1999). For example, it is known that 2 % of individuals with schizophrenia have 22q11.2 deletion syndrome (Bassett and Chow, 1999). If a genetic syndrome is found, the patient may be referred to a medical genetics program in order to

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Fig. 1. Steps in the process of genetic counseling in psychiatry.

(continued)
arrange a complete assessment (Austin and Honer, 2007). Furthermore, the family history is also used for risk assessment (Austin and Honer, 2007).

During counseling sessions, information is provided in four components: etiology (most extensively discussed), recurrence risks, decision-making support, and follow-up support (Austin and Honer, 2007). The counselor typically discusses the importance of the genetic and environmental factors for the pathogenesis of the illness. This discussion should be done in simple language understandable for laymen and should explain current knowledge, ongoing research about the pathogenesis of the illness, and options for genetic testing. In addition, it is important to discuss feelings of doubt a patient or family member may have for decision-making in such a way that they can explore all options in a safe and comfortable environment. Experience when appraising such information. The second component is the discussion of recurrence risks whenever deemed appropriate by the patient, family, or counselor. These risks are typically provided by the counselor as an estimate of the probability that the person will be unaffected as well as the chance that the person will be affected, in context of population rates (Inglis et al., 2017; Austin et al., 2006). Nevertheless, it should be noted that there are limitations to the estimation of the recurrence risk, as it is usually based on empirical data derived from twin studies and in familial disease probability. Next, the counselor provides decision-making support to the patient, for example when the patient has to make decisions regarding the treatment of their illness (Austin and Honer, 2007). Lastly, the counselor grants follow-up support and counseling (Hodgkinson et al., 2001). Usually, this is done by providing a follow-up letter discussing the information given during the counseling session(s). This information may be shared with family members and family doctors. Furthermore, the process of psychiatric genetic counseling has evolved throughout the years and may be even more helpful nowadays, as the underlying genetics are better understood these days.

3. Who should receive psychiatric genetic counseling?

There is a wide range of people who may wish to receive and may benefit from psychiatric genetic counseling. First, generally most individuals with psychiatric disorders indicate that they would like to receive genetic counseling (Lyus, 2007; DeLisi and Bertsch, 2006; Quaid et al., 2001; Schulz et al., 1982). Besides affected individuals in general, potential candidates for genetic counseling are affected individuals and their partners who are planning to have children (Austin and Honer, 2007). In these counseling sessions, concerns like recurrence risk for the child and pregnancy-associated risks, such as medication use during pregnancy and the possible effects of pregnancy on the mental health of the affected individual, are discussed (Inglis et al., 2017). The counselor may provide these individuals with information and support for decision-making in such a way that they can explore all options in a safe environment and make a well-informed decision (Viguera et al., 2002).

Another group of affected individuals who could benefit greatly from genetic counseling are individuals who maintain risky behaviors, such as non-adherence to treatment and substance use disorders (SUDs) (Austin and Honer, 2007). This risk behavior is often a result of the belief that current actions of the individual cannot influence the course of their psychiatric disorder (Austin and Honer, 2007). To reshape such reasoning and often ensuing behavior, individuals need to be informed about genetic vulnerability. Counseling can help the affected individual obtain a greater sense of personal control over their psychiatric disorder, which can boost health-enhancing behaviors (Gemm et al., 2004) and improve effectiveness of coping strategies (Austin and Honer, 2007). Furthermore, family members of affected individuals may also be in need of receiving genetic counseling (Lyus, 2007; DeLisi and Bertsch, 2006; Quaid et al., 2001; Schulz et al., 1982). A lack of understanding of the etiology of the psychiatric disorder contributes to feelings of guilt and shame that parents and siblings often experience (Austin and Honer, 2007). By reducing the concerns and feelings of guilt and shame, coping abilities of parents and siblings can be improved and the disease burden and possible conflicts in the family may be decreased (Swallow and Jacoby, 2001; Magliano et al., 2000). Lastly, adoptive parents of children with affected biological parents may also seek genetic counseling to receive information about recurrence risks (Austin and Peay, 2006).

4. Outcomes of genetic counseling in psychiatry so far

Multiple studies have evaluated the effects of genetic counseling in psychiatry and have shown that it is beneficial to affected individuals and their family members (Moldovan et al., 2017). First, genetic counseling has a positive impact on patients’ understanding of their disease and their risk perception (Moldovan et al., 2017; Hippman et al., 2016). In addition, of all patients receiving genetic counseling, over 85% indicated that they “felt better” afterwards and 90 % indicated that the counseling was greatly valued (Costain et al., 2014a). Moreover, family members of patients expressed similar levels of satisfaction (Costain et al., 2014b). Furthermore, another study reported that 100% of the participating parents of patients felt that a genetic counseling session was beneficial to them as it improved their knowledge about the psychiatric disorder and reduced concerns about recurrence risks (Austin and Honer, 2008). In addition, genetic counseling may also reduce the guilt and stigma associated with having a psychiatric disorder (Austin and Honer, 2007). Stigma may lead to increased social isolation, worsening of medical conditions, and decreased quality of life (Austin and Honer, 2007). By reducing stigma, adherence to treatment can be improved and self-care behaviors can be promoted (Austin and Honer, 2007; Semaka and Austin, 2019). Nevertheless, genetic testing and genetic counseling may come with undesired effects. Affected individuals and family members often expect simple and clear answers after being genetically tested, but usually receive inconclusive genetic test results. This can result in frustration and in the feeling that genetic counseling is less useful when there are higher levels of uncertainty (Hippman et al., 2013). Thus, genetic counseling can have a positive effect on affected individuals and their family members, but research on genetic testing and risk assessment is needed to help (future) affected individuals in the best way possible.

5. Genetic testing of rare variants and CNVs in psychiatry

Over the last decades, researchers have tried to determine the underlying molecular origins of psychiatric disorders. When the pathogenesis of a psychiatric disorder is known, it may facilitate a more accurate diagnosis and risk prediction. However, psychiatric disorders are typically highly polygenic disorders (Hohe and Morris-Rosendahl, 2018). Various genes and variants are involved, which all have a small impact on risk, and these are solely neither necessary nor sufficient to give rise to the disorder. This results in difficulties in interpretation of findings at the level of the individual. The International Society of Psychiatric Genetics (ISPG) does not currently recommend the use of genetic testing for diagnosis and risk prediction (Genetic Testing Statement, 2019). Nonetheless, there are a few situations in which clinical genetic testing may be beneficial. For example, the introduction of next-generation sequencing (NGS) has allowed the use of gene panels and whole-exome sequencing (WES) in the clinic (Hohe and Morris-Rosendahl, 2018). As soon as the genes involved in a psychiatric disorder are identified, the risk of the disorder can be determined using multiple-gene panel tests to test for pre-selected disease-specific genes (Pavel et al., 2010). The use of gene panels is the cheapest and fastest NGS testing option and is already clinically and commercially available and could be relevant for a small subgroup of patients (Osmou and Wolanynzyk, 2017). Furthermore, WES is used to sequence all coding exons in the human genome and allows identification of rare variations (Hohe and Morris-Rosendahl, 2018). In previous WES studies, de novo mutations were found in individuals with schizophrenia (Froemer et al., 2014; Xu et al., 2012). Pathogenic variants that cause a disruption in
these genes can have a significant impact on the risk of psychiatric disorders. Clinically, nearly all of these relevant variants are found in the coding regions of the genome (Demkow and Wolanczyk, 2017). Furthermore, analyzing rare or de novo copy number variants (CNVs) also has the potential to be used in the clinic. Over the years, CNVs associated with an increased risk for psychiatric disorders have been identified using mostly genome-wide association studies (GWASs) (Hohe and Morris-Rosendahl, 2018). These deletions or duplications at specific chromosomal locations can result in a loss or gain of function of genes and may have deleterious effects on brain function (Gershon and Allye-Rodriguez, 2013). Moreover, individuals with autism and schizophrenia display an increased mutation rate of de novo CNVs of 7.2 % and 6.1 % respectively, while controls have a rate of about 1.0 % (Gershon and Allye-Rodriguez, 2013). Furthermore, CNVs account for 2–4 % of the cases of schizophrenia and about 8 % of autism cases (Ye et al., 2012; Gilman et al., 2011). Even though CNVs are individually rare in psychiatric disorders, the net effects may be substantial. In some cases of psychiatric disorders it may be helpful to identify pathogenic CNVs as they may provide information about recurrence risks and may help affected individuals and their family members to improve their understanding of the etiology.

6. PRS for psychiatric disorders (Table 1)

The aforementioned tests to detect rare variants and CNVs may be used to estimate the susceptibility of an individual to a disease, also known as risk prediction. In the past, clinical risk prediction was based on basic demographic characteristics (e.g., age, gender), health parameters (e.g., body mass index), lifestyle factors (e.g., alcohol consumption, smoking, physical exercise), clinical risk factors (e.g., blood pressure levels), environmental exposures (e.g., environmental toxins), and family history (Torkamani et al., 2018). Genomic analysis has often been absent from this list, but is of interest for risk prediction (Torkamani et al., 2018). Genomic analysis based on the calculation of a PRS is believed to have high potential in clinical practice. Over recent years, PRSs have not yet been used in clinical settings, but have been of high interest in research (Visscher et al., 2017). A PRS is a continuous measure which provides an individual with an estimate of the genetic liability to a certain disease; it is the sum of the number of risk alleles carried by the individual, where the allele weights are defined by the measured effects in a GWAS of a different sample (Coombes and Bierncacka, 2019). The clinical utility of PRSs is usually assessed by determining if it, together with clinical risk factors, divides the population into distinct tiers of absolute risk on which clinical and personal decision-making can be based (Torkamani et al., 2018). These tiers of risk are usually risk deciles or quintiles and also enable assessment of cross-treat risks (McLaughlin et al., 2017). As many genes are associated with not only one disorder, but with two or more, PRS analysis is often used to assess polygenic overlap between psychiatric disorders (Schipjen et al., 2019). For example, 2.4 % of the phenotypic variance in bipolar disorder can be explained by the schizophrenia PRS (Schipjen et al., 2019). Furthermore, people in the highest PRS centile versus those in the lowest PRS centile have an odds ratio of 44 to develop schizophrenia (95 % confidence interval = 31–63) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2020). However, predicting diagnosis in the general population cannot be done using only PRS. Nonetheless, PRS is of great use as a quantitative estimate of genetic liability to schizophrenia. For example, it could be used for patient stratification or PRSs may provide clues to potential cross-disorder therapeutic targets, enabling drug repositioning, i.e., reusing licensed drugs for new indications (Hodgkinson et al., 2001; Hohe and Morris-Rosendahl, 2018). Moreover, individuals with bipolar affective disorder with a low PRS for schizophrenia respond better to lithium treatment than patients with a high schizophrenia PRS (Amare et al., 2018). Therefore, PRSs may also be of interest for prediction of treatment response. Currently, we are unable to accurately predict the course of psychiatric disorders in affected individuals (Schipjen et al., 2019). However, people with first-episode psychosis who were later diagnosed with schizophrenia versus people with first-episode psychosis who were later diagnosed with another psychotic disorder have a significantly higher schizophrenia PRS (Vassos et al., 2017). This suggests that PRSs might allow identification of at-risk individuals for schizophrenia and other psychiatric disorders. Nevertheless, the clinical utility of PRSs depends on the kind of disease (Schipjen et al., 2019). In addition, as GWAS sample sizes increase in the future, better effect estimates for single nucleotide polymorphisms (SNPs) can be developed, which can improve the accuracy of PRSs (Schipjen et al., 2019). Furthermore, the odds ratios of PRSs currently come with large confidence intervals, at some times relatively low accuracy (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Vivian-Griffiths et al., 2019). This accuracy is based on the Area Under the Curve (AUC), which quantifies a model’s discriminatory accuracy (Amir et al., 2010). An AUC of 0.5 suggests that the model has no discriminatory ability, while an AUC of 1.0 indicates a perfect discriminatory ability (Amir et al., 2010). Moreover, a model with an AUC of 0.7–0.8 is considered to have a good discriminatory ability. The most recent GWAS of schizophrenia reports such an AUC as (0.71).

To comprehensively collect studies done on the use of PRS in psychiatry, PubMed was used to search for all published articles on the use of PRSs in psychiatry using the following terms: “(PRS OR “polygenic risk score”) AND psychiatrist”.” The search results displayed over 600 research papers on PRSs in psychiatry. Although one study reports a prediction accuracy in schizophrenia of 82 % (AUC = 0.82), most risk prediction models in psychiatry currently display low accuracy (Table 1) (So and Sham, 2017). For example, the PRS risk prediction accuracy in schizophrenia in one study was 62 % (AUC = 0.62), which illustrates the relatively low accuracy of risk prediction models in psychiatry (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In addition, the prediction accuracy is even lower in other psychiatric disorders, such as major depression disorder (58.5 %, AUC = 0.585) (So and Sham, 2017). Importantly, the reproducibility of PRS research is restricted due to underreporting of key PRS information, e.g., about one third of papers on PRS does not report sufficient variant information (Lambert et al., 2020). In addition, researchers use different variables in their prediction models. For example, some may use age and sex while others may include just one of those. Therefore, it is desirable that consensus is reached and that the same variables are used in all prediction models. To solve this issue, the Polygenic Score Catalog (www.PGSCatalog.org), an open resource of published source data allowing researchers to generate PRSs, was created. Currently, it contains 338 metadata and scoring files (risk variants, effect alleles/weights) needed to calculate your own PRS of 125 traits. About 4 % of these PRSs are for psychiatric disorders, facilitating the re-use and evaluation of PRSs, thereby establishing their predictive ability in the future and promoting further research to study the clinical utility of PRS in psychiatry.

7. Genetic testing and counseling in other medical specialties: lessons learned (Table 1 and Fig. 2)

In some medical specialties, genetic counseling is more developed than in psychiatry, e.g., breast cancer in oncology, Alzheimer’s Disease (AD) in neurology, and cardiovascular disease (CVD) in cardiology. We reasoned that given the recent advances achieved in those specialties with regards to PRS in clinical practice, by critically appraising the literature available for these fields lessons may be learned for the field psychiatry with regards to the possible clinical implementation of PRS. To that end, we performed PubMed searches, using the search terms (PRS OR “polygenic risk score”) AND (“breast cancer” OR Alzheimer OR “cardiovascular disease”). We list the lessons learned from that body of literature below and summarize recommendations in Fig. 2.
7.1. Lessons learned from the field of breast cancer

In the field of hereditary breast and ovarian cancer, screening as well as genetic testing and counseling is promoted by several medical associations (Allen et al., 2019). The hereditary breast and ovarian cancer syndrome is a cancer syndrome in which breast and ovarian cancer develop as a result of inherited BRCA1/2 mutations (Lynch et al., 2015). Therefore, individuals with BRCA1/2 mutations are at high risk of developing breast and ovarian cancer. Although underused, genetic testing is available to such at-risk individuals and several companies offer these tests (Lynch et al., 2015). Besides BRCA1/2 mutations, there are other genes that are also associated with an increased risk of breast cancer (Campeau et al., 2008). Although only few of these genes on their own are appropriate for genomic analysis, the effects of these genes together with other genetic risk factors may be combined into PRSs and thus be used for future predictive testing in the clinic. A risk prediction model including breast cancer PRS and other known risk factors can identify 16% of the population in the US that is recommended to start screening at 40 years of age instead of 50 years (Maas et al., 2016). Moreover, chemoprevention and risk-reducing surgeries (e.g., mastectomy) are used to prevent that healthy women with a BRCA1/2 mutation develop cancer (Kuchenbaecker et al., 2017). As such decisions may weigh heavily on individuals, personal risk estimations may improve the decision-making process. Moreover, individuals who carry the BRCA1 mutation and have a low PRS for breast cancer risk have a 21% absolute risk of breast cancer by the age of 50 years and a 56% absolute risk by the age of 80 years (Kuchenbaecker et al., 2017). In contrast, individuals with a high PRS for breast cancer risk have a 39% absolute risk of breast cancer by the age of 80 years (Kuchenbaecker et al., 2017).

### Table 1

Overview of PRS risk prediction accuracy in several fields of medicine.

| Disease              | Study                                             | Name cohort                                                                 | Location cohort                          | Sample size (case + control) | AUC  |
|----------------------|---------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------|-------------------------------|------|
| Breast cancer        | Terry et al. (2019)                               | Breast Cancer Prospective Family Study Cohort (ProF-SC)                     | Australia, Canada, US                    | 18 856                        | 0.7  |
|                      | Fischer et al. (2013)                             | German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC)        | Germany                                  | 7352                          | 0.81 |
|                      | Macinnis et al. (2013)                            | Australian Breast Cancer Family Registry (ABCFR)                            | Australia                                | 4176                          | 0.7  |
|                      | Eccott-Price et al. (2015)                        | Subset of Genetic and Environmental Risk in Alzheimer’s Disease (GERAD)        | Europe and US                            | 4603                          | 0.782|
|                      | Chaudhary et al. (2019)                           | Drugs for Dementia Research (BDR)                                           | United Kingdom                           | 439                           | 0.825|
|                      | Eccott-Price et al. (2017a)                       | GERAD consortium*                                                            | Europe and US                            | 7139                          | 0.76 |
|                      | D’Agostino et al. (2008)                          | The Framingham study and The Framingham offspring study                     | US                                        | 8491                          | 0.79 |
|                      | Harari et al. (2017)                              | Cardiovascular Occupational Risk Determination in Israel Study (CORDIS)      | Israel                                    | 4089                          | 0.815|
|                      | Hippisley-Cox et al. (2007)                       | QRESEARCH database                                                           | United Kingdom                           | 283 174                      | 0.77 |
|                      | Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) | (Part of the) SGENE-plus and follow-up samples                              | Denmark (Aarhus)                         | 1790                          | 0.62 |
|                      | So and Sham (2017)                                | Dataset from meta-analysis of GWAS study from Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) | Europe and East-Asia                     | 79 845                        | 0.82 |
|                      | Vivian-Griffiths et al. (2019)                    | CLOZUK                                                                     | United Kingdom                           | 11 853                        | 0.66 |

AUC = Area Under the Curve.

*Part of the International Genomics of Alzheimer’s Project (IGAP) that compromises four datasets: Alzheimer’s Disease Genetic consortium (ADGC), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), European Alzheimer’s Disease Initiative (EADI), and the Genetic and Environmental Risk in Alzheimer’s Disease (GERAD).
cancer at the age of 50 years and a 75 % absolute risk at the age of 80 years. Furthermore, women who are in the lowest PRS decile have an estimated odds ratio for developing breast cancer of 0.32 (95% confidence interval = 0.25 to 0.40) compared to women in the middle PRS decile; women in the highest PRS decile have an estimated odds ratio of 3.36 (95% confidence interval = 2.95–3.83) compared to women in the middle PRS decile (Mavaddat et al., 2015). Family history plays an important role in these risk estimates as women without a family history of breast cancer in the lowest PRS decile have a 5.2% risk and a 16.6% risk in the highest PRS decile (Mavaddat et al., 2015). In contrast, women with a family history of breast cancer have an 8.6% and 24.4% risk in the lowest and highest PRS decile, respectively. Besides a higher lifetime risk, the age of onset is lower for women with a family history of breast cancer (Mavaddat et al., 2015). In the field of breast cancer, multiple risk prediction models are available (Terry et al., 2019). BOADICEA (Breast and Ovarian analysis of Disease Incidence and Carrier Estimation Algorithm) is such a risk prediction model of breast and ovarian cancer (Lee et al., 2019). The CanRisk tool (www.canrisk.org) is a new interface to BOADICEA, a model that provides a reliable breast cancer risk prediction in healthy women (Lee et al., 2019). This web application is a user-friendly tool and is already widely used in genetic counseling in breast cancer in 450 countries (Lee et al., 2014). To calculate the breast cancer risk, pedigree data and model parameters (i.e., BRCA1/2 mutation frequency, BRCA1/2 mutation search sensitivity, cancer incidence rates, and output data display format) have to be uploaded. An important advantage of this model is that it combines rare genetic variants, common variants (by using PRSs), full family history, and other known risk factors into one prediction model (Lee et al., 2019). This model has been validated by multiple studies demonstrating a good accuracy up to 81% (AUC = 0.81) (Terry et al., 2019; Fischer et al., 2013; Macinnis et al., 2013). Large-scale studies and reproducible methods seem to play an important role in validation of these models. In addition, similarly to the PGS catalog, a freely available PRS online repository including phenome-wide PRS association results was recently created for 35 common cancer traits, allowing cancer researchers to test a range of PRS-related hypotheses (Fritsche et al., 2020).

7.2. Lessons learned from the field of AD

AD is also of interest for genetic testing and counseling. First-degree relatives and adult children of parents diagnosed with AD show substantial interest in genetic testing and counseling for AD (Roberts, 2000; Roberts et al., 2005). Most of the individuals with AD do not carry a clear genetic etiology, as AD can be very polygenic and it is thought that new genetic etiology, as AD can be very polygenic and it is thought that new genetic factors in a risk prediction model, PRSs would be a good addition to enable the use of PRS in the clinic (Roberts et al., 2020). Furthermore, multiple studies have established odds ratios for AD in individuals with a high PRS for AD. For example, individuals with a family history of late-onset AD who have a high PRS, have a higher risk of late-onset AD and, in addition, their odds ratio for AD is 1.29 (95% confidence interval = 1.21–1.37) (Tosto et al., 2017). However, such a relatively low odds ratio is usually not clinically relevant for genetic counseling. The prediction accuracy of AD prediction models has also been investigated. One study uses a model that includes the number of ε4 alleles in the APOE gene, the PRS, the age, and sex (Escott-Price et al., 2015). In this model a prediction accuracy of 78.2% (AUC = 0.782) is reached. Two other studies report that their risk model predicts AD with an 82.5% (AUC = 0.825) and 82% (AUC = 0.82) accuracy (Chaudhury et al., 2019; Escott-Price et al., 2017a). Most studies use big data sets for their models, which illustrates how large-scale studies have laid the foundation of accurate risk prediction in AD. However, there are still some controversial issues in the field as the genetic component of AD is very large, which makes it difficult to improve the estimation of risk to AD (Sierksma et al., 2020). Therefore, a more precise PRS calculation should be made by including not only the SNPs in AD-associated loci reaching genome wide significance, but also the SNPs not reaching this threshold (Sierksma et al., 2020). This in turn strongly improves the prediction accuracy of AD from 75% in a clinical cohort to 84% in a disease cohort (Escott-Price et al., 2017b). Moreover, environmental and lifestyle factors could affect the risk of developing AD in a given individual (Chaudhury et al., 2019). Lifestyle factors known to be risk factors for dementia are alcohol consumption, diet, smoking status, and physical activity (Lourida et al., 2019). When considering PRS for the field of AD, it seems that environmental factors are particularly well incorporated into PRS models. For example, a seminal study reports that individuals at high genetic risk for AD who maintain a favorable lifestyle substantially reduce their chances of AD relative to those with unfavorable lifestyle habits (Lourida et al., 2019). Similar projects will likely further the insight into the interplay between polygenic risk of disease, lifestyle and risk of AD. Thus, a lesson to be learned from the field of AD is that PRSs should also be seen in relation to environmental factors such as lifestyle.

7.3. Lessons learned from the field of CVD

The use of risk prediction models seems to be most implemented in the field of CVD as some of these models are already included in clinical guidelines and are used to predict 10-year risk of CVD (Damen et al., 2016). These statistical risk prediction models include a combination of risk factors such as clinical, biochemistry, and lifestyle risk factors, reaching a good prediction accuracy of 80–85% (Lewis and Vassos, 2020). However, in contrast to the two previous discussed fields, PRSs are often not included in risk prediction models for CVD. Although PRSs on their own have a lower AUC than the combination of multiple risk factors in a risk prediction model, PRSs would be a good addition to...
these models to improve their prediction accuracy even more (Lewis and Vassos, 2020). To illustrate this, one preprint study reports an even higher predictive accuracy of the risk prediction model QRISK when combined with PRS (Riveros-Mckay et al., 2020). The odds ratio for individuals in the highest PRS tertile of coronary heart disease, a subgroup of CVD, vs. individuals in the lowest PRS tertile of coronary heart disease is $1.72$ (95% confidence interval $= 1.53–1.92$) (Mega et al., 2015). Similarly, another study reports that individuals in the highest PRS tertile have an odds ratio of $1.70$ (95% confidence interval $= 1.48–1.94$) of coronary heart disease compared to the lowest tertile (Tada et al., 2016). However, when 23 additional SNPs are included, the odds ratio increases to $1.92$ (95% confidence interval $= 1.67–2.20$), thereby improving the risk prediction. Moreover, PRSS have a potential impact on predicting treatment response as, for example, relative risk reduction of a first coronary event by statin use is higher in individuals at high genetic risk for CVD (Lewis and Vassos, 2020). Furthermore, the prediction accuracy of risk prediction models for CVD is good (Table 1). The Framingham model has been validated multiple times, always showing good accuracy (Damen et al., 2016). In one of the validation studies the AUC ranged from 0.76 to 0.79 (D Agostino et al., 2008). Similarly, the SCORE (Systemic Coronary Risk Evaluation) model has an AUC of about 0.81 (Mortensen et al., 2015; Harari et al., 2017). Lastly, the QRISK model has an AUC of 0.79 (Hippisley-Cox et al., 2007). Thus, various risk prediction models for estimating the risk of CVD have been developed over the past years (Damen et al., 2016). The three aforementioned models are included in clinical guidelines from The National Institute for Health and Care Excellence (NICE) from the United Kingdom and The American College of Cardiology/American Heart Association (ACC/AHA) (Goff et al., 2013; National Institute for Health and Clinical Excellence, 2020). The Framingham, SCORE and QRISK model are the most validated models according to a systematic review conducted in 2016 (Damen et al., 2016). However, almost two third of the developed risk prediction models has never been validated, illustrating the excess of risk prediction models for CVD. In this field of medicine, most developed risk prediction models are not suitable for risk prediction of CVD due to multiple factors, including the lack of external validation. In sum, a lesson learned from the field of CVD is to not develop a profusion of new risk prediction models, but instead take advantage of existing evidence and improve, validate, or even combine existing models to create promising models that can be implemented in clinical practice. In addition, most prediction models in psychiatry so far seem to focus on either PRS or other factors, while combining genetic risk scores and additional factors, such as childhood trauma, possibly can increase the accuracy of risk prediction (Pries et al., 2020).

8. Barriers for the incorporation of PRS in clinical practice in psychiatry

The utility of PRSS in risk prediction looks promising and can help to identify at-risk individuals who may benefit from prevention options. Nevertheless, there are a few barriers that should be overcome in future research to boost the clinical utility of PRSS in psychiatry. One of these barriers is the limited level of accuracy of PRS in predicting risk (Torkamani et al., 2018). This uncertainty is due to the fact that polygenic risk prediction is largely or solely based on genetic variants that do not show a direct causal link with the disease (Torkamani et al., 2018). This could lead to uncertainty in the prediction of the effect size of each variant that is included in the PRS. In addition, the uncertainty lowers the generalizability of PRS risk predictions between populations (Torkamani et al., 2018). One way to improve prediction accuracy methods in psychiatry is through integration with other layers of data, such as gene expression, neuroimaging and computational modelling. For example, multi-omics applied to estimate suicide risk reached prediction accuracies of up to 93 % (Bhak et al., 2019). Another study using multimodal instead of unimodal neuroimaging features to predict treatment response to electroconvulsive therapy reported improved prediction performance (Gong et al., 2020). As a final example, computational modeling in predicting conversion to psychosis in clinically-high-risk patients may provide a framework to elucidate the onset of psychosis (Hoyes et al., 2020). Moreover, most research on PRSs has been done using data from European ancestries as the majority of GWASs are based on European ancestries, hampering the generalizability of PRSs to other ethnicities (Lambert et al., 2019). We urge researchers to include other populations and cross-validate PRSS accuracies across populations. Finally, with guidelines to convey polygenic risk of disease currently lacking, genetic counselors usually refer to risks as relative to average, e.g., “a slightly below average risk for a certain disease”. Given the current state of PRS research as outlined above and communication uncertainties, we recommend further research be undertaken to ascertain the impact of communicating PRS on individuals. A trial is currently being set up in our institute to elucidate this.

Much could be gained from better informing clinical psychiatrists of developments in the field of psychiatric genetics. In a study performed in 2008, a random selection of psychiatrists of the U.S. were polled on genetic testing in psychiatry. Only 9 % of the psychiatrists considered themselves qualified enough to offer genetic testing and interpret the results (Hoop et al., 2008). In addition, relatively recent training in genetics offered to psychiatrists is associated with a feeling of better preparation to provide genetic counseling (Hoop et al., 2008). Moreover, the number of genetic counselors trained to provide psychiatric genetic counseling and able to interpret the results of genetic tests, may not be great enough to handle the future demand for these services (Hoop et al., 2008). Therefore, psychiatrists may in future provide genetic testing and counseling to affected individuals and family members. Furthermore, there are also some ethical concerns regarding PRS utility, for example whether family members have the right to know if they are at risk and if the physician should warn these family members (Gershon and Alliley-Rodriguez, 2013). In the Netherlands, the National Society for Clinical Genetics (VKGN) has developed guidelines for situations in which physicians should inform family members about possible heritable diseases. The guidelines state that at-risk family members who have a chance of at least 50 % to have inherited the disease, should be informed if this has an effect on their own health or on the health of their (future) children (Vereniging Klinische Genetica Nederland, 2019). In psychiatry, twin-based within-family recurrence estimates are lower than this and thus currently according to this guideline family members should generally not be approached actively when a person with a psychiatric disorder undergoes genetic testing.

9. Conclusions

Currently in psychiatry, most substantial evidence supporting the use of PRSS in clinical practice is for risk prediction. However, in comparison to other fields of medicine, such as breast cancer, AD, and CVD, the level of evidence is substantially smaller. For example, the PRS risk prediction accuracy in schizophrenia is only 62 % according to a large study (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Lessons to be learned from the three other fields of medicine include integrating PRS with environmental factors (e.g., lifestyle), setting up large-scale studies, and applying reproducible methods allowing for cross-validation between cohorts. Particularly in breast cancer, large-scale studies and consistent replication studies have allowed researchers to build an online tool with about 80 % accuracy. In psychiatry, the use of PRSS in such an online tool may be helpful to support genetic counseling sessions in the future. During counseling sessions, the use of PRS may thus boost screening and prevention strategies, as well as treatment decision-making. In addition, PRS utility carries the potential to reduce risky behaviors and enhance preventive behaviors, such as lifestyle adjustments. PRS utility could therefore contribute to personalized health care, which can result in improved treatment of affected individuals as well as better quality of
life of family members.

Declaration of Competing Interest
The authors report no declarations of interest.

Acknowledgement
We thank Jehanne Austin for valuable feedback on previous versions of this manuscript.

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