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## Special Feature Article

### Reconsidering the Basics of Research Ethics and Human Resource Development in the Context of Revised Ethical Guidelines

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#### Abstract

We discuss the basics of research ethics, which have not changed following the revision of ethical guidelines; moreover, we discuss human resources training based on these basics. In the "Seven Requirements for Determining Whether a Research Trial Is Ethical" published in 2000, which both the past and the present guidelines refer to, the minimum requirements for research are: 1) it has social and academic value, and 2) scientific validity was consistent. Clinical research with social value is defined as "research that is intended to the patients' benefit" and "research that considers the patients' views". To ensure scientific validity, it is necessary to consider the study design. Prospective cohort studies should be considered to minimize bias. In the present study, we conducted a prospective cohort study of pregnant and nursing women, which aimed to identify predictable risk and protective factors for depression in the first postpartum month from pregnancy to the early postpartum using electronic signatures. In addition, we aimed to elucidate the pathogenesis of psychiatric disorders, which is the wish of patients and their families, and drug discovery based on pathogenesis, which has been promoted through multi-center collaboration and cooperation among various experts. Further progress in multi-center collaboration is expected with the revision of the guidelines. In addition, to realize genomic medicine for mental disorders using genome analysis, which is the starting point for elucidating pathophysiology, it is necessary to train psychiatrists

who can provide genetic counseling, which is required by the ethical guidelines. Finally, we emphasize the importance of human resource development to clarify the pathogenesis of mental disorders, which is the wish of the patients and their families, with ethical consideration.

**Keywords:** research ethics, patient and family needs, elucidation of pathophysiology, genetic counseling, human resource development

### Introduction

The author's first clinical study was a retrospective examination of psychiatric problems in 25 kidney transplant patients, which was published in 1986.<sup>20)</sup> The background of this study was that all kidney transplant patients at the hospital where the author worked were treated by a psychiatrist starting in 1984, i.e., liaison psychiatry activities were initiated. At that time, kidney transplant liaison activities themselves were completely new to us, and we checked related publications, but there were no national or international literature databases, PubMed, or the Central Journal of Medicine (MEDLINE apparently existed, but the author was unaware of this and had no way to access it). My supervisor, Dr. Yoshihiro Narita, told me what related papers were available, and I searched for references that were cited in those papers. While discussing each case with Dr. Narita and the urology staff during liaison psychiatry activities based on

the literature-based information, it became natural for me to summarize and present what was known in the published literature and what I had learned from clinical experience.

Thereafter, we conducted clinical studies such as measurement of noradrenaline in blood of patients with sleep apnea syndrome<sup>21)</sup> and biopterin<sup>3)</sup> in blood of depressed patients, and basic research such as measurement of the monoamine system in the brains of a rat model of Parkinson's disease,<sup>21)</sup> rats treated with dopamine receptor agonist,<sup>22)</sup> and rats during self-stimulation of the brain.<sup>23)</sup> However, there was no training course on research ethics available to us, and we lacked knowledge and awareness of such research ethics. In 1990, soon after arriving at the National Institute of Mental Health (NIMH), the author attended an ethics course on clinical research on humans and research involving animal models. The content of the clinical research course was similar

to the "Seven Ethical Requirements for Clinical Research," which I will discuss later. I remember that we were taught, using "videos of abusive research on animals (case studies at the time)," and that we should consider how to reduce the suffering of model animals and "whether the research to be conducted on model animals was really necessary and whether it could actually be conducted using cultured cells or computer simulations."

I learned many things at NIMH, where I worked until 1995, including genome analysis of psychiatric disorders, but the most important things I learned were: (i) clinical research (and animal model studies) must be reviewed by an ethical review committee and proceed in accordance with approved guidelines, and (ii) the results of clinical research must be presented to the public, including patients and their families who have collaborated with us in the research. In the U.S., the research ethics system is already in place, and I was impressed by the fact that the social and scientific value and validity of each research project, the explanation and consent of the participants, and protection of personal information are discussed by the review committee, which includes laypersons and legal ethics experts, and that clinical research is conducted on the basis of the research results.

In this article, based on the author's research and experience with the Ethics Committee of the Japanese Society of Psychiatry and Neurology, the author discusses the basics of research ethics, which will not change even if the ethical guidelines are revised, and human resource development founded on these basics. The following studies cited in this article were approved by the Bioethics Review Committee of the Nagoya University School of Medicine, and were conducted in accordance with the approved items.

**I. "Seven Ethical Requirements for Clinical Research" (2000, Emanuel, E. J.) and "Revised Guidance on Ethical Guidelines" (2021)**

The General Provisions, Purpose, and Basic Policies of the "Guidance for Ethical Guidelines for Medical and Health Research Involving Human Subjects"<sup>11)</sup> state that "All parties shall comply with the following basic policies and proceed with research in accordance with these guidelines." The content is exactly the same as the 2014 "Ethical Guidelines for Medical and Health Research Involving Human Subjects,"<sup>10)</sup> published in 2000. It is based on the "Seven Ethical Requirements for Clinical Research"<sup>2)</sup> published by Emanuel, E. J. (in the Bioethics Division of NIH) et al. in 2000 (Table 1). In particular, the policies of:

(i) having social and academic significance, and (ii) ensuring scientific rationality as the minimum requirement for research, are consistent among all of them.

Only research that has academic significance and scientific rationality, i.e., is scientifically necessary and valid, should be done on living humans (and animals). This is the most important ethical principle, and research that is not scientifically necessary or reasonable, even if it is non-invasive or with the consent of the subject, is not ethically permissible.<sup>17)</sup> Academic significance, or "novelty," is obtained by clarifying "known matters" in the relevant literature and identifying "unknown areas" to be studied. To "ensure scientific rationality," the research design should be examined to find a method to obtain data with high reproducibility and validity, and the sample size should be considered from a statistical perspective.<sup>24)</sup>

In addition, "research with social significance" is defined in the guidelines as "research that contributes broadly to the maintenance and promotion of the health of the public, and to the recovery of patients from injury or disease and the improvement of their quality of life, and that contributes to the development of the health and welfare of humankind."<sup>10)</sup> If this "social significance" is focused on clinical

practice, it means that we must consider "whether the research is intended to benefit the patients themselves" and "whether the research is based on the ideas of the patients themselves."<sup>8)</sup>

## II. Importance of Prospective Cohort Studies: Ensuring Scientific Rationality

In the previous section, it was stated that study design is essential to "ensure scientific rationality." In this section, we explain the importance of prospective cohort studies, using the example of a prospective cohort study of pregnant women (Table 2) that we conducted to develop methods for identifying groups in need of psychiatric support and support measures.

Studies can be broadly classified into two types according to their design: case-control studies, in which data are collected retrospectively, and prospective cohort studies, in which data are collected prospectively (Figure 1).<sup>9)</sup> Case-control studies are conducted by comparing the disease and control groups by checking past environmental and genetic factors, etc., to identify the causes of disease onset. Prospective cohort studies, on the other hand, follow a certain population over time to determine whether they are exposed to specific environmental factors and whether they develop disease, and to examine the causal relationship

between environmental factors and disease onset.

Case-control studies have the advantages of a relatively short study period, low cost, and small sample size. However, case-control studies have the following biases.

The first is called sampling bias, which arises in the process of selecting subjects for patient and control groups. Among the sampling biases are "prevalence bias," which means that those with mild disease or those who have died are not included, and "diagnostic bias," which means that those with exposure are more likely to be diagnosed, while those without exposure are less likely to be diagnosed as a case group.

The second is measurement bias. Because case-control studies examine factors that have occurred in the past, uncertainty is inevitable in the measurement of factors. Among the measurement biases are "recall bias," in which the case group recalls more information about their exposure, and "family information bias," in which the case group is more likely to be aware of the disease if they have a family member with the same disease. Recall bias is particularly likely to occur with respect to psychosocial factors.

Prospective cohort studies, on the other hand, involve the difficulty of requiring long-term follow-up of a large

number of cases, but have the major advantage of establishing a temporal relationship between exposure and disease. In the case of multifactorial diseases associated with multiple exposures, it is difficult to examine the relationship between exposure and disease in a case-control study, and a cohort study is necessary to confirm the relationship between exposure and disease.

We determined that a prospective cohort study was necessary to achieve our goals: (i) to identify risk factors for depression (including depression due to bipolar disorder in addition to depression) at 1 month postpartum, from pregnancy to the early postpartum period, and to identify groups that require psychiatric support, and (ii) to identify protective factors for postpartum depression in order to develop support measures for the group identified in (i) above.

Prospective cohort studies have the following issues: require a large number of subjects and long observation period. The number of subjects depends on the incidence of the disease, which is high in the case of postpartum depression. The follow-up period can be set to be relatively short, from pregnancy to postpartum. Above all, if we can obtain the understanding and support of obstetricians, we can target expectant

and nursing mothers who are visiting medical institutions.

Based on the above, we have conducted a prospective cohort study of pregnant women since 2004 (1,600 analyzed at this time) and have attempted to identify risk and protective factors for depression during pregnancy and early postpartum at 1 month postpartum, the occurrence of suicidal ideations, and weak emotional bonding with the child (Table 2). As a result, the following risk factors for depression were identified: primiparas,<sup>13)</sup> history of depression,<sup>5)</sup> depressive tendencies during pregnancy,<sup>4)</sup> high damage avoidance, high levels of kynurenine and kynurenic acid in blood,<sup>27)</sup> and maternity blues immediately after delivery. In addition, a history of depression<sup>6)</sup> was identified as a risk factor for suicidal ideation, and weak emotional bonding during pregnancy<sup>18)</sup> was identified as a risk factor for weak emotional bonding toward the child. Furthermore, we identified that feeling strong support from the surroundings during pregnancy was protective against depression,<sup>12)</sup> the occurrence of suicidal ideation, and weak emotional bonding with the child (Figure 2).<sup>19)</sup>

Some of these findings were incorporated into the "Guide for the Examination of Pregnant and Maternal Women with Potential Complications of Psychiatric Disorders," published

jointly by the Japanese Society of Psychiatry and Neurology and the Japan Society of Obstetrics and Gynecology. We hope that the results of this study will help to respond to the wishes of people with bipolar disorder, such as "I want to get advice to relieve my anxiety about future pregnancies, childbirth, and child rearing," and "I want the fact that childbirth is possible even with mental illness better understood by the public."

Incidentally, since the expansion of COVID-19 in the spring of 2020, it has been impossible to explain research in person to expectant and nursing mothers and obtain their consent. Since the new guideline clearly stipulates the acceptability of e-consent, we have been able to conduct the study, including the survey of patients and their families described in the next section, by means of online explanation, consent with electronic signatures, and data input since the summer of 2021.

### **III. Pathophysiological Clarification and Drug Discovery Based on the Wishes of Patients and Their Families: Collaborative Research and Human Resource Development for Practicing Genomic Medicine**

With the support of the Japan Agency for Medical Research and Development (AMED), we are conducting a survey of people with mental disorders and their

families to determine "what kind of psychiatric research they would like to see" in order to create basic data for considering "whether the research is based on the ideas of the people concerned," as described in section I. In this survey, patients and family members were invited to participate from the stage of creating the questionnaire to be used, and the survey began in 2019 and had been analyzed with the cooperation of 780 people as of March 2020. The results of the survey showed that the most common requests were "clarification of the pathophysiology" and "development of a curative therapy," followed by "development of a curative therapy," both of which exceeded 70%.

To elucidate the pathophysiology of mental disorders and realize pathophysiology-based drug discovery, it is necessary to adopt a collaborative approach involving various experts using multiple modalities starting from genomic information on mental disorders. In other words: (i) starting from genomic variants with large effect sizes identified through large-scale clinical and genomic studies and data sharing, phenotypic and functional abnormalities occurring at each level of the hierarchy (molecular, cellular, neural circuit, brain, and individual) are identified, and (ii) models are constructed based on the

multidimensional omics information related to the abnormalities obtained in (i) above, and then an integrated analysis of the data is performed using the constructed model to link the multilevel layers, leading to elucidation of the pathological condition (Figure 3). To achieve this: (i) a multilevel and comprehensive approach is essential, in which experts from psychiatry, genomics, neuroscience, and mathematical sciences collaborate, and (ii) a sustainable system must also be developed to collaborate with pharmaceutical companies to develop stratification and treatment methods based on pathological conditions from pathological clarification. In fact, our participation in elucidation of pathophysiology based on genome analysis is the result of collaboration among various experts at multiple institutions in Japan and overseas.<sup>1)7)25)26)</sup>

Regarding the field of psychiatric drug discovery, many pharmaceutical companies are withdrawing from this field because the conventional pipeline approach, in which a single company proceeds on its own, has a lower probability of success. In this context, platform-type approaches are required for common issues that are difficult to solve (biomarker development, development of patient stratification technology, construction of large-scale

patient databases, etc.), where researchers and companies collaborate from the pre-competitive phase, transcending barriers (Figure 4).<sup>14)</sup> The revised guidelines are expected to further promote multicenter collaborative research, leading to the elucidation of pathological conditions and realization of drug discovery.

#### **IV. Developing Human Resources to Practice Genomic Medicine in Psychiatry**

Among the results of genome analysis, which is the starting point for the elucidation of pathological conditions described in the previous section, information that can be used to improve the medical health of patients is fed back to the parties concerned and their families with psychosocial considerations, i.e., genetic counseling has been required in previous ethical guidelines. Many intractable diseases have been identified as a result of advances in genomic medicine, including 22q11.2 deletion syndrome, Rett syndrome, and tuberous sclerosis, all of which are associated with a high rate of mental disorders. For example, 22q11.2 deletion syndrome is associated with intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety, and epilepsy in childhood, schizophrenia and mood disorders in

adolescence, and Parkinson's disease in middle age, and a variety of mental disorders can occur across the life stages. All of the aforementioned intractable diseases cause diseases of multiple organs, including the brain, and genomic medicine is already being practiced in collaboration with various medical departments, including psychiatry. Although not yet designated as intractable diseases, causative variants of rare diseases of multiple organs including the brain, such as 3q29 deletion, are being newly identified. In addition to rare and intractable diseases, in liaison psychiatry, which collaborates with other medical departments, genomic medicine has been implemented in society, including in the fields of oncology and perinatal care, and its scope continues to expand.

On the other hand, even now, there is a growing concern about the relationship between the onset of mental disorders and "heredity" (i.e., the disease was transmitted from parents to children, and may occur in other family members in the future) and "upbringing" (did I develop the disease because of the way my parents raised me?). For example, the causative variant of the aforementioned rare intractable diseases is often de novo, but it is not uncommon for the possibility of de novo disease (i.e., the disease was not transmitted from parents to children)

not to be communicated to the patients and their families. In addition, the fact that "hereditary mental disorders" were once the subject of the Eugenic Protection Act has also led to misunderstanding and prejudice. Because of this historical background, "heredity" issues are still avoided in clinical psychiatry, and the results of genome medicine are not utilized in a form based on genetic counseling, and as a result, the requests of patients and their families cannot be adequately met. In fact, as of May 31, 2022, there were only 11 psychiatrists certified as clinical genetic specialists (out of 1,638 in total), with a regional bias (Figure 5).<sup>16)</sup>

To solve such problems in the field of psychiatry and further promote genomic medicine in psychiatry, it is essential to increase the number of psychiatrists who are familiar with genomic medicine.<sup>15)</sup> Although several intractable diseases are complicated by mental disorders, genomic and genetic issues are still avoided in clinical psychiatry, and the requests of patients and their families have not been fully met. In order to improve the literacy of psychiatrists, which is indispensable for providing appropriate counseling to patients and their families, it is necessary to incorporate genomic medicine into the system of psychiatric specialists.

### **Conclusion: Human Resource Development**

The Japanese Society of Psychiatry and Neurology is promoting a system of certified psychiatric specialists that calls for the "fostering of a research mind." In this paper, we have discussed: (i) social and academic significance and (ii) scientific rationality, as the basics of research ethics, and it is important to foster human resources with the ability to conduct research based on these basics.<sup>24)</sup> To elucidate the pathophysiology, which is the wish of the patients and their families, collaboration between basic and clinical research is essential, and psychiatrists must increase their literacy in basic research. Above all, the development of treatments based on pathological conditions does not happen overnight, and the wishes of patients and their families cannot be realized without the next generation of human resources. The authors would like to work together with members of the society to further promote the development of the next generation.

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表1 「臨床研究7つの倫理要件」(2000年, Emanuel, E. J.)  
と「改訂倫理指針ガイダンス」(2021年)

臨床研究7つの倫理要件	改訂倫理指針ガイダンス： 総則, 目的及び基本方針
1. 社会的・科学的な価値	1. 社会的および学術的意義を有する研究を実施
2. 科学的な妥当性	2. 研究分野の特性に応じた科学的合理性を確保
3. 公正な被験者選択	3. 利益および研究対象者への負担その他の不利益を比較考量
4. リスク・ベネフィットの適切性	4. 倫理審査委員会の審査
5. 第三者による審査	5. 対象者への事前の十分な説明と, 自由な意思に基づく同意
6. インフォームド・コンセント	6. 弱い立場にある者への特別な配慮
7. 被験者の尊重	7. 個人情報等を適切に管理
	8. 研究の質および透明性を確保

Table 1: "Seven Ethical Requirements for Clinical Research" (2000, Emanuel, E.J.) and "Revised Ethical Guidelines Guidance" (2021)

#### Seven Ethical Requirements for Clinical Research

1. Social and scientific value
2. Scientific validity
3. Fair subject selection
4. Appropriateness of risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for subjects

#### Revised Ethical Guidance: General Provisions, Objectives, and Basic Policies

1. Conducting research of social and scientific significance
2. Ensure scientific rationality in accordance with the characteristics of the research field
3. Weighing the benefits and burden or other disadvantages to the research subjects
4. Review by an ethical review committee
5. Providing sufficient explanation to the research subjects in advance, and obtaining their free and voluntary consent
6. Special consideration for vulnerable persons

7. Appropriate management of personal information

8. Ensure quality and transparency of the research

表 2 妊産婦前向きコホート研究プロトコール概要

	妊娠 25 週	妊娠 36 週	産後 1 日目	産後 2 日目	産後 3 日目	産後 4 日目	産後 5 日目	産後 1 ヶ月
採血	ゲノム 血漿・血清					ゲノム 血漿・血清		
調査 項目	生活背景							児の状態
	EPDS	EPDS					EPDS	EPDS
	HS	HS	HS	HS	HS	HS	HS	HS
	MIBQ	MIBQ					MIBQ	MIBQ
	TCI							TCI
	SSQ							SSQ
	PBI							PBI
	IDDL							
面接			MB	MB	MB	MB	MB	SCID

・対象者：産婦人科を受診した 20 歳以上の妊産婦

・名古屋大学生命倫理審査委員会の承認のもと、参加者に書面で説明し同意を得た

生活背景：既往歴，経済状況など。児の状態：性別，体重など。調査項目：Edinburgh Post-natal Depression Scale (EPDS), Highs Scale (HS), Mother-Infant Bonding Questionnaire (MIBQ), Temperament and Character Inventory (TCI), Social Support Questionnaire (SSQ), Parental Bonding Instrument (PBI), lifetime version of the Inventory to Diagnose Depression (IDDL), Stein's Scale (MB), Structured Clinical Interview for DSM-IV-TR (SCID)

Table 2: Outline of the Protocol for a Prospective Cohort Study of Pregnant Women

25 weeks of gestation

36 weeks of gestation

Day 1 postpartum

Day 2 postpartum

Day 3 postpartum

Day 4 postpartum

Day 5 postpartum

One month postpartum

Blood collection

Genomic plasma/serum

Genomic plasma/serum

Survey items

Life background

Status of the child

EPDS EPDS EPDS EPDS

HS HS HS HS HS HS HS HS

MIBQ MIBQ MIBQ MIBQ MIBQ

TCI TCI

SSQ SSQ

PBI PBI

IDDL

MB MB MB MB MB MB

Interview SCID

- Subjects: Expectant and nursing mothers aged 20 years or older who visited an obstetrics and gynecology clinic.

- The participants were informed in writing and their consent was obtained with the approval of the Bioethics Review Committee of Nagoya University.

Life background: medical history, financial situation, etc.

Status of the child: sex, weight, etc.

Survey items: Edinburgh Postnatal Depression Scale (EPDS), Highs Scale (HS), Mother-Infant Bonding Questionnaire (MIBQ), Temperament and Character Inventory (TCI), Social Support Questionnaire (SSQ), Parental Bonding Instrument (PBI), lifetime version of the Inventory to Diagnose Depression (IDDL), Stein's Scale (MB), Structured Clinical Interview for DSM-IV-TR (SCID)

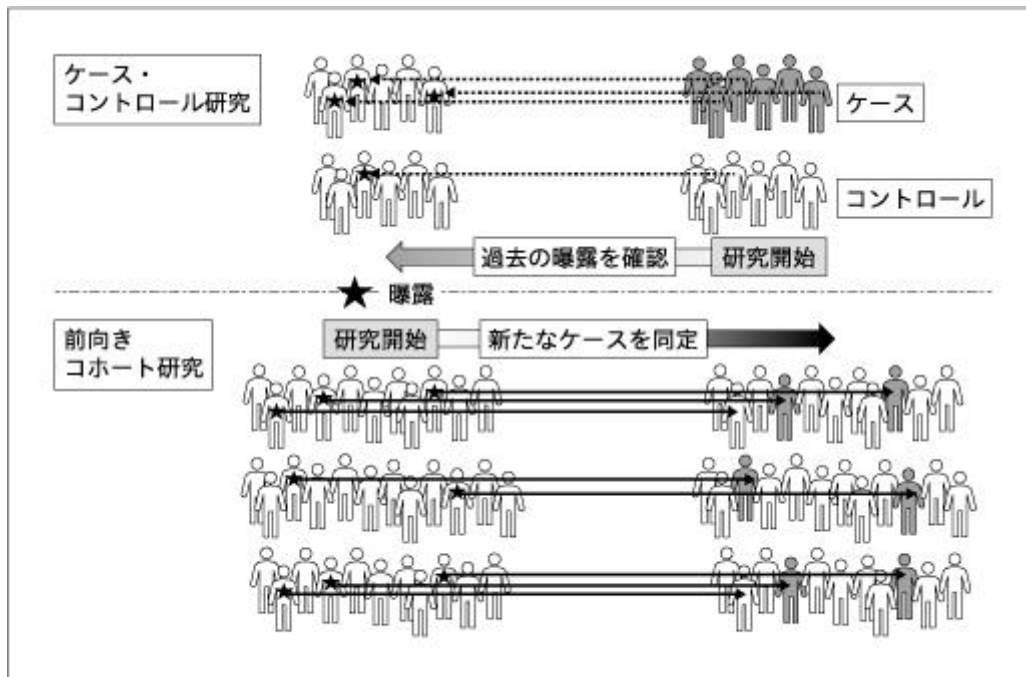


図1 ケース・コントロール研究と前向きコホート研究

Figure 1: Case-control and Prospective Cohort Studies

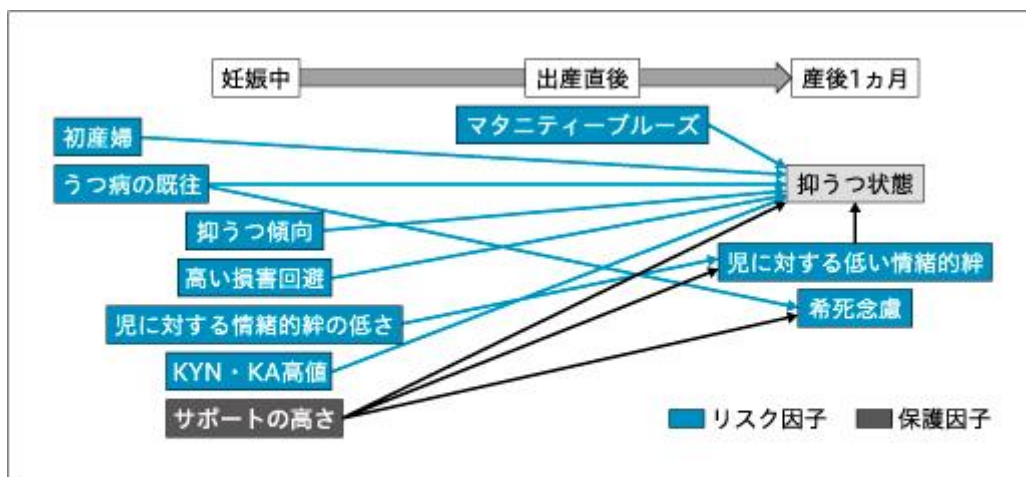


図2 産後の抑うつ状態・児に対する情緒的絆の低さ・希死念慮のリスク因子と保護因子

KYN : kynurenine, KA : kynurenic acid

Figure 2: Risk and Protective Factors for Postpartum Depression, Weak Emotional Bonding with the Child, and Suicidal Ideation

KYN: kynurenine, KA: kynurenic acid

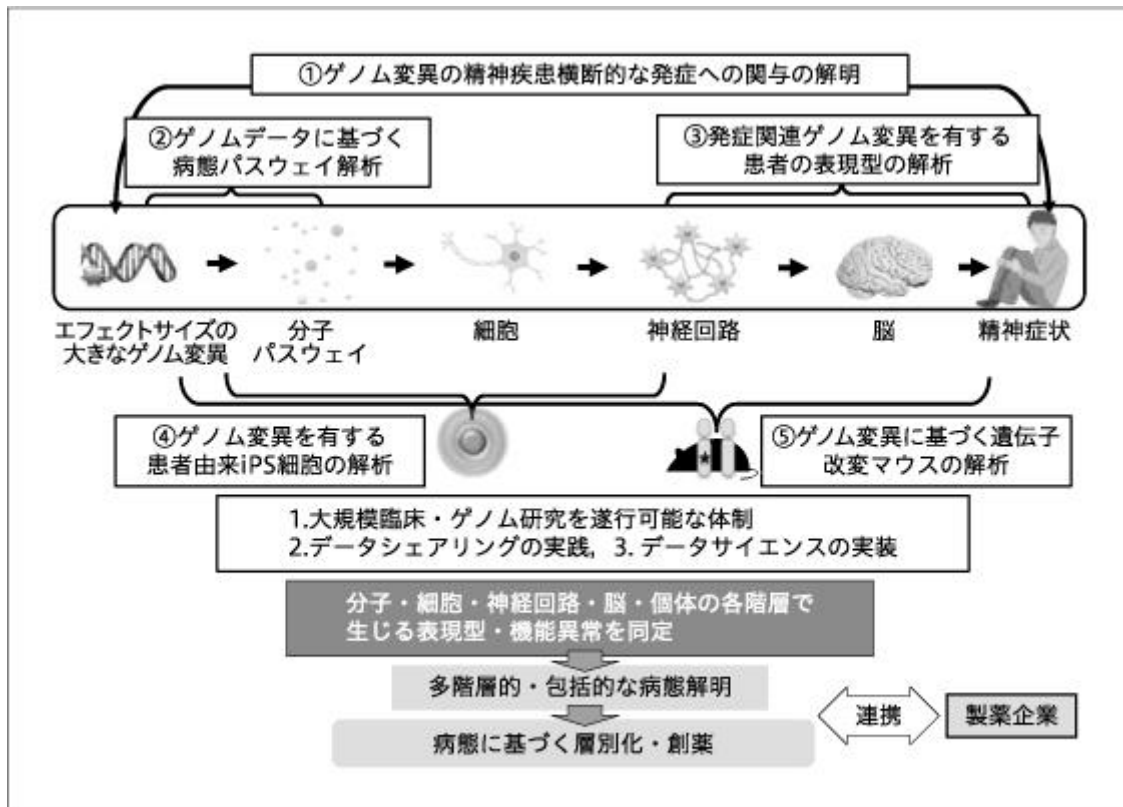


図3 ゲノム情報を起点とした精神疾患の病態解明と創薬

Figure 3: Elucidation of Pathophysiology of Psychiatric Disorders and Drug Discovery Based on Genome Information

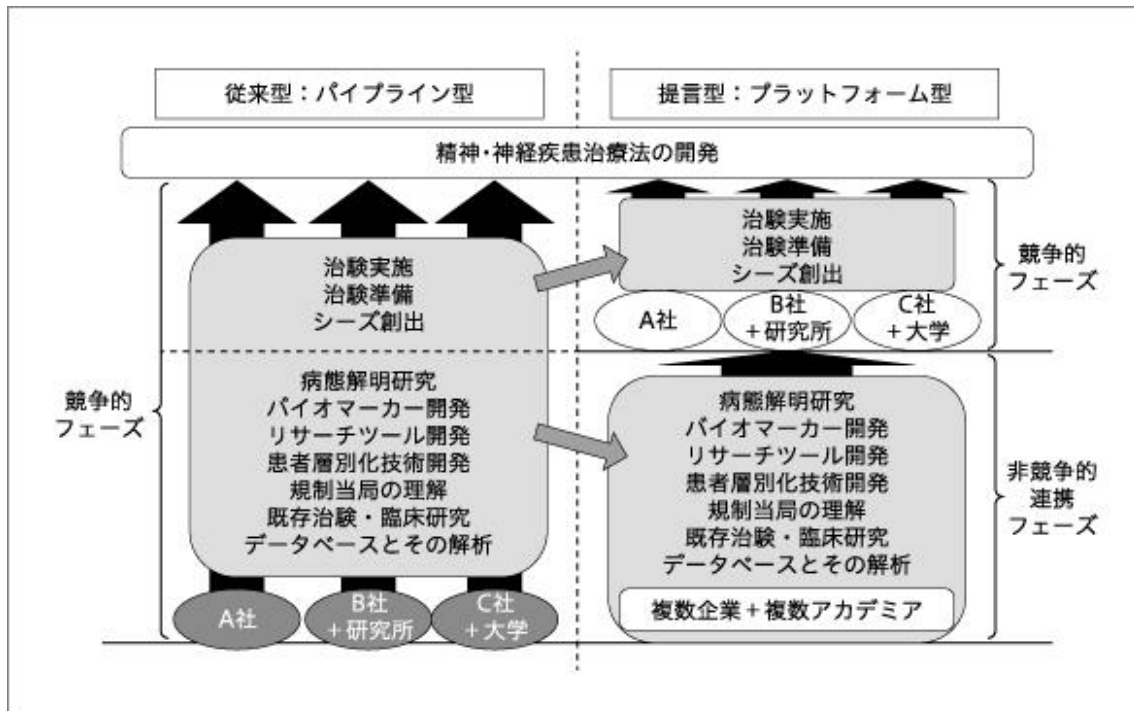


図4 精神・神経疾患治療法開発のため非競争的フェーズでの連携を提案

Figure 4: Proposed Collaboration in Non-competitive Phase to Develop Treatments for Psychiatric and Neurological Disorders

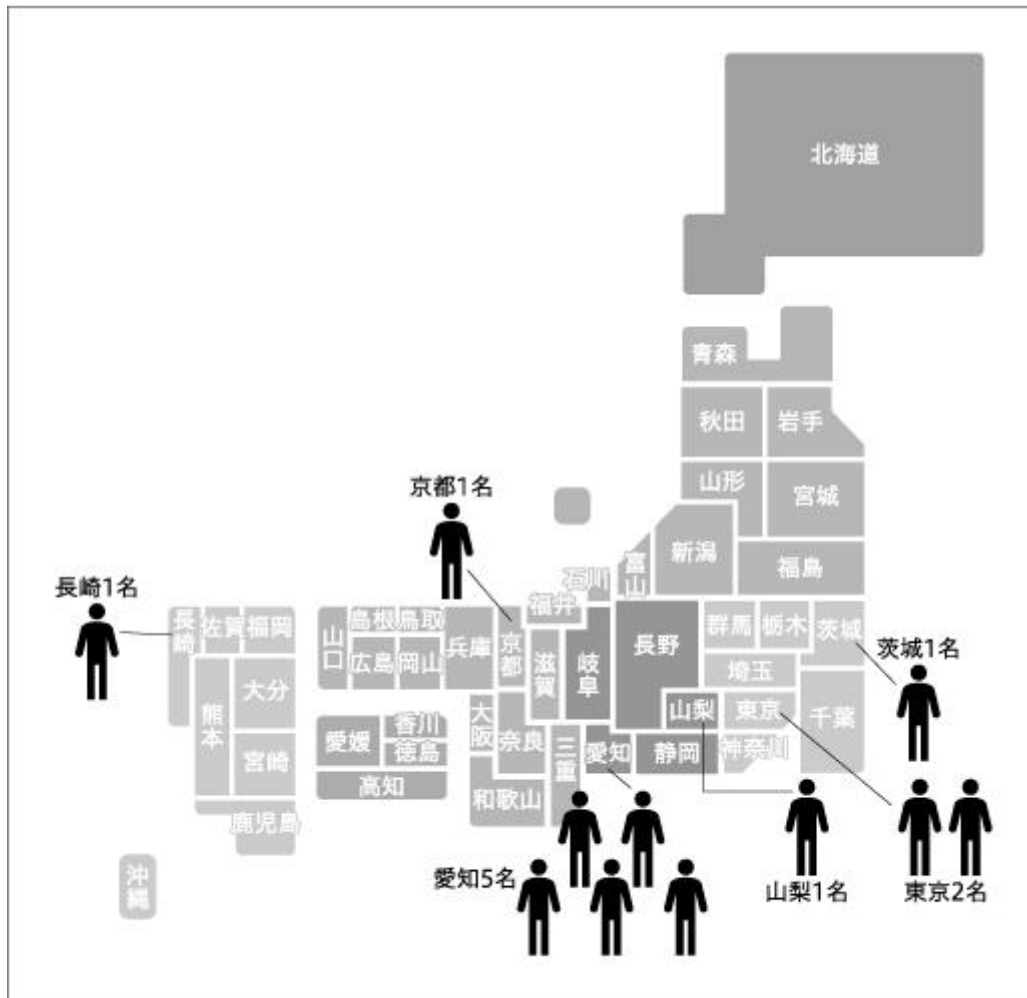


図5 臨床遺伝専門医（全1,638名）中の精神科医：2022年5月31日現在

Figure 5: Psychiatrists Among Clinical Geneticists (total of 1,638), as of May 31, 2022