tion studies, which now identify hundreds of genes in association with schizophrenia as well as with developmental problems, support the thesis that much of the molecular pathology of schizophrenia resides in general brain development that underlies social behavior, attention, and other brain functions.

These clinical and genetic findings suggest a broadened reconceptualization of schizophrenia as a general alteration of neurodevelopmental processes, rather than the outcome of a psychosis-specific pathogenesis. This reconceptualization is congruent with a common characteristic of population-wide primary prevention: beneficial effects on development that extend broadly beyond a narrow disease target. Folic acid, for example, has positive effects on cognition and behavior, in addition to its targeted use to prevent spina bifida and facial clefts. Vitamin D, included in prenatal vitamins to support bone development, appears to be helpful in the prevention of autism spectrum disorder and schizophrenia. Thus, folic acid, vitamin D, and now choline, along with other primary interventions to protect the uterine environment as part of good obstetrical care, have broad beneficial effects for the offspring, in addition to the possible prevention of later psychiatric illness. An example is the significant protective effects of prenatal choline on the development of attention in offspring of women who contract respiratory viruses in gestation[9]. These findings can provide guidance for treatment of pregnant women in the COVID-19 pandemic, so that their children might not add another stone to the pillar of evidence linking prenatal infection to schizophrenia.

Most beneficial effects will appear in early childhood, long before preventive effects for psychosis and other psychiatric illnesses can be definitely ascertained. If expectant families are to see the benefit of improved childhood behavior and cognition with the eventual possible prevention of psychosis, psychiatry cannot be the only discipline to promulgate these prenatal interventions. Prenatal nutrients such as choline that have early beneficial childhood effects require widespread acceptance by obstetricians and maternal-fetal medicine specialists, family medicine physicians, midwives and pediatricians. Working relationships with obstetricians for the assessment of perinatal depression is a model for what needs to happen to allow choline and other prenatal primary preventive interventions to become truly population-wide.

Robert Freedman[1], Sharon K. Hunter[1], Amanda J. Law[1-3], M. Camille Hoffman[1,4]
[1]Department of Psychiatry, University of Colorado School of Medicine, Aurora, CO, USA; [2]Department of Cell and Developmental Biology, University of Colorado School of Medicine, Aurora, CO, USA; [3]Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA; [4]Department of Obstetrics and Gynecology, Division of Maternal and Fetal Medicine, University of Colorado School of Medicine, Aurora, CO, USA

The perspective of this commentary came from the authors' discussions with the late R.G. Ross. This work was supported by the US National Institute of Child Health and Human Development (K12HD 001271-11), the US National Center for Advancing Translational Sciences (UL1 TR001082), the Institute for Children's Mental Disorders, and the Anschutz Foundation.

1. Fusar-Poli P, Correll C, Arango C et al. World Psychiatry 2021;20:200-21.
2. Birnbaum R, Jaffe AE, Hyde TM et al. Am J Psychiatry 2014;171:758-67.
3. Kerwin R, Patel S, Meldrim N. Neurosci 1990; 39:25-32.
4. Hyde TM, Lipska BK, Ali T et al. J Neurosci 2011; 31:11088-95.
5. Lozada AF, Wang X, Gounko NV et al. J Neurosci 2012;32:7651-61.
6. Ross R, Hunter SK, Hoffman MC et al. Am J Psychiatry 2016;173:509-16.
7. Rossi A, Pollice R, Daneluzzo E et al. Schizophr Res 2000;44:121-8.
8. Addington J, Cornblatt BA, Cadenhead KS et al. Am J Psychiatry 2011;168:800-5.
9. Freedman R, Hunter SK, Law AJ et al. J Psychiatr Res 2020;128:1-4.

DOI:10.1002/wps.20853

Prevention in psychiatry: a role for epigenetics?

In their landmark paper on the current state of knowledge in the field of preventive psychiatry, Fusar-Poli et al[1] state that "robust genetic and environmental epidemiological knowledge is required to inform evidence-based preventive approaches". Indeed, in order to most effectively tailor selective and indicated preventive interventions to an individual's needs, a valid biological and biographical marker panel predictive of future disease risk is essential.

The classical vulnerability-stress model and the extended vulnerability-stress-coping model assume an intricate interplay of biological, particularly genetic, factors with both negative and positive environmental influences in shaping the spectrum of risk and resilience towards mental disorders[2]. However, as rightfully stated by the authors[1], there is currently a "lack of valid biomarkers of risk", and "the variance explained [by polygenic risk scores] is still too small for implementation in selective prevention and does not provide singular neurobiological targets". In other words, to date the field of genetic research, including gene-environment interaction studies and genome-wide approaches, has not fulfilled its initial promise to unambiguously unravel the pathogenetic mechanisms of mental disorders. Consequently, at the present stage, genetic markers are indeed not suitable as valid biomarkers that could inform targeted preventive interventions.

In recent years, however, increasing evidence has accumulated for epigenetic mechanisms such as DNA methylation and histone modifications to crucially govern gene function beyond variation of the DNA itself, and to dynamically respond to environmental influences[3]. Along these lines, epigenetic markers have been suggested to represent an adaptive (or maladaptive) mechanism in the face of environmental challenge, a "molecular embodiment of biography", a "biological archiving" of trauma, adversity, lifestyle and sociocultural context at the crossroads between biology and environment.

Thus, beyond the static genetic level, plastic epigenetic mechanisms seem to be of particular relevance in the conferral of risk or resilience towards mental disorders. Accordingly, epigenetic signatures such as alterations in DNA methylation in blood or saliva have been associated with a number

of mental disorder phenotypes[4,5]. Furthermore, there is initial evidence for peripheral epigenetic markers to be modifiable by psychotherapeutic interventions such as cognitive-behavioral therapy, in that disease-associated DNA methylation patterns have been shown to "normalize" along with treatment response[5]. Overall, these findings suggest a great potential for epigenetic signatures to represent: a) predictive disorder risk markers reflecting both biological and biographical vulnerability, and b) malleable targets for preventive interventions.

Indeed, in plants there is ample evidence for an epigenetic memory of resistance towards environmental pathogens, which has been proposed as a potential new direction in preventing disease in crops[6]. Also, oncological research has identified numerous epigenetic targets in cancer treatment, such as histone deacetylases (HDACs) or DNA methyltransferases (DNMTs), which could further inform preventive strategies for various diseases[7].

With respect to mental disorders, a study probing the effects of a randomized controlled family-centered prevention training program (Strong African American Families, SAAF) discerned parental depressive symptoms to be predictive of accelerated epigenetic aging in the offspring and, reciprocally, the preventive intervention to confer a protective effect regarding epigenetic aging[8].

Additionally, a lifestyle intervention such as physical activity, which is considered to contribute to the promotion of mental health, has been shown to impact the epigenetic machinery. Finally, the field of "nutritional psychiatry" has recently been refueled by evidence for folic acid and vitamin B12 to influence DNA methylation status. In turn, nutritional supplements or epigenetic modifiers such as the natural methyl-group donor S-adenosyl methionine have been suggested as promising adjuncts in the prevention of mental disorders[5].

Given this burgeoning evidence for a possible role of epigenetic processes as targetable risk markers in selective and indicated prevention of mental disorders, further research – ideally expanding to an epigenome-wide and environment-wide level as well as applying a longitudinal study design covering the critical time windows of mental disorder manifestation – is needed to validate and confirm the potential of epigenetic signatures to integratively reflect both a genetic and environmental risk, and thereby confer vulnerability to mental disorder onset.

Additionally, future studies are warranted to explore the malleability of epigenetic markers by preventive interventions. These might comprise classical preventive measures derived from cognitive-behavioral therapy, as well as explore psychopharmacological options, given that several psychoactive substances – such as selective serotonin reuptake inhibitors, antipsychotics, lithium and valproate – have already been reported to impact the epigenetic machinery. Along those lines, "epigenetic drugs" such as HDAC or DNMT inhibitors, if designed specifically enough, might catalyze preventive effects by enhancing learning and neuronal plasticity.

However, some caveats have to be considered when pursuing this line of research. While there is some evidence from studies in rodents and rhesus monkeys, or human positron emission tomography (PET) studies, for a certain comparability of peripheral and central epigenetic processes, some epigenetic signatures seem to be tissue- or even cell-specific, which might limit their use as reliable peripheral biomarkers of mental disorder risk. Also, a number of factors impacting epigenetic mechanisms – such as smoking, exercise, nutrition, body weight, alcohol and drug consumption, or physical diseases – might confound the validity of epigenetic processes as risk markers of mental disorders. Finally, as a general proviso in biomarker research, ethical guidelines and social as well as legal policies for clinical and scientific use of epigenetic information should be implemented alongside such research efforts.

In sum, epigenetics is to be considered a promising field in mental disorder prevention research. First, epigenetic markers – as accessible, integrated and dynamic biosensors of biological as well as biographical risk of mental disorders – might be particularly suited as both indicators and targets of preventive interventions. Second, epigenetic processes – if modifiable by selective or indicated preventive measures – could biologically and thus mechanistically confer resilience towards mental disorders. Finally, as epigenetically imprinted trauma has been reported to potentially be transmissible to future generations via the germline[9], successful preventive interventions embodied in epigenetic signatures might even promote a "transgenerational prevention" of mental disorders, by providing an epigenetic memory of the ability to adapt to a changing environment to future generations.

Katharina Domschke
Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, and Center for Basics in NeuroModulation, Faculty of Medicine, University of Freiburg, Freiburg, Germany

This work was partly supported by the German Research Foundation (project no. 44541416) and the German Ministry of Research and Education (01EE1402F).

1. Fusar-Poli P, Correll C, Arango C et al. World Psychiatry 2021;20:200-21.
2. Schiele MA, Herzog K, Kollert L et al. Br J Psychiatry 2020;217:645-50.
3. Schuebel K, Gitik M, Domschke K et al. Int J Neuropsychopharmacol 2016;19:pyw058.
4. Schiele MA, Domschke K. Genes Brain Behav 2018;17:e12423.
5. Schiele MA, Gottschalk MG, Domschke K. Clin Psychol Rev 2020;77:101830.
6. Furci L, Jain R, Stassen J et al. Elife 2019;8:e40655.
7. Feinberg AP. N Engl J Med 2018;378:1323-34.
8. Brody GH, Yu T, Chen E et al. J Child Psychol Psychiatry 2016;57:566-74.
9. Bohacek J, Mansuy IM. Nat Rev Genet 2015;16:641-52.

DOI:10.1002/wps.20854

Primary challenges and practical solutions in preventive psychiatry

Fusar-Poli et al[1] provide a scholarly and detailed overview of the state of knowledge on preventive approaches in psychiatry. Their paper should be considered an obligatory read for anyone entering or already practicing in this emerging field.