Review

Not peer-reviewed version

Concerns regarding Transfusions of Blood Products Derived from Genetic Vaccine Recipients and Proposals for Specific Measures

Jun Ueda *, Hideyuki Motohashi, Yuriko Hirai, Kenji Yamamoto, Yasufumi Murakami, Masanori Fukushima, Akinori Fujisawa *

Posted Date: 15 March 2024

doi: 10.20944/preprints202403.0881.v1

Keywords: COVID-19 vaccine; genetic vaccine; blood product; blood transfusion; spike protein; post-vaccination syndrome; harm–benefit assessment; prion; spikeopathy; inspection standard; diagnostic criteria

Review

Concerns regarding Transfusions of Blood Products Derived from Genetic Vaccine Recipients and Proposals for Specific Measures

Jun Ueda [1,*], Hideyuki Motohashi [2], Yuriko Hirai [3], Kenji Yamamoto [4], Yasufumi Murakami [5], Masanori Fukushima [6] and Akinori Fujisawa [7,*]

[1] Department of Advanced Medical Science, Asahikawa Medical University, Asahikawa 078-8510, Hokkaido, Japan; junueda@asahikawa-med.ac.jp
[2] Pre-Clinical Research Center, Tokyo Medical University Hospital, 6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Tokyo, Japan; moto@tokyo-med.ac.jp
[3] MCL Corporation, Jimukino-Ueda bldg. 603, 21 Sakaimachi Gojo-Takakurakado, Shimogyo-Ku, Kyoto 600-8191, Kyoto, Japan; hirai@mcl-corp.jp
[4] Department of Cardiovascular Surgery, Center of Varicose Veins, Okamura Memorial Hospital, 293-1 Kakita Shimizu-cho, Sunto-gun, Shizuoka 411-0904, Japan; yamamoto@okamura.or.jp
[5] Department of Biological Science and Technology, Faculty of Advanced Engineering, Tokyo University of Science, 6-3-1 Niijuku, Katsushika-ku, Tokyo 125-8585, Japan; yasufumi@rs.tus.ac.jp
[6] Foundation of Learning Health Society Institute, Nagoya 450-0003, Aichi, Japan; mfukushima@imrd.jp
[7] Kokoro Medical Corporation, Honbetsu Cardiovascular Medicine Clinic, Honbetsu 089-3314, Hokkaido, Japan; fujisawa.peace@mac.com
* Correspondence: junueda@asahikawa-med.ac.jp (J.U.); fujisawa.peace@mac.com (A.F.); Tel.: +81-166-68-2385 (J.U.); +81-156-22-8888 (A.F.)

Abstract: The coronavirus pandemic was declared by the World Health Organization (WHO) in 2020, and a global genetic vaccination program has been rapidly implemented as a fundamental solution. However, many countries around the world have reported that so-called genetic vaccines, such as those using modified mRNA encoding the spike protein and lipid nanoparticles as the drug delivery system, have resulted in post-vaccination thrombosis and subsequent cardiovascular damage, as well as a wide variety of diseases involving all organs and systems, including the nervous system. In this article, based on these circumstances and the volume of evidence that has recently come to light, we call the attention of medical professionals to the various risks associated with blood transfusions using blood products derived from people who have suffered from long COVID and from genetic vaccine recipients, including those who have received mRNA vaccines, and we make proposals regarding specific tests, testing methods, and regulations to deal with these risks. We expect that this proposal will serve as a basis for discussion on how to address post-vaccination syndrome and its consequences following these genetic vaccination programs.

Keywords: COVID-19 vaccine; genetic vaccine; blood product; blood transfusion; spike protein; post-vaccination syndrome; harm–benefit assessment; prion; spikeopathy; inspection standard; diagnostic criteria

1. Introduction

On March 11, 2020, the coronavirus pandemic was declared by the Director-General of the World Health Organization (WHO) [1], and countries actively implemented classical public health measures, including quarantine, isolation, disinfection, and lockdowns. However, hopes for a vaccine grew as the general consensus was that rapid herd immunity was the best solution to overcome the pandemic. Since 2021, as a means to combat SARS-CoV-2 infection, several global pharmaceutical companies including Pfizer-BioNTech, Moderna, and AstraZeneca have developed various genetic vaccines that use the spike protein of the Wuhan strain of SARS-CoV-2 as an antigen, and rapid

 doi:10.20944/preprints202403.0881.v1

vaccination has been promoted on a global scale [2,3]. During this period, virological studies of SARS-CoV-2 have been intensively conducted, and the pathogenic mechanism of this virus has been elucidated in detail [4,5]. In brief, the key pathogenic processes include the binding of the spike protein of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2) receptor on vascular endothelial cells, allowing viral entry and amplification [6]; the triggering of red blood cell and platelet aggregation by the spike protein [7–11]; and the formation of microthrombi [12,13].

However, it has been reported from various countries around the world that genetic vaccines such as mRNA vaccines encoding spike proteins have also caused a wide variety of diseases in all organs and systems, including the nervous system, in addition to thrombosis and resulting cardiovascular disorders in vaccine recipients [14–21]. This is because when the foreign gene was introduced into autologous cells using gene-transfer capable lipid nanoparticles (LNPs) or other means, the spike proteins produced from the mRNA or DNA introduced via the gene vaccine induced thrombosis in the vaccine recipient. While evidence for specific problems has been reported individually, Parry et al. have proposed the theory of spikeopathy (spike disease) as a hypothesis that synthesizes all of the evidence for this problem [22]. Furthermore, there are two general mechanisms by which a modified gene introduced into the body by genetic vaccination and some of the antigens produced because of the expression of that gene can be transmitted throughout the body. First, LNPs encapsulating mRNA can spread through the body via the bloodstream from the injection site. It has already been shown that LNPs have a tendency to accumulate in specific organs, such as the liver, spleen, ovaries, testes, and bone marrow [22,23]. The other is the release of pseudouridinated mRNA molecules and synthesized spike proteins as extracellular vesicles, or exosomes, from cells that have incorporated LNPs. These exosomes are transported in the circulation throughout the body to reach various organs [24–27]. And it has already been proven that spike proteins produced by cells that have taken up the modified gene travel throughout the body in the bloodstream [28,29]. Thus, it must be emphasized that the transport, distribution, and expression of the components of the genetic vaccine beyond the administration site to organs and tissues of the whole body after vaccination involve the risk of inducing various conditions.

Although the Director-General of the WHO declared the end of the COVID-19 public health emergency on May 5, 2023, post-vaccination syndrome (PVS), caused by genetic vaccines that have been promoted worldwide and have been given to billions of people, has become a major global problem [19,21,27,30] requiring a reasonable harm–benefit assessment of the global use of genetic vaccines [27,31–33]. Since the beginning of the coronavirus pandemic and genetic vaccination, there has been much debate about the safety of blood products and their use in transfusions [34–39]. However, because the pathology of SARS-CoV-2 was not fully understood at the beginning, there was no specific discussion based on data or analysis of what was a problem and what could be a risk; only concerns were expressed, and no clear conclusions or policies were drawn. For example, Jacobs et al. argued that there was no requirement to collect or share the genetic vaccination status of blood donors and that hospitals were not required to inform patients about the genetic vaccination status of blood donors [37], because there were no reports of health issues from genetic vaccination in 2021. However, this argument was not based on data. Contrary to initial expectations, it was found that genes and proteins from genetic vaccines persist in the blood of vaccine recipients for prolonged periods of time [22,28,40–44], and a variety of adverse events resulting from genetic vaccines are now being reported worldwide. Roubinian et al. reported that transfusions of plasma and platelet blood components collected before and after COVID-19 vaccination were not associated with increased adverse outcomes in transfusion recipients who did not develop COVID-19 [39]. However, they evaluated only plasma and platelet preparations, not red blood cell or whole blood preparations. The long-term effects remain unclear, as the study only followed up recipients to the point of 30-day readmission rates.

Considering the current situation and the volume of evidence that has recently come to light, the purpose of this article is to raise awareness among relevant parties and point toward future directions by making specific recommendations regarding the use of blood products derived from genetic vaccine recipients, including those who have received mRNA vaccines. To be more precise,

 doi:10.20944/preprints202403.0881.v1

genetic vaccines are the equivalent of biomedicine (i.e. immune therapeutics) rather than conventional vaccines in terms of their mechanism of action [45,46]. The various genetic vaccines now treated as vaccines should originally have been treated as biomedicine, but because they were classified as vaccines, huge numbers of people were inoculated with them [2,3]. As a result, extensive areas of medicine are now beginning to be affected because most of the population in many countries has been vaccinated [19,21,27,30,47]. This has never happened before in the history of biomedicine, and consequently, it is highly suspected that blood products for transfusion have been affected by these so-called genetic vaccines. Therefore, this review was prepared to examine the risks of blood transfusions at the current stage when genetic vaccines are administered in large quantities. The vaccine recipients described in this proposal are limited to genetic vaccine recipients.

2. Overview of Cases of Blood Abnormalities after Genetic Vaccination

A wide variety of diseases related to blood and blood vessels, such as thrombosis, have developed after genetic vaccination, including with mRNA vaccines, and many cases of serious health injuries have been reported. For example, a PubMed search on diseases such as thrombocytopenia, thrombotic disorders with thrombocytopenia, deep vein thrombosis, thrombocytopenic purpura, cutaneous vasculitis, and sinus thrombosis combined with the essential keywords “COVID-19 vaccine” and “side effects” yielded several hundred articles in only about two years since the rollout of genetic vaccines [14,17,20,21,48]. In addition to abnormally shaped red blood cells, amorphous material has been found floating in the blood of mRNA-vaccinated individuals under microscopic observation, some of which has shown grossly abnormal findings (Table 1, point 5) [7–10,49]. Recent studies have also reported that the spike protein has amyloidogenic potential [50–54], is neurotoxic [55–57], and can cross the blood–brain barrier [58–60]. Thus, there is no longer any doubt that the spike protein used as an antigen in genetic vaccines is itself toxic [22,61,62].

In addition to thrombosis, individuals who have received multiple doses of a genetic vaccine may have multiple exposures to the same antigen within a brief period, thereby being imprinted with a preferential immune response to that antigen [63,64]. This phenomenon, called original antigenic sin or immune imprinting, has caused COVID-19 vaccine recipients to become more susceptible to contracting COVID-19 [65]. In addition, antibody-dependent enhancement of infection is also known; antibodies produced by vaccination may rather promote viral infection and symptoms [66,67]. On the other hand, it has also been suggested that repeated administration of genetic vaccines may result in immune tolerance because of a class switch to non-inflammatory immunoglobulin G4 (IgG4) [68–71], whereby the immune system of the recipient does not mount an excessive response such as cytokine storm [27,72], and case reports of IgG4-related disease have begun to appear [73–75]. This raises concern that alterations in immune function due to immune imprinting and immunoglobulin class switching to IgG4 may also occur in genetic vaccine recipients. This may increase the risk of serious illness due to opportunistic infections or pathogenic viruses that would not normally be a problem if the immune system were normal [76–82]. For example, cases of suspected viremia have been reported [82]. Therefore, from the perspective of traditional containment of infectious diseases, greater caution is required in the collection of blood from genetic vaccine recipients and the subsequent handling of blood products, as well as during solid organ transplantation and even surgical procedures [83–87] in order to avoid the risk of accidental blood-borne infection (Table 1, point 3) [84–87]. The phenomenon of immune imprinting can occur even when spike protein is not used as an antigen or when another antigen is used (e.g. inactivated influenza vaccine) [88]. However, compared to conventional inactivated vaccines, genetic vaccines, which produce an antigen within the body, are expected to prolong the period of exposure to the same antigen, and as a result, the risk of immune imprinting may be higher than with conventional vaccines. It is not actually known how long the vaccine components remain in the body after a person has received a genetic vaccine [22,40,43], but it is expected that they will remain in the body for a longer period than originally thought, in part because spike protein has been detected in the bodies of people several months after vaccination (Table 1, point 1) [22,28,41,42]. In addition, since long-term exposure to a specific identical antigen (in this case, spike protein) causes immunoglobulins to become IgG4 [68,70] and some of the

 doi:10.20944/preprints202403.0881.v1

B cells that produce them are likely to differentiate into memory B cells that survive in the body for a sustained period [70,89], the immune dysfunction of genetic vaccine recipients is expected to be prolonged (Table 1, point 3 & 6). More details on these points are expected to be revealed in the future.

In summary, there is an undeniable risk that patients may experience some problems if they receive blood products derived from blood collected in, at least, a brief deferral period after genetic vaccination. Although it is unknown at present whether secondary damage is caused by transfusion of blood products derived from genetic vaccine recipients, it is necessary for medical institutions and administrative organizations to respond and investigate cooperatively, keeping various possibilities in mind, because mechanisms such as the toxicity of the spike protein itself and the effects of LNPs and modified mRNA on the immune response have not been fully elucidated and are still under study. It should be emphasized that a significant proportion of the COVID-19 PVS in mRNA vaccine recipients is due to toxic spike proteins, and the inclusion of structures in the receptor-binding domain within these proteins that may induce prion disease is particularly alarming, as Seneff et al. and Perez et al. have warned [50,90–96]. Furthermore, it has been shown that prion similarity in the receptor-binding domain exists not only in the spike protein of the Wuhan strain, which is still used as an antigen in genetic vaccines, but also in the spike protein of variants of SARS-CoV-2, such as the Delta strain, with the exception of the Omicron strain [93,97]. Whether we should be uniformly vigilant for the spike protein of the coronavirus or just the spike protein of certain variants, such as the Wuhan strain, awaits further analysis.

Table 1. Major concerns with the use of blood products derived from gene vaccine recipients.

	Concerns	Description	References
1	Spike protein contamination	The spike protein, which is the antigen of SARS-CoV-2 and genetic vaccines, has already been found to have various toxicities, including effects on red blood cells and platelet aggregation, amyloid formation, and neurotoxicity. It is essential to recognize that the spike protein itself is toxic to humans. It has also been reported that the spike protein can cross the blood–brain barrier. Therefore, it is essential to remove the spike protein derived from the gene vaccine itself from blood products.	[22,29,55–60]
2	Contamination with amyloid aggregates and microthrombi formed by spike proteins	It is not yet clear how the amyloid aggregates and microthrombi formed by the spike proteins develop into visible thrombi. However, once formed, amyloid aggregates may not be readily cleared and therefore need to be removed from blood products. These amyloid aggregates have also been shown to be toxic.	[51,52,98]
3	Events attributable to decreased donor immune system and immune abnormalities due to immune imprinting or class switch to IgG4, etc. resulting from multiple doses of genetic vaccines	When the immune function of a donor is impaired by gene vaccination, there is a risk that the donor has some (subclinical) infectious disease or is infected with a pathogenic virus and has developed viremia or other conditions, even if the donor has no subjective symptoms. For this reason, healthcare professionals who perform surgical procedures, including blood sampling and organ transplantation, as well as using blood products, should manage the blood of genetic vaccine recipients with care to prevent infection through blood. It will also be necessary to inform all healthcare professionals of these risks.	[63–65,68–71,76–80,82–87]
4	Lipid nanoparticles (LNPs) and pseudouridinated mRNA (mRNA vaccines only)	In the case of mRNA vaccines, LNPs and pseudouridinated mRNA may remain in the blood of recipients if blood is collected without a sufficient deferral period after gene vaccination. LNPs are highly inflammatory and have been found to be thrombogenic themselves, posing a risk to transfusion recipients. LNPs itself has potent adjuvant activity and is at risk of inducing Adjuvant-Induced Autoimmune Syndrome (ASIA syndrome). An additional risk is that if the pseudouridinated mRNA is incorporated into the recipient's blood while still packaged in LNPs, additional spike protein may be produced in the recipient's body.	[23,40,44,99–105]
5	Contamination with aggregated red blood cells or platelets	The spike protein causes red blood cells and platelets to aggregate and therefore these aggregates will be carried into the recipient's blood unless they are removed from the blood product.	[7–11,49]
6	Memory B cells producing IgG4 and IgG4 produced from them	Large amounts (serum concentration typically above 1.25–1.4 g/L) of non-inflammatory IgG4-positive plasma cells can cause chronic inflammation such as fibroinflammatory disease.	[73–75,106,107]

 doi:10.20944/preprints202403.0881.v1

3. Specific Proposals for Blood Sampling and Blood Products from Vaccine Recipients

In the previous section, we discussed a variety of blood-related abnormalities that have occurred following genetic vaccination. In this section, we provide specific proposals on how to respond to these circumstances. Because blood contamination affects so many areas of health care, it is especially important to anticipate the worst [95,96,108–110] and to plan and act from the start to ensure that there are no lapses or omissions.

3.1. Additional Requirements for Blood Collection (Donation)

Currently, in Japan, the Japanese Red Cross Society (https://www.jrc.or.jp/english/) plays a central role in blood collection activities, and its blood products are used for blood transfusions and other purposes. The Japanese Red Cross Society has a rule that blood can be collected from genetic vaccine recipients after a deferral period (48 hours for mRNA vaccine recipients and 6 weeks for AstraZeneca DNA vaccine recipients), but the data and rationale for the rule have not been specified. As with infections such as human immunodeficiency virus (HIV) and prion diseases, a history of genetic vaccination (DNA and/or mRNA type), including timing and number of doses, should be obtained by interview, and kept in the official record when blood is collected (Figure 1, Table 2). Additional caution is needed, particularly if not many days have passed since the genetic vaccine was administered, because LNPs [23,101–103] and spike protein mRNA, which can induce inflammation, may remain in the blood (Table 1, point 4) [22,40,43,44]. If certain events such as anaphylactic shock occur immediately after genetic vaccination, the effects of LNPs should also be suspected [100]. It has also been reported that negatively charged LNPs themselves interact with fibrinogen to form thrombi [99]. Therefore, the presence of LNPs may itself be a factor in the need for caution with transfusion products.

On the other hand, even if a person has not received a genetic vaccine, if they have had long COVID, it is possible that the spike protein remains in their body, and thus it would be better to keep an official record of whether they have long COVID or not [51,111–113]. As the degradation rates of pseudouridinated mRNA and spike protein in the body are unknown at present, blood products derived from genetic vaccine recipients should be used with extreme caution, being conscious of the cases of AIDS, bovine spongiform encephalopathy (BSE), and variant Creutzfeldt-Jakob disease (vCJD) caused by the use of contaminated blood products in the past [110,114–121].

 doi:10.20944/preprints202403.0881.v1

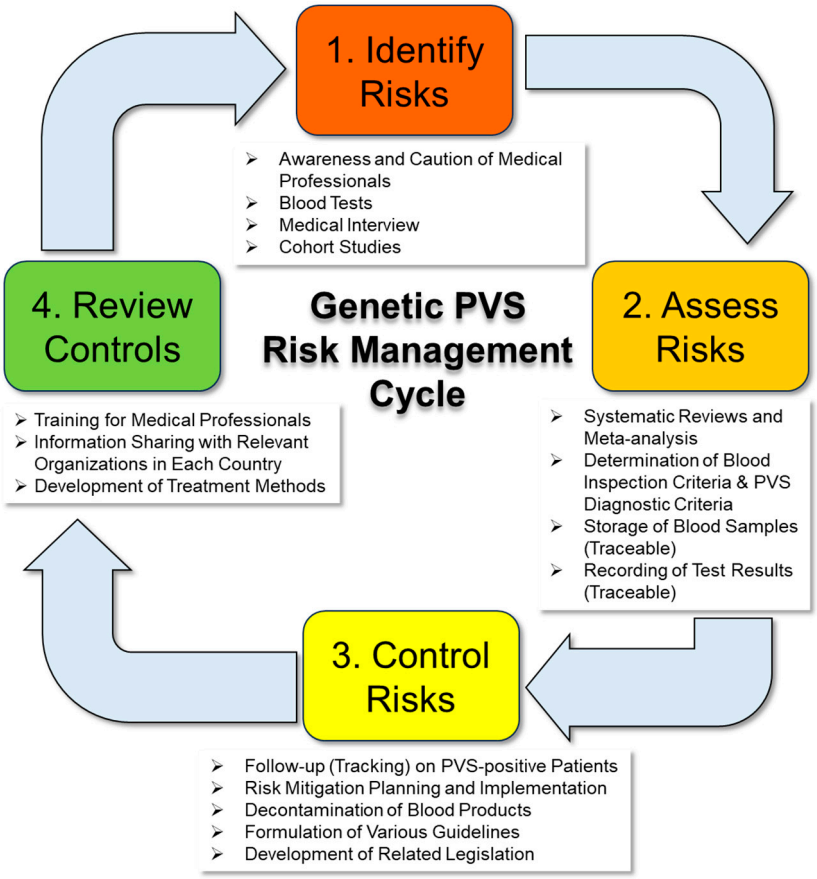

Figure 1. Summary of items and procedures required for management of blood products derived from gene vaccine recipients or contaminated with spike protein and modified genes. As with any risk management exercise, it is important to constantly revise policies and procedures as risks and problems are identified. PVS, post-vaccination syndrome.

Table 2. Tests needed to confirm the safety of blood products.

	Concerns	Description	References
1	Spike protein content in blood	Immunochemical techniques include enzyme-linked immunosorbent assay, immunophenotyping, mass spectrometry, liquid biopsy, and a combination of liquid biopsy and proteomics. First, we propose mass spectrometry that can directly measure the protein itself.	[28,29,122–126]
2	Spike protein mRNA	PCR and/or liquid biopsy are the options. If mRNA for the spike protein is detected, LNPs may be present (mRNA vaccines only).	[124,127,128]
3	Spike protein DNA	PCR and liquid biopsy are the options. This test is necessary because AstraZeneca's viral vector is a DNA vaccine. For mRNA vaccines, it is believed that pseudouridinated mRNA is not reverse transcribed, but this test is required if the spike protein remains for a prolonged period.	[124,128]
4	Markers associated with autoimmune disorders	Long-term persistence of the spike protein in the blood increases the risk of autoimmune disease. Therefore, it would be useful to test for autoimmune disease using antinuclear antibodies as biomarkers in people who are positive for the spike protein, taking into account the results of interviews regarding the subjective symptoms.	[27,105,129,130]
5	Interview	A history of genetic vaccination and COVID-19, current and previous medical history, and subjective symptoms (e.g. headache, chest pain, shortness of breath, malaise) should be obtained from blood donors and formally recorded. The types of questions included in the interview are critical to facilitate diagnosis and treatment of COVID-19 PVS, as more people are complaining of psychiatric and neurological symptoms after genetic vaccination.	[15,131,132]

 doi:10.20944/preprints202403.0881.v1

6	Proteins resulting from frameshifting of pseudouridinated mRNA	Although it is not yet clear whether proteins other than the spike protein are translated from pseudouridinated mRNAs, mass spectrometry may be useful in confirming this.	[133]
7	Components of amyloid aggregates and thrombi	Common markers of thrombosis, such as D-dimer, are used first. Once the major components of amyloid aggregates and thrombi have been identified, their use as biomarkers is proposed. Understanding the composition of amyloid aggregates will be important in the future, as amyloid aggregates have been reported to be toxic. Understanding the composition of amyloid aggregates may provide clues to how amyloid is broken down.	[51,52,98,134]
8	Components of SARS-CoV-2 other than the spike protein gene	This test will help determine whether the spike protein is from the genetic vaccine or from SARS-CoV-2. Potential candidates include nucleocapsid.	[4,5,41,128]
9	Immunoglobulin subclasses	It may be necessary to analyze immunoglobulin subclasses (the amount of IgG4) if immunosuppression from multiple doses of the genetic vaccine is a concern.	[68–71]
10	Anti-nucleocapsid antibodies	The presence or absence and amount of anti-nucleocapsid antibodies as well as antibody isotypes may be an indicator(s) in distinguishing whether genetic vaccination or long COVID is the cause.	[135–137]
11	Other	Myocarditis and pericarditis after genetic vaccination have been reported in various countries. Therefore, those with subjective symptoms may also be tested for myocarditis marker, such as cardiac troponin T.	[18,19,29,138–140]

3.2. Handling of Existing Blood Products

At present, the genetic vaccination status of blood donors is not confirmed or controlled by organizations including medical institutions, and the use of blood collected from these donors for transfusions may pose risks to patients. Therefore, when blood products derived from gene vaccine recipients are used, it is necessary to confirm the presence or absence of spike protein or modified mRNA as in other tests for pathogens (Figure 1, Table 2). These should be quantified by an immunochemical enzyme-linked immunosorbent assay (ELISA), by immunophenotyping, by direct mass spectrometry of the protein itself, by an exosome-based liquid biopsy as used in cancer screening, or by PCR [28,29,122–128]. For protein assays, as it may take time to generate a good-quality anti-spike protein antibody or a positive control for a recombinant spike protein to be compared with, and to sort and distribute them to each laboratory, we suggest that mass spectrometry be used as an initial step to identify and quantify the spike protein itself in blood [28,125]. In parallel with this, an analysis of the components of the spike protein-induced amyloid material will be needed [51,98]. Once the components of amyloid aggregates are identified, they can be used as biomarkers in the future. Exosome analysis will also be useful as a test as it has already been shown that spike proteins and their genes are transported in the circulation around the body by exosomes [24–27].

If the blood product is found to contain the spike protein or a modified gene derived from the genetic vaccine, it is essential to remove them. However, there is currently no reliable way to do so. As noted above, the prion-like structure within the spike protein molecule [91,95,96] suggests that this molecule may be a persistent, sparingly soluble, heat-resistant, and radiation-resistant protein [141,142]. The prion protein can be inactivated by thiocyanate, hydroxide, and hypochlorite [143–145], but it is not yet known whether these can be applied to the spike protein and the resulting amyloid materials. Therefore, as there is no way to reliably remove the pathogenic protein or mRNA, we suggest that all such blood products be discarded until a definitive solution is found. Discarding blood products prepared from blood collected from many dedicated blood donors can be very painful, but it is necessary because the spike protein itself has been shown to induce thrombosis and similar diseases. However, some medical facilities may have difficulty disposing of blood products immediately, in which case it is essential to add the possibility of contamination with spike protein or other foreign substances to the transfusion consent form and to fully explain this to the patient. In any case, to prevent and reduce medical accidents caused by contaminated blood, it is imperative to underscore the importance of confirming the history and frequency of genetic vaccination at the time of blood collection and this information should be documented as an official record, managed and stored by both medical and governmental organizations (see Figure 1, Table 2).

 doi:10.20944/preprints202403.0881.v1

3.3. The Need for Regular Checkups and Cohort Studies to Gain a Complete Picture of Blood Contamination

As the residual status of spike protein or modified gene fragments derived from genetic vaccines is currently unknown, it will be necessary in the future to include measurement of these amounts in routine health checkups. It is also necessary to include a section in the routine medical checkup questionnaire to check genetic vaccination status and the number of vaccinations to obtain an overall picture of the residual status of spike proteins in the blood. This is because a variety of conditions following genetic vaccination involve thrombosis and immunological conditions [12,14,16,17,21,22,68,70]. Therefore, abnormalities in blood components related to these events should also be analyzed.

On the other hand, when exosomes collected from vaccine recipients were administered to mice that had not been vaccinated with the genetic vaccine, the spike protein was transmitted [25]. Therefore, it cannot be denied that the spike protein and its modified genes can be transmitted through exosomes. For this reason, we suggest that full testing be done initially, regardless of genetic vaccination status, and that a cohort study be conducted to quickly capture the full picture (Figure 1). This is a steady, labor-intensive effort that requires collaboration between all parties involved, but such analyses may lead to the development of diagnostic criteria and testing for COVID-19 PVS. In addition, as mentioned above, it cannot be ruled out that even those who have not been vaccinated with the genetic vaccine, but have had long COVID, may have residual spike proteins or fibrin-derived microthrombi in their bodies, so it would be advisable to conduct the same testing and follow-up as for genetic vaccine recipients [51,52,111–113]. The presence or absence and amount of anti-nucleocapsid antibodies as well as antibody isotypes may be an indicator(s) in distinguishing whether genetic vaccination or long COVID is the cause (Table 2, point 10) [135–137]. In any case, these cohort studies are expected to help establish cutoff values for blood levels of spike protein and other substances to determine the safety of blood products. Faksova et al. conducted a large cohort study of 99 million people using a multinational Global Vaccine Data Network™ (GVDN®) and found a significantly increased risk of myocarditis, pericarditis, Guillain-Barre syndrome, and cerebral venous sinus thrombosis in genetic vaccine recipients [140]. This type of study will be increasingly necessary in the future.

3.4. The Need for Early Development of Clinical Practice Guidelines and Diagnostic Criteria for COVID-19 PVS

Although the spectrum of COVID-19 PVS is diverse, it is characterized by a high prevalence of hematologic and immune-related diseases [21]. Considering this, regardless of the transfusion issues discussed in this review, blood tests are likely to be the first step in the diagnosis of COVID-19 PVS. The ability to rapidly develop highly accurate testing systems, particularly blood tests, in collaboration with other countries will be critical in treating patients suffering from PVS due to the COVID-19 vaccine. Additional meta-analysis of data from systematic reviews and cohort analyses will be needed to prevent bias in diagnostic criteria and to develop appropriate clinical practice guidelines (Figure 1) [146–148].

4. Problems following Blood Transfusion Using Blood Products Prepared from Donated Blood of Genetic Vaccine Recipients and the Need for Traceability of Blood Products for Transfusion

With the advent of genetic vaccination, there has been considerable debate about the safety of blood products prepared from donated blood of the vaccine recipients and their use in blood transfusion [36–39]. However, what happens in the body when a genetic vaccine such as an mRNA vaccine is administered in the first place is not well understood at this stage, and as mentioned above, the results of tests on the vaccine recipient's blood need to be evaluated. Cases of encephalitis caused by blood from dengue vaccine recipients have been reported as recently as 2023 [149], indicating that the current system for managing and tracking blood products is not adequate. Unless accurate tests are established, no conclusions can be drawn about the risk or safety of blood transfusions using blood products from gene vaccine recipients. Thorough and continuous investigation is therefore

 doi:10.20944/preprints202403.0881.v1

necessary. To accomplish this, all potential donors should be registered, traceability of blood products should be ensured, and rigorous recipient outcome studies and meta-analysis should be maintained. Furthermore, as we have repeatedly stated, it is essential to rigorously obtain from donors a history of vaccination and COVID-19 infection, preserve official records, and store samples of blood products for later detection and verification of substances such as spike proteins and exosomes (Figure 1). Given the wide variety of tests and records, the movement of people around the world, and the import/export of blood products, it may be necessary in the future to establish traceability by introducing blockchain technology into the management of blood products while maintaining anonymity [150,151].

5. The Need for the Development of Relevant Legislation

The issue of blood products derived from genetic vaccine recipients described in this review is expected to affect a very wide range of areas in countries around the world. In Japan, the "Act on Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases" (https://www.japaneselawtranslation.go.jp/en/laws/view/2830/en) has been enacted to prevent the spread of infectious diseases through blood products, and the "Act on Organ Transplantation" has been enacted to handle organ transplants. The Ministry of Health, Labour and Welfare (MHLW) has issued the "Guidelines for Blood Transfusion Therapy" regarding blood transfusions. These laws and guidelines specify the responsibilities of the public, physicians, and national and local governments and protect their rights. However, as the spike protein used as an antigen or its gene is not an organism, there are likely to be number of difficult issues, such as how to legally define its pathogenicity. From this point of view, when the risks of and health injuries caused by blood products derived from genetic vaccination recipients have been roughly clarified (Table 2), it will be essential to formulate regulations to reduce and prevent risks and contamination, by developing related laws with the participation of the legislative branch, legal experts, medical administration personnel, healthcare providers, and medical researchers, and by taking measures such as checking vaccination status and dates, and legally regulating the import/export of blood products (Figure 1). The wide range of issues makes coordination between agencies and healthcare professionals essential from the outset.

Second, it is expected that the situation will already be complicated because, in contrast to previous drug disasters, genetic vaccination was implemented on a global scale and simultaneously for a substantial number of people [2,3]. This means, as in the context of the coronavirus pandemic, or even more critically, that there is an urgent necessity for legislation and international treaties explicitly elucidating bilateral and multilateral agreements concerning the management of blood products. These legal frameworks should delineate regulations governing the handling of blood products and establish protocols for governmental compensation and response to issues and hazards associated with these products, including penalties and prohibitions. For example, the International Health Regulations (IHR) 2005 may be helpful [152,153], but given the WHO's strong push for genetic vaccination [154], another framework may be needed. In relation to the cohort studies described in Section 3.3 of this article, it will also be necessary for countries to conduct active epidemiological surveys [155], as was the case with COVID-19, to compile the results of these surveys, and to establish an international organization tasked with monitoring response efforts and assessing damages within each country (Figure 2). It is expected that it will be important to incorporate not only the perspective of infectious diseases but also biosafety and biosecurity [153,156].

As for Japan, Article 15 (2) of the Infectious Disease Act (https://www.japaneselawtranslation.go.jp/ja/laws/view/2830/en#je_ch3at5) stipulates that the Japanese government is responsible for conducting epidemiological studies. Given the significant health risks associated with COVID-19 PVS, we urge the Japanese government to prioritize the analysis and safety verification of blood products derived from gene vaccine recipients. This is imperative given the urgent nature of the situation.

 doi:10.20944/preprints202403.0881.v1

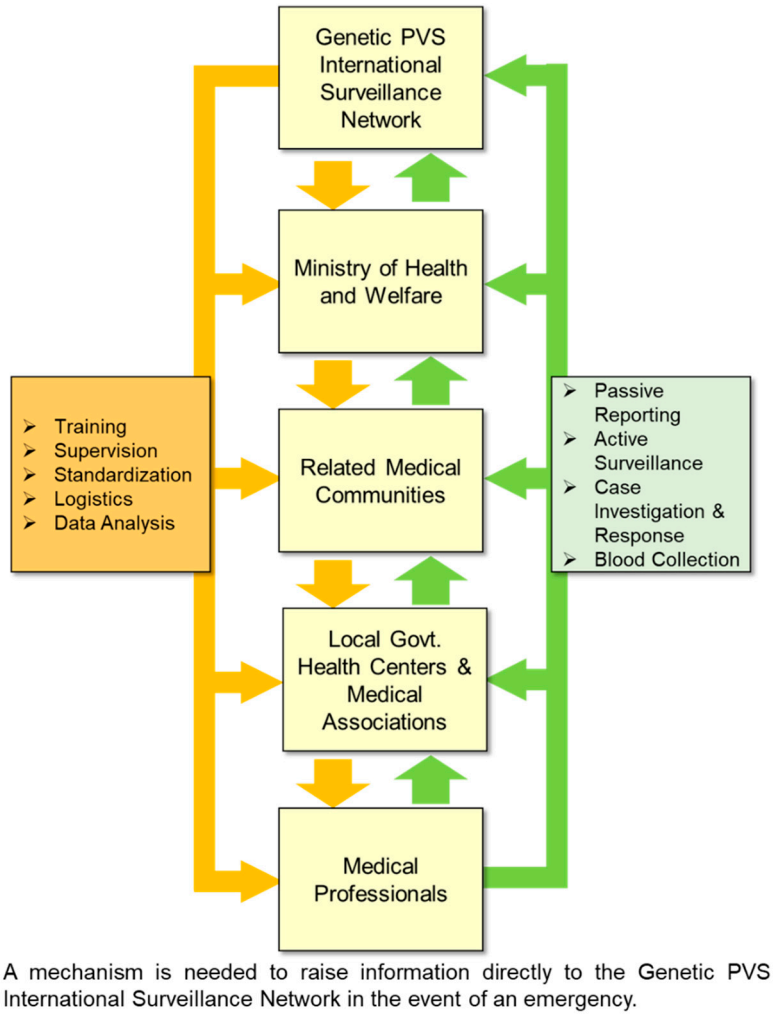

Figure 2. An example of a system for managing health injuries among genetic vaccine recipients. Given the global nature of genetic vaccination and the movement of vaccine recipients and blood products between countries, there will be a need for an international surveillance network to coordinate countries.

6. Other Important Considerations

There is an urgent need to develop methods to identify as well as remove spike proteins and modified genes derived from gene vaccines in blood products. In order to develop a uniform inspection standard, there is an urgent need in Japan for the Japanese Society of Hematology (http://www.jshem.or.jp/modules/en/index.php?content_id=1), the Japanese Society of Transfusion and Cell Therapy (http://yuketsu.jstmct.or.jp/en/), and their related organizations to develop guidelines on how to handle blood products that contain residual spike proteins or their modified genes. Also, as noted earlier, gene vaccination has been promoted on a global scale [2,3], which will necessitate coordination and exchange of information with national administrations and relevant international medical societies (Figure 1). International guidelines on the handling of blood products and the establishment of an international investigatory organization will be necessary (Figure 2). However, there is an urgent need to share the risks of transfusion of blood products derived from genetic vaccine recipients among the parties concerned, and prompt investigation and response by all parties concerned is essential. The most important initial action is to make the relevant medical personnel aware of this situation.

In the development of various guidelines, it will be helpful to refer to the response of each country when the transmission of BSE and vCJD, also through blood transfusion, became a problem (e.g. the Creutzfeldt-Jakob Disease International Surveillance Network in

 doi:10.20944/preprints202403.0881.v1

https://www.eurocjd.ed.ac.uk/) [110,114,115,121,157]. For example, in the United Kingdom, when BSE became a social problem and the mode of transmission of prion protein was unknown, leukodepletion of blood products was conducted universally. Whether this was effective in preventing transmission of BSE and vCJD through blood products is controversial [110,120,121,158], but it was not common at the time to remove white blood cells from all blood products, as is now routinely done with collected blood. However, because of leukodepletion, the safety of blood products has increased [159]. In the case of the spike protein, which causes abnormalities such as agglutination of red blood cells and platelets [8–11,49], we do not expect the problem to be eliminated by leukodepletion alone. However, it is worth confirming whether washing of red blood cells can be effective [160,161]. In urgent cases, autotransfusion may be an option [162].

Recent studies have shown that RNA pseudouridylation can result in frameshifting [133]. It is not yet clear whether a portion of the pseudouridinated mRNA for the spike protein is translated into another protein of unknown function in vaccine recipients. If these proteins are also pathogenic, additional testing for such frameshift proteins may be needed in the future. Even if a frameshift protein is not toxic, it must be foreign to the body and could cause autoimmune disease. In addition, LNPs themselves are highly inflammatory substances [23,100–102], as described in Section 3.1, but LNPs have been found to have stronger adjuvant activity than the adjuvants used in conventional vaccines [104], and there is also concern about autoimmune diseases resulting from this aspect (Table 1, point 4) [105,163]. Thus, although it is not clear what the causative agent of autoimmune disease is, the large number of reported cases of autoimmune disease following genetic vaccination is extremely concerning [15,21,27,30,105,164]. The very mechanism of gene vaccines that causes one's own cells to produce the antigens of pathogens carries the risk of inducing autoimmune diseases, which cannot be completely avoided even if mRNA pseudouridylation technology is used. In this context, individuals with a positive blood test for spike protein may need to have interviews and additional tests for autoimmune disease indicators, such as antinuclear antibodies (Table 2, point 4) [27,105,129,130]. Alternatively, if the amino acid sequence of the protein resulting from the frameshift is predictable, these candidate proteins could be included in the initial mass spectrometry assay (Table 2, point 6). In any case, it is particularly important to develop tests and establish medical care settings in anticipation of these situations.

7. Conclusion

Finally, we would like to state that if we continue to use genetic vaccines such as pseudouridinated mRNAs and mRNA-LNP platforms [46,103], there will be further risks like those described in this review. It should also be stressed that the issues discussed here are matters that pertain to all organ transplants, including bone marrow transplants, and not just blood products. The impact of these genetic vaccines on blood products and the actual damage caused by them are unknown at present. Therefore, in order to avoid these risks and prevent further expansion of blood contamination and complication of the situation, we strongly request that the vaccination campaign using genetic vaccines be suspended and that a harm–benefit assessment be carried out as early as possible, as called for by Fraiman et al. and Polykretis et al. [27,31–33]. As we have repeatedly stated, the health injuries caused by genetic vaccination are already extremely serious, and it is high time that countries and relevant organizations take concrete steps together to identify the risks and to control and resolve them.

Author Contributions: Conceptualization, J.U. M.F. and A.F.; investigation, J.U. H.M. Y.M. M.F. and A.F.; resources, Y.H.; data curation, J.U. H.M. M.F. and A.F.; writing—original draft preparation, J.U.; writing—review and editing, J.U. H.M. Y.H. K.Y. M.F. and A.F.; visualization, J.U.; supervision, J.U. M.F. and A.F.; project administration, J.U. M.F. and A.F.; funding acquisition, M.F. and A.F. All authors have read and agreed to the published version of the manuscript.

Funding: The study was supported by donations from members of the Japanese Society for Vaccine-related Complications and the Volunteer Medical Association.

Institutional Review Board Statement: Not applicable.

 doi:10.20944/preprints202403.0881.v1

Acknowledgments: We would like to express our deep appreciation to the members of the Volunteer Medical Association for their help in the discussions that led to the preparation of this review.

Conflicts of Interest: The authors declare no conflict of interest in connection with this research.

References

1. Sohrabi, C.; Alsafi, Z.; O'Neill, N.; Khan, M.; Kerwan, A.; Al-Jabir, A.; Iosifidis, C.; Agha, R. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery* **2020,** 76, 71–76.
2. Francis, A.I.; Ghany, S.; Gilkes, T.; Umakanthan, S. Review of COVID-19 vaccine subtypes, efficacy and geographical distributions. *Postgraduate Medical Journal* **2022,** 98, 389–394.
3. Patel, R.; Kaki, M.; Potluri, V.S.; Kahar, P.; Khanna, D. A comprehensive review of SARS-CoV-2 vaccines: Pfizer, Moderna & Johnson & Johnson. *Human Vaccines & Immunotherapeutics* **2022,** 18.
4. Harrison, A.G.; Lin, T.; Wang, P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. *Trends in Immunology* **2020,** 41, 1100–1115.
5. Lamers, M.M.; Haagmans, B.L. SARS-CoV-2 pathogenesis. *Nature Reviews Microbiology* **2022,** 20, 270–284.
6. Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H.; Fan, S.; Zhang, Q.; Shi, X.; Wang, Q.; Zhang, L.; Wang, X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* **2020,** 581, 215–220.
7. Zhang, S.; Liu, Y.; Wang, X.; Yang, L.; Li, H.; Wang, Y.; Liu, M.; Zhao, X.; Xie, Y.; Yang, Y.; Zhang, S.; Fan, Z.; Dong, J.; Yuan, Z.; Ding, Z.; Zhang, Y.; Hu, L. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *Journal of Hematology & Oncology* **2020,** 13.
8. Berzuini, A.; Bianco, C.; Migliorini, A.C.; Maggioni, M.; Valenti, L.; Prati, D. Red blood cell morphology in patients with COVID-19-related anaemia. *Blood Transfus* **2021,** 19, 34–36.
9. Melkumyants, A.; Buryachkovskaya, L.; Lomakin, N.; Antonova, O.; Serebruany, V. Mild COVID-19 and Impaired Blood Cell–Endothelial Crosstalk: Considering Long-Term Use of Antithrombotics? *Thrombosis and Haemostasis* **2021,** 122, 123–130.
10. Boschi, C.; Scheim, D.E.; Bancod, A.; Militello, M.; Bideau, M.L.; Colson, P.; Fantini, J.; Scola, B.L. SARS-CoV-2 Spike Protein Induces Hemagglutination: Implications for COVID-19 Morbidities and Therapeutics and for Vaccine Adverse Effects. *International Journal of Molecular Sciences* **2022,** 23.
11. Scheim, D.E. A Deadly Embrace: Hemagglutination Mediated by SARS-CoV-2 Spike Protein at Its 22 N-Glycosylation Sites, Red Blood Cell Surface Sialoglycoproteins, and Antibody. *International Journal of Molecular Sciences* **2022,** 23.
12. McFadyen, J.D.; Stevens, H.; Peter, K. The Emerging Threat of (Micro)Thrombosis in COVID-19 and Its Therapeutic Implications. *Circulation Research* **2020,** 127, 571–587.
13. Grobbelaar, Lize M.; Venter, C.; Vlok, M.; Ngoepe, M.; Laubscher, Gert J.; Lourens, Petrus J.; Steenkamp, J.; Kell, Douglas B.; Pretorius, E. SARS-CoV-2 spike protein S1 induces fibrin(ogen) resistant to fibrinolysis: implications for microclot formation in COVID-19. *Bioscience Reports* **2021,** 41.
14. Bilotta, C.; Perrone, G.; Adelfio, V.; Spatola, G.F.; Uzzo, M.L.; Argo, A.; Zerbo, S. COVID-19 Vaccine-Related Thrombosis: A Systematic Review and Exploratory Analysis. *Front Immunol* **2021,** 12, 729251.
15. Garg, R.K.; Paliwal, V.K. Spectrum of neurological complications following COVID-19 vaccination. *Neurological Sciences* **2021,** 43, 3–40.
16. Oldenburg, J.; Klamroth, R.; Langer, F.; Albisetti, M.; von Auer, C.; Ay, C.; Korte, W.; Scharf, R.E.; Pötzsch, B.; Greinacher, A. Diagnosis and Management of Vaccine-Related Thrombosis following AstraZeneca COVID-19 Vaccination: Guidance Statement from the GTH. *Hämostaseologie* **2021,** 41, 184–189.
17. Sharifian-Dorche, M.; Bahmanyar, M.; Sharifian-Dorche, A.; Mohammadi, P.; Nomovi, M.; Mowla, A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. *J Neurol Sci* **2021,** 428, 117607.
18. Lane, S.; Yeomans, A.; Shakir, S. Reports of myocarditis and pericarditis following mRNA COVID-19 vaccination: a systematic review of spontaneously reported data from the UK, Europe and the USA and of the scientific literature. *BMJ Open* **2022,** 12.
19. Oster, M.E.; Shay, D.K.; Su, J.R.; Gee, J.; Creech, C.B.; Broder, K.R.; Edwards, K.; Soslow, J.H.; Dendy, J.M.; Schlaudecker, E.; Lang, S.M.; Barnett, E.D.; Ruberg, F.L.; Smith, M.J.; Campbell, M.J.; Lopes, R.D.; Sperling, L.S.; Baumblatt, J.A.; Thompson, D.L.; Marquez, P.L.; Strid, P.; Woo, J.; Pugsley, R.; Reagan-Steiner, S.; DeStefano, F.; Shimabukuro, T.T. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. *Jama* **2022,** 327.

20. Yasmin, F.; Najeeb, H.; Naeem, U.; Moeed, A.; Atif, A.R.; Asghar, M.S.; Nimri, N.; Saleem, M.; Bandyopadhyay, D.; Krittanawong, C.; Fadelallah Eljack, M.M.; Tahir, M.J.; Waqar, F. Adverse events following COVID-19 mRNA vaccines: A systematic review of cardiovascular complication, thrombosis, and thrombocytopenia. *Immun Inflamm Dis* **2023,** 11, e807.
21. Konishi, N.; Hirai, Y.; Hikota, H.; Miyahara, S.; Fujisawa, A.; Motohashi, H.; Ueda, J.; Inoue, M.; Fukushima, M. Quantifying side effects of COVID-19 vaccines: A PubMed survey of papers on diseases as side effects presented at academic conferences in Japan. *Rinsho Hyoka (Clinical Evaluation)* **2024,** 51.
22. Parry, P.I.; Lefringhausen, A.; Turni, C.; Neil, C.J.; Cosford, R.; Hudson, N.J.; Gillespie, J. 'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA. *Biomedicines* **2023,** 11.
23. Ndeupen, S.; Qin, Z.; Jacobsen, S.; Bouteau, A.; Estanbouli, H.; Igyártó, B.Z. The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. *iScience* **2021,** 24.
24. Maugeri, M.; Nawaz, M.; Papadimitriou, A.; Angerfors, A.; Camponeschi, A.; Na, M.; Hölttä, M.; Skantze, P.; Johansson, S.; Sundqvist, M.; Lindquist, J.; Kjellman, T.; Mårtensson, I.-L.; Jin, T.; Sunnerhagen, P.; Östman, S.; Lindfors, L.; Valadi, H. Linkage between endosomal escape of LNP-mRNA and loading into EVs for transport to other cells. *Nature Communications* **2019,** 10.
25. Bansal, S.; Perincheri, S.; Fleming, T.; Poulson, C.; Tiffany, B.; Bremner, R.M.; Mohanakumar, T. Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer–BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines. *The Journal of Immunology* **2021,** 207, 2405–2410.
26. Seneff, S.; Nigh, G.; Kyriakopoulos, A.M.; McCullough, P.A. Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs. *Food Chem Toxicol* **2022,** 164, 113008.
27. Polykretis, P.; Donzelli, A.; Lindsay, J.C.; Wiseman, D.; Kyriakopoulos, A.M.; Mörz, M.; Bellavite, P.; Fukushima, M.; Seneff, S.; McCullough, P.A. Autoimmune inflammatory reactions triggered by the COVID-19 genetic vaccines in terminally differentiated tissues. *Autoimmunity* **2023,** 56.
28. Brogna, C.; Cristoni, S.; Marino, G.; Montano, L.; Viduto, V.; Fabrowski, M.; Lettieri, G.; Piscopo, M. Detection of recombinant Spike protein in the blood of individuals vaccinated against SARS-CoV-2: Possible molecular mechanisms. *Proteomics Clin Appl* **2023,** 17, e2300048.
29. Yonker, L.M.; Swank, Z.; Bartsch, Y.C.; Burns, M.D.; Kane, A.; Boribong, B.P.; Davis, J.P.; Loiselle, M.; Novak, T.; Senussi, Y.; Cheng, C.A.; Burgess, E.; Edlow, A.G.; Chou, J.; Dionne, A.; Balaguru, D.; Lahoud-Rahme, M.; Arditi, M.; Julg, B.; Randolph, A.G.; Alter, G.; Fasano, A.; Walt, D.R. Circulating Spike Protein Detected in Post-COVID-19 mRNA Vaccine Myocarditis. *Circulation* **2023,** 147, 867–876.
30. Chen, Y.; Xu, Z.; Wang, P.; Li, X.M.; Shuai, Z.W.; Ye, D.Q.; Pan, H.F. New-onset autoimmune phenomena post-COVID-19 vaccination. *Immunology* **2022,** 165, 386–401.
31. Polykretis, P.; McCullough, P.A. Rational harm-benefit assessments by age group are required for continued COVID-19 vaccination. *Scandinavian Journal of Immunology* **2022,** 98.
32. Fraiman, J.; Erviti, J.; Jones, M.; Greenland, S.; Whelan, P.; Kaplan, R.M.; Doshi, P. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. *Vaccine* **2022,** 40, 5798–5805.
33. Bardosh, K.; Krug, A.; Jamrozik, E.; Lemmens, T.; Keshavjee, S.; Prasad, V.; Makary, M.A.; Baral, S.; Høeg, T.B. COVID-19 vaccine boosters for young adults: a risk benefit assessment and ethical analysis of mandate policies at universities. *Journal of Medical Ethics* **2024,** 50, 126–138.
34. Stanworth, S.J.; New, H.V.; Apelseth, T.O.; Brunskill, S.; Cardigan, R.; Doree, C.; Germain, M.; Goldman, M.; Massey, E.; Prati, D.; Shehata, N.; So-Osman, C.; Thachil, J. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. *The Lancet Haematology* **2020,** 7, e756–e64.
35. Chang, L.; Yan, Y.; Wang, L. Coronavirus Disease 2019: Coronaviruses and Blood Safety. *Transfusion Medicine Reviews* **2020,** 34, 75–80.
36. Bouhou, S.; Lahjouji, K.; Masrar, A. Blood donor eligibility after COVID-19 vaccination: the current state of recommendations. *Pan Afr Med J* **2021,** 40, 207.
37. Jacobs, J.W.; Bibb, L.A.; Savani, B.N.; Booth, G.S. Refusing blood transfusions from COVID-19-vaccinated donors: are we repeating history? *British Journal of Haematology* **2021,** 196, 585–588.
38. Hunain, R.; Uday, U.; Rackimuthu, S.; Nawaz, F.A.; Narain, K.; Essar, M.Y.; Rehman, M.U.; Ahmad, S.; Butt, A. Effects of SARS-CoV-2 vaccination on blood donation and blood banks in India. *Ann Med Surg (Lond)* **2022,** 78, 103772.

39. Roubinian, N.H.; Greene, J.; Liu, V.X.; Lee, C.; Mark, D.G.; Vinson, D.R.; Spencer, B.R.; Bruhn, R.; Bravo, M.; Stone, M.; Custer, B.; Kleinman, S.; Busch, M.P.; Norris, P.J. Clinical outcomes in hospitalized plasma and platelet transfusion recipients prior to and following widespread blood donor SARS-CoV-2 infection and vaccination. *Transfusion* **2023,** 64, 53–67.
40. Fertig, T.E.; Chitoiu, L.; Marta, D.S.; Ionescu, V.-S.; Cismasiu, V.B.; Radu, E.; Angheluta, G.; Dobre, M.; Serbanescu, A.; Hinescu, M.E.; Gherghiceanu, M. Vaccine mRNA Can Be Detected in Blood at 15 Days Post-Vaccination. *Biomedicines* **2022,** 10.
41. Mörz, M. A Case Report: Multifocal Necrotizing Encephalitis and Myocarditis after BNT162b2 mRNA Vaccination against COVID-19. *Vaccines* **2022,** 10.
42. Yamamoto, M.; Kase, M.; Sano, H.; Kamijima, R.; Sano, S. Persistent varicella zoster virus infection following mRNA COVID-19 vaccination was associated with the presence of encoded spike protein in the lesion. *Journal of Cutaneous Immunology and Allergy* **2022,** 6, 18–23.
43. Castruita, J.A.S.; Schneider, U.V.; Mollerup, S.; Leineweber, T.D.; Weis, N.; Bukh, J.; Pedersen, M.S.; Westh, H. SARS-CoV-2 spike mRNA vaccine sequences circulate in blood up to 28 days after COVID-19 vaccination. *APMIS* **2023,** 131, 128–132.
44. Krauson, A.J.; Casimero, F.V.C.; Siddiquee, Z.; Stone, J.R. Duration of SARS-CoV-2 mRNA vaccine persistence and factors associated with cardiac involvement in recently vaccinated patients. *NPJ Vaccines* **2023,** 8, 141.
45. Xu, S.; Yang, K.; Li, R.; Zhang, L. mRNA Vaccine Era-Mechanisms, Drug Platform and Clinical Prospection. *Int J Mol Sci* **2020,** 21.
46. Bitounis, D.; Jacquinet, E.; Rogers, M.A.; Amiji, M.M. Strategies to reduce the risks of mRNA drug and vaccine toxicity. *Nat Rev Drug Discov* **2024**.
47. Yamamoto, K. Adverse effects of COVID-19 vaccines and measures to prevent them. *Virology Journal* **2022,** 19.
48. Rodriguez, Y.; Rojas, M.; Beltran, S.; Polo, F.; Camacho-Dominguez, L.; Morales, S.D.; Gershwin, M.E.; Anaya, J.M. Autoimmune and autoinflammatory conditions after COVID-19 vaccination. New case reports and updated literature review. *J Autoimmun* **2022,** 132, 102898.
49. Perico, L.; Morigi, M.; Galbusera, M.; Pezzotta, A.; Gastoldi, S.; Imberti, B.; Perna, A.; Ruggenenti, P.; Donadelli, R.; Benigni, A.; Remuzzi, G. SARS-CoV-2 Spike Protein 1 Activates Microvascular Endothelial Cells and Complement System Leading to Platelet Aggregation. *Front Immunol* **2022,** 13, 827146.
50. Idrees, D.; Kumar, V. SARS-CoV-2 spike protein interactions with amyloidogenic proteins: Potential clues to neurodegeneration. *Biochemical and Biophysical Research Communications* **2021,** 554, 94–98.
51. Charnley, M.; Islam, S.; Bindra, G.K.; Engwirda, J.; Ratcliffe, J.; Zhou, J.; Mezzenga, R.; Hulett, M.D.; Han, K.; Berryman, J.T.; Reynolds, N.P. Neurotoxic amyloidogenic peptides in the proteome of SARS-COV2: potential implications for neurological symptoms in COVID-19. *Nature Communications* **2022,** 13.
52. Kruger, A.; Vlok, M.; Turner, S.; Venter, C.; Laubscher, G.J.; Kell, D.B.; Pretorius, E. Proteomics of fibrin amyloid microclots in long COVID/post-acute sequelae of COVID-19 (PASC) shows many entrapped pro-inflammatory molecules that may also contribute to a failed fibrinolytic system. *Cardiovascular Diabetology* **2022,** 21.
53. Nyström, S.; Hammarström, P. Amyloidogenesis of SARS-CoV-2 Spike Protein. *Journal of the American Chemical Society* **2022,** 144, 8945–8950.
54. Chesney, A.D.; Maiti, B.; Hansmann, U.H.E. SARS-COV-2 spike protein fragment eases amyloidogenesis of alpha-synuclein. *J Chem Phys* **2023,** 159.
55. Olajide, O.A.; Iwuanyanwu, V.U.; Adegbola, O.D.; Al-Hindawi, A.A. SARS-CoV-2 Spike Glycoprotein S1 Induces Neuroinflammation in BV-2 Microglia. *Molecular Neurobiology* **2021,** 59, 445–458.
56. Oh, J.; Cho, W.-H.; Barcelon, E.; Kim, K.H.; Hong, J.; Lee, S.J. SARS-CoV-2 spike protein induces cognitive deficit and anxiety-like behavior in mouse via non-cell autonomous hippocampal neuronal death. *Scientific Reports* **2022,** 12.
57. O'Brien, B.C.V.; Weber, L.; Hueffer, K.; Weltzin, M.M. SARS-CoV-2 spike ectodomain targets alpha7 nicotinic acetylcholine receptors. *J Biol Chem* **2023,** 299, 104707.
58. Buzhdygan, T.P.; DeOre, B.J.; Baldwin-Leclair, A.; Bullock, T.A.; McGary, H.M.; Khan, J.A.; Razmpour, R.; Hale, J.F.; Galie, P.A.; Potula, R.; Andrews, A.M.; Ramirez, S.H. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood-brain barrier. *Neurobiol Dis* **2020,** 146, 105131.

 doi:10.20944/preprints202403.0881.v1

59. Rhea, E.M.; Logsdon, A.F.; Hansen, K.M.; Williams, L.M.; Reed, M.J.; Baumann, K.K.; Holden, S.J.; Raber, J.; Banks, W.A.; Erickson, M.A. The S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice. *Nature Neuroscience* **2020,** 24, 368–378.
60. Zhang, L.; Zhou, L.; Bao, L.; Liu, J.; Zhu, H.; Lv, Q.; Liu, R.; Chen, W.; Tong, W.; Wei, Q.; Xu, Y.; Deng, W.; Gao, H.; Xue, J.; Song, Z.; Yu, P.; Han, Y.; Zhang, Y.; Sun, X.; Yu, X.; Qin, C. SARS-CoV-2 crosses the blood–brain barrier accompanied with basement membrane disruption without tight junctions alteration. *Signal Transduction and Targeted Therapy* **2021,** 6.
61. Trougakos, I.P.; Terpos, E.; Alexopoulos, H.; Politou, M.; Paraskevis, D.; Scorilas, A.; Kastritis, E.; Andreakos, E.; Dimopoulos, M.A. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. *Trends in Molecular Medicine* **2022,** 28, 542–554.
62. Halma, M.T.J.; Plothe, C.; Marik, P.; Lawrie, T.A. Strategies for the Management of Spike Protein-Related Pathology. *Microorganisms* **2023,** 11.
63. Monge, S.; Pastor-Barriuso, R.; Hernán, M.A. The imprinting effect of covid-19 vaccines: an expected selection bias in observational studies. *Bmj* **2023**.
64. Wang, Q.; Guo, Y.; Tam, A.R.; Valdez, R.; Gordon, A.; Liu, L.; Ho, D.D. Deep immunological imprinting due to the ancestral spike in the current bivalent COVID-19 vaccine. *Cell Rep Med* **2023,** 4, 101258.
65. Shrestha, N.K.; Burke, P.C.; Nowacki, A.S.; Simon, J.F.; Hagen, A.; Gordon, S.M. Effectiveness of the Coronavirus Disease 2019 Bivalent Vaccine. *Open Forum Infectious Diseases* **2023,** 10.
66. Arvin, A.M.; Fink, K.; Schmid, M.A.; Cathcart, A.; Spreafico, R.; Havenar-Daughton, C.; Lanzavecchia, A.; Corti, D.; Virgin, H.W. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. *Nature* **2020,** 584, 353–363.
67. Lee, W.S.; Wheatley, A.K.; Kent, S.J.; DeKosky, B.J. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat Microbiol* **2020,** 5, 1185–1191.
68. Irrgang, P.; Gerling, J.; Kocher, K.; Lapuente, D.; Steininger, P.; Habenicht, K.; Wytopil, M.; Beileke, S.; Schäfer, S.; Zhong, J.; Ssebyatika, G.; Krey, T.; Falcone, V.; Schülein, C.; Peter, A.S.; Nganou-Makamdop, K.; Hengel, H.; Held, J.; Bogdan, C.; Überla, K.; Schober, K.; Winkler, T.H.; Tenbusch, M. Class switch toward noninflammatory, spike-specific IgG4 antibodies after repeated SARS-CoV-2 mRNA vaccination. *Science Immunology* **2023,** 8.
69. Kiszel, P.; Sík, P.; Miklós, J.; Kajdácsi, E.; Sinkovits, G.; Cervenak, L.; Prohászka, Z. Class switch towards spike protein-specific IgG4 antibodies after SARS-CoV-2 mRNA vaccination depends on prior infection history. *Scientific Reports* **2023,** 13.
70. Uversky, V.; Redwan, E.; Makis, W.; Rubio-Casillas, A. IgG4 Antibodies Induced by Repeated Vaccination May Generate Immune Tolerance to the SARS-CoV-2 Spike Protein. *Vaccines* **2023,** 11.
71. Yoshimura, M.; Sakamoto, A.; Ozuru, R.; Kurihara, Y.; Itoh, R.; Ishii, K.; Shimizu, A.; Chou, B.; Nabeshima, S.; Hiromatsu, K. The appearance of anti-spike receptor binding domain immunoglobulin G4 responses after repetitive immunization with messenger RNA-based COVID-19 vaccines. *Int J Infect Dis* **2024,** 139, 1–5.
72. Murata, K.; Nakao, N.; Ishiuchi, N.; Fukui, T.; Katsuya, N.; Fukumoto, W.; Oka, H.; Yoshikawa, N.; Nagao, T.; Namera, A.; Kakimoto, N.; Oue, N.; Awai, K.; Yoshimoto, K.; Nagao, M. Four cases of cytokine storm after COVID-19 vaccination: Case report. *Front Immunol* **2022,** 13, 967226.
73. Masset, C.; Kervella, D.; Kandel-Aznar, C.; Fantou, A.; Blancho, G.; Hamidou, M. Relapse of IgG4-related nephritis following mRNA COVID-19 vaccine. *Kidney International* **2021,** 100, 465–466.
74. Patel, A.H. Acute Liver Injury and IgG4-related Autoimmune Pancreatitis following mRNA based COVID-19 vaccination. *Hepatology Forum* **2022**.
75. Aochi, S.; Uehara, M.; Yamamoto, M. IgG4-related Disease Emerging after COVID-19 mRNA Vaccination. *Internal Medicine* **2023,** 62, 1547–1551.
76. Katsikas Triantafyllidis, K.; Giannos, P.; Mian, I.T.; Kyrtsonis, G.; Kechagias, K.S. Varicella Zoster Virus Reactivation Following COVID-19 Vaccination: A Systematic Review of Case Reports. *Vaccines* **2021,** 9.
77. Lensen, R.; Netea, M.G.; Rosendaal, F.R. Hepatitis C Virus Reactivation Following COVID-19 Vaccination—A Case Report. *Int Med Case Rep J* **2021,** 14, 573–576.
78. Psichogiou, M.; Samarkos, M.; Mikos, N.; Hatzakis, A. Reactivation of Varicella Zoster Virus after Vaccination for SARS-CoV-2. *Vaccines* **2021,** 9.
79. Fathy, R.A.; McMahon, D.E.; Lee, C.; Chamberlin, G.C.; Rosenbach, M.; Lipoff, J.B.; Tyagi, A.; Desai, S.R.; French, L.E.; Lim, H.W.; Thiers, B.H.; Hruza, G.J.; Fassett, M.; Fox, L.P.; Greenberg, H.L.; Blumenthal, K.;

 doi:10.20944/preprints202403.0881.v1

Freeman, E.E. Varicella-zoster and herpes simplex virus reactivation post-COVID-19 vaccination: a review of 40 cases in an International Dermatology Registry. *J Eur Acad Dermatol Venereol* **2022,** 36, e6–e9.

80. Gringeri, M.; Battini, V.; Cammarata, G.; Mosini, G.; Guarnieri, G.; Leoni, C.; Pozzi, M.; Radice, S.; Clementi, E.; Carnovale, C. Herpes zoster and simplex reactivation following COVID-19 vaccination: new insights from a vaccine adverse event reporting system (VAERS) database analysis. *Expert Rev Vaccines* **2022,** 21, 675–684.
81. Hertel, M.; Heiland, M.; Nahles, S.; von Laffert, M.; Mura, C.; Bourne, P.E.; Preissner, R.; Preissner, S. Real-world evidence from over one million COVID-19 vaccinations is consistent with reactivation of the varicella-zoster virus. *Journal of the European Academy of Dermatology and Venereology* **2022,** 36, 1342–1348.
82. Shafiee, A.; Amini, M.J.; Arabzadeh Bahri, R.; Jafarabady, K.; Salehi, S.A.; Hajishah, H.; Mozhgani, S.-H. Herpesviruses reactivation following COVID-19 vaccination: a systematic review and meta-analysis. *European Journal of Medical Research* **2023,** 28.
83. Culver, J. Preventing transmission of blood-borne pathogens: a compelling argument for effective device-selection strategies. *Am J Infect Control* **1997,** 25, 430–433.
84. Beltrami, E.M.; Williams, I.T.; Shapiro, C.N.; Chamberland, M.E. Risk and Management of Blood-Borne Infections in Health Care Workers. *Clinical Microbiology Reviews* **2000,** 13, 385–407.
85. Ison, M.G.; Grossi, P.; Practice, A.S.T.I.D.C. o. Donor-derived infections in solid organ transplantation. *Am J Transplant* **2013,** 13 Suppl 4, 22-30.
86. Fishman, J.A.; Grossi, P.A. Donor-derived infection--the challenge for transplant safety. *Nat Rev Nephrol* **2014,** 10, 663–672.
87. Bahakel, H.K.; Pellet Madan, R.; Danziger-Isakov, L. Approach to suspected donor-derived infections. *Front Pediatr* **2023,** 11, 1265023.
88. Tobin, G.J.; Trujillo, J.D.; Bushnell, R.V.; Lin, G.; Chaudhuri, A.R.; Long, J.; Barrera, J.; Pena, L.; Grubman, M.J.; Nara, P.L. Deceptive imprinting and immune refocusing in vaccine design. *Vaccine* **2008,** 26, 6189–6199.
89. Gatto, D.; Brink, R. The germinal center reaction. *J Allergy Clin Immunol* **2010,** 126, 898–907; quiz 08-9.
90. Seneff, S.; Nigh, G. Worse Than the Disease? Reviewing Some Possible Unintended Consequences of the mRNA Vaccines Against COVID-19. *International Journal of Vaccine Theory, Practice, and Research* **2021,** 2, 38–79.
91. Bernardini, A.; Gigli, G.L.; Janes, F.; Pellitteri, G.; Ciardi, C.; Fabris, M.; Valente, M. Creutzfeldt-Jakob disease after COVID-19: infection-induced prion protein misfolding? A case report. *Prion* **2022,** 16, 78–83.
92. Lukiw, W.J.; Jaber, V.R.; Pogue, A.I.; Zhao, Y. SARS-CoV-2 Invasion and Pathological Links to Prion Disease. *Biomolecules* **2022,** 12.
93. Tetz, G.; Tetz, V. Prion-like Domains in Spike Protein of SARS-CoV-2 Differ across Its Variants and Enable Changes in Affinity to ACE2. *Microorganisms* **2022,** 10.
94. Makhoul, K.; Beeber, T.; Cordero, R.; Khan, A.; Saliaj, M. Prion Disease After COVID-19: A Case Report. *Am J Case Rep* **2023,** 24, e940564.
95. Perez, J.-C.; Moret-Chalmin, C.; Montagnier, L. Emergence of a New Creutzfeldt-Jakob Disease: 26 Cases of the Human Version of Mad-Cow Disease, Days After a COVID-19 Injection. *International Journal of Vaccine Theory, Practice, and Research* **2023,** 3, 727–770.
96. Seneff, S.; Kyriakopoulos, A.M.; Nigh, G.; McCullough, P.A. A Potential Role of the Spike Protein in Neurodegenerative Diseases: A Narrative Review. *Cureus* **2023**.
97. Perez, J.C.; Lounnas, V.; Montagnier, M. The Omicron Variant Breaks the Evolutionary Lineage of Sars-Cov2 Variants. *International Journal of Research -GRANTHAALAYAH* **2021,** 9, 108–132.
98. Bhardwaj, T.; Gadhave, K.; Kapuganti, S.K.; Kumar, P.; Brotzakis, Z.F.; Saumya, K.U.; Nayak, N.; Kumar, A.; Joshi, R.; Mukherjee, B.; Bhardwaj, A.; Thakur, K.G.; Garg, N.; Vendruscolo, M.; Giri, R. Amyloidogenic proteins in the SARS-CoV and SARS-CoV-2 proteomes. *Nature Communications* **2023,** 14.
99. Faizullin, D.; Valiullina, Y.; Salnikov, V.; Zuev, Y. Direct interaction of fibrinogen with lipid microparticles modulates clotting kinetics and clot structure. *Nanomedicine* **2020,** 23, 102098.
100. Moghimi, S.M. Allergic Reactions and Anaphylaxis to LNP-Based COVID-19 Vaccines. *Molecular Therapy* **2021,** 29, 898–900.
101. Moghimi, S.M.; Simberg, D. Pro-inflammatory concerns with lipid nanoparticles. *Molecular Therapy* **2022,** 30, 2109–2110.

 doi:10.20944/preprints202403.0881.v1

102. Tahtinen, S.; Tong, A.-J.; Himmels, P.; Oh, J.; Paler-Martinez, A.; Kim, L.; Wichner, S.; Oei, Y.; McCarron, M.J.; Freund, E.C.; Amir, Z.A.; de la Cruz, C.C.; Haley, B.; Blanchette, C.; Schartner, J.M.; Ye, W.; Yadav, M.; Sahin, U.; Delamarre, L.; Mellman, I. IL-1 and IL-1ra are key regulators of the inflammatory response to RNA vaccines. *Nature Immunology* **2022,** 23, 532–542.
103. Halma, M.T.J.; Rose, J.; Lawrie, T. The Novelty of mRNA Viral Vaccines and Potential Harms: A Scoping Review. *J* **2023,** 6, 220–235.
104. Alameh, M.G.; Tombacz, I.; Bettini, E.; Lederer, K.; Sittplangkoon, C.; Wilmore, J.R.; Gaudette, B.T.; Soliman, O.Y.; Pine, M.; Hicks, P.; Manzoni, T.B.; Knox, J.J.; Johnson, J.L.; Laczko, D.; Muramatsu, H.; Davis, B.; Meng, W.; Rosenfeld, A.M.; Strohmeier, S.; Lin, P.J.C.; Mui, B.L.; Tam, Y.K.; Kariko, K.; Jacquet, A.; Krammer, F.; Bates, P.; Cancro, M.P.; Weissman, D.; Luning Prak, E.T.; Allman, D.; Locci, M.; Pardi, N. Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust T follicular helper cell and humoral responses. *Immunity* **2021,** 54, 2877–2892 e7.
105. Jara, L.J.; Vera-Lastra, O.; Mahroum, N.; Pineda, C.; Shoenfeld, Y. Autoimmune post-COVID vaccine syndromes: does the spectrum of autoimmune/inflammatory syndrome expand? *Clinical Rheumatology* **2022,** 41, 1603–1609.
106. Varghese, J.L.; Fung, A.W.S.; Mattman, A.; Quach, T.T.T.; Gauiran, D.T.V.; Carruthers, M.N.; Chen, L.Y.C. Clinical utility of serum IgG4 measurement. *Clin Chim Acta* **2020,** 506, 228–235.
107. Katz, G.; Stone, J.H. Clinical Perspectives on IgG4-Related Disease and Its Classification. *Annu Rev Med* **2022,** 73, 545–562.
108. Chapman, C.W. S. *Project risk management: Process, techniques and insight*. Wiley: London, UK, 2003.
109. Aven, T. Risk assessment and risk management: Review of recent advances on their foundation. *European Journal of Operational Research* **2016,** 253, 1–13.
110. Watson, N.; Brandel, J.-P.; Green, A.; Hermann, P.; Ladogana, A.; Lindsay, T.; Mackenzie, J.; Pocchiari, M.; Smith, C.; Zerr, I.; Pal, S. The importance of ongoing international surveillance for Creutzfeldt–Jakob disease. *Nature Reviews Neurology* **2021,** 17, 362–379.
111. Maltezou, H.C.; Pavli, A.; Tsakris, A. Post-COVID Syndrome: An Insight on Its Pathogenesis. *Vaccines* **2021,** 9.
112. Theoharides, T.C. Could SARS-CoV-2 Spike Protein Be Responsible for Long-COVID Syndrome? *Molecular Neurobiology* **2022,** 59, 1850–1861.
113. Greene, C.; Connolly, R.; Brennan, D.; Laffan, A.; O'Keeffe, E.; Zaporojan, L.; O'Callaghan, J.; Thomson, B.; Connolly, E.; Argue, R.; Martin-Loeches, I.; Long, A.; Cheallaigh, C.N.; Conlon, N.; Doherty, C.P.; Campbell, M. Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. *Nat Neurosci* **2024**.
114. Houston, F.; Foster, J.D.; Chong, A.; Hunter, N.; Bostock, C.J. Transmission of BSE by blood transfusion in sheep. *Lancet* **2000,** 356, 999–1000.
115. Hunter, N.; Foster, J.; Chong, A.; McCutcheon, S.; Parnham, D.; Eaton, S.; MacKenzie, C.; Houston, F. Transmission of prion diseases by blood transfusion. *J Gen Virol* **2002,** 83, (Pt 11), 2897–2905.
116. Seki, Y.; Yamazaki, Y.; Inoue, Y.; Wakabayashi, C.; Seto, S. How HIV infected haemophiliacs in Japan were informed of their HIV-positive status. *AIDS Care* **2002,** 14, 651–664.
117. Llewelyn, C.A.; Hewitt, P.E.; Knight, R.S.; Amar, K.; Cousens, S.; Mackenzie, J.; Will, R.G. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* **2004,** 363, 417–421.
118. Cullinane, J. Tainted Blood and Vengeful Spirits: The Legacy of Japan's Yakugai Eizu (AIDS) Trial. *Culture, Medicine and Psychiatry* **2005,** 29, 5–31.
119. Hewitt, P.E.; Llewelyn, C.A.; Mackenzie, J.; Will, R.G. Creutzfeldt–Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. *Vox Sanguinis* **2006,** 91, 221–230.
120. McLeod, N.P.; Nugent, P.; Dixon, D.; Dennis, M.; Cornwall, M.; Mallinson, G.; Watkins, N.; Thomas, S.; Sutton, J.M. Evaluation of efficacy of prion reduction filters using blood from an endogenously infected 263K scrapie hamster model. *Transfusion* **2015,** 55, 2390–2397.
121. Seed, C.R.; Hewitt, P.E.; Dodd, R.Y.; Houston, F.; Cervenakova, L. Creutzfeldt-Jakob disease and blood transfusion safety. *Vox Sanguinis* **2018,** 113, 220–231.
122. Tighe, P.J.; Ryder, R.R.; Todd, I.; Fairclough, L.C. ELISA in the multiplex era: Potentials and pitfalls. *PROTEOMICS—Clinical Applications* **2015,** 9, (3–4), 406–422.
123. Macklin, A.; Khan, S.; Kislinger, T. Recent advances in mass spectrometry based clinical proteomics: applications to cancer research. *Clinical Proteomics* **2020,** 17.

124. Zhou, B.; Xu, K.; Zheng, X.; Chen, T.; Wang, J.; Song, Y.; Shao, Y.; Zheng, S. Application of exosomes as liquid biopsy in clinical diagnosis. *Signal Transduction and Targeted Therapy* **2020,** 5.
125. Wang, D.; Baudys, J.; Bundy, J.L.; Solano, M.; Keppel, T.; Barr, J.R. Comprehensive Analysis of the Glycan Complement of SARS-CoV-2 Spike Proteins Using Signature Ions-Triggered Electron-Transfer/Higher-Energy Collisional Dissociation (EThcD) Mass Spectrometry. *Analytical Chemistry* **2020,** 92, 14730–14739.
126. Ding, Z.; Wang, N.; Ji, N.; Chen, Z.-S. Proteomics technologies for cancer liquid biopsies. *Molecular Cancer* **2022,** 21.
127. Pu, R.; Liu, S.; Ren, X.; Shi, D.; Ba, Y.; Huo, Y.; Zhang, W.; Ma, L.; Liu, Y.; Yang, Y.; Cheng, N. The screening value of RT-LAMP and RT-PCR in the diagnosis of COVID-19: systematic review and meta-analysis. *J Virol Methods* **2022,** 300, 114392.
128. Mustafa Hellou, M.; Górska, A.; Mazzaferri, F.; Cremonini, E.; Gentilotti, E.; De Nardo, P.; Poran, I.; Leeflang, M.M.; Tacconelli, E.; Paul, M. Nucleic acid amplification tests on respiratory samples for the diagnosis of coronavirus infections: a systematic review and meta-analysis. *Clinical Microbiology and Infection* **2021,** 27, 341–351.
129. Agmon-Levin, N.; Damoiseaux, J.; Kallenberg, C.; Sack, U.; Witte, T.; Herold, M.; Bossuyt, X.; Musset, L.; Cervera, R.; Plaza-Lopez, A.; Dias, C.; Sousa, M.J.; Radice, A.; Eriksson, C.; Hultgren, O.; Viander, M.; Khamashta, M.; Regenass, S.; Andrade, L.E.C.; Wiik, A.; Tincani, A.; Rönnelid, J.; Bloch, D.B.; Fritzler, M.J.; Chan, E.K.L.; Garcia-De La Torre, I.; Konstantinov, K.N.; Lahita, R.; Wilson, M.; Vainio, O.; Fabien, N.; Sinico, R.A.; Meroni, P.; Shoenfeld, Y. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. *Annals of the Rheumatic Diseases* **2014,** 73, 17–23.
130. Xiao, Z.X.; Miller, J.S.; Zheng, S.G. An updated advance of autoantibodies in autoimmune diseases. *Autoimmun Rev* **2021,** 20, 102743.
131. Tsang, S.; Royse, C.F.; Terkawi, A.S. Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine. *Saudi J Anaesth* **2017,** 11, (Suppl 1), S80-S89.
132. Semmler, A.; Mundorf, A.K.; Kuechler, A.S.; Schulze-Bosse, K.; Heidecke, H.; Schulze-Forster, K.; Schott, M.; Uhrberg, M.; Weinhold, S.; Lackner, K.J.; Pawlitzki, M.; Meuth, S.G.; Boege, F.; Ruhrländer, J. Chronic Fatigue and Dysautonomia following COVID-19 Vaccination Is Distinguished from Normal Vaccination Response by Altered Blood Markers. *Vaccines* **2023,** 11.
133. Mulroney, T.E.; Pöyry, T.; Yam-Puc, J.C.; Rust, M.; Harvey, R.F.; Kalmar, L.; Horner, E.; Booth, L.; Ferreira, A.P.; Stoneley, M.; Sawarkar, R.; Mentzer, A.J.; Lilley, K.S.; Smales, C.M.; von der Haar, T.; Turtle, L.; Dunachie, S.; Klenerman, P.; Thaventhiran, J.E.D.; Willis, A.E. N1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting. *Nature* **2023**.
134. Islam, A.; Bashir, M.S.; Joyce, K.; Rashid, H.; Laher, I.; Elshazly, S. An Update on COVID-19 Vaccine Induced Thrombotic Thrombocytopenia Syndrome and Some Management Recommendations. *Molecules* **2021,** 26.
135. Schaffner, A.; Risch, L.; Weber, M.; Thiel, S.; Jungert, K.; Pichler, M.; Wohlwend, N.; Lung, T.; Ritzler, M.; Hillmann, D.; Copeland, S.; Renz, H.; Paprotny, M.; Risch, M. Sustained SARS-CoV-2 nucleocapsid antibody levels in nonsevere COVID-19: a population-based study. *Clin Chem Lab Med* **2020,** 59, e49–e51.
136. Chansaenroj, J.; Yorsaeng, R.; Posuwan, N.; Puenpa, J.; Wanlapakorn, N.; Sudhinaraset, N.; Sripramote, M.; Chalongviriyalert, P.; Jirajariyavej, S.; Kiatpanabhikul, P.; Saiyarin, J.; Soudon, C.; Thienfaidee, O.; Palakawong Na Ayuthaya, T.; Brukesawan, C.; Chirathaworn, C.; Intharasongkroh, D.; Chaiwanichsiri, D.; Issarasongkhram, M.; Kitphati, R.; Mungaomklang, A.; Nagavajara, P.; Poovorawan, Y. Long-term specific IgG response to SARS-CoV-2 nucleocapsid protein in recovered COVID-19 patients. *Sci Rep* **2021,** 11, 23216.
137. Van Elslande, J.; Oyaert, M.; Ailliet, S.; Van Ranst, M.; Lorent, N.; Vande Weygaerde, Y.; Andre, E.; Lagrou, K.; Vandendriessche, S.; Vermeersch, P. Longitudinal follow-up of IgG anti-nucleocapsid antibodies in SARS-CoV-2 infected patients up to eight months after infection. *J Clin Virol* **2021,** 136, 104765.
138. Mevorach, D.; Anis, E.; Cedar, N.; Bromberg, M.; Haas, E.J.; Nadir, E.; Olsha-Castell, S.; Arad, D.; Hasin, T.; Levi, N.; Asleh, R.; Amir, O.; Meir, K.; Cohen, D.; Dichtiar, R.; Novick, D.; Hershkovitz, Y.; Dagan, R.; Leitersdorf, I.; Ben-Ami, R.; Miskin, I.; Saliba, W.; Muhsen, K.; Levi, Y.; Green, M.S.; Keinan-Boker, L.; Alroy-Preis, S. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. *New England Journal of Medicine* **2021,** 385, 2140–2149.
139. Nakahara, T.; Iwabuchi, Y.; Miyazawa, R.; Tonda, K.; Shiga, T.; Strauss, H.W.; Antoniades, C.; Narula, J.; Jinzaki, M. Assessment of Myocardial (18)F-FDG Uptake at PET/CT in Asymptomatic SARS-CoV-2-vaccinated and Nonvaccinated Patients. *Radiology* **2023,** 308, e230743.

140. Faksova, K.; Walsh, D.; Jiang, Y.; Griffin, J.; Phillips, A.; Gentile, A.; Kwong, J.C.; Macartney, K.; Naus, M.; Grange, Z.; Escolano, S.; Sepulveda, G.; Shetty, A.; Pillsbury, A.; Sullivan, C.; Naveed, Z.; Janjua, N.Z.; Giglio, N.; Perala, J.; Nasreen, S.; Gidding, H.; Hovi, P.; Vo, T.; Cui, F.; Deng, L.; Cullen, L.; Artama, M.; Weintraub, E.; Lu, H.; Clothier, H.J.; Batty, K.; Paynter, J.; Petousis-Harris, H.; Buttery, J.; Black, S.; Hviid, A. COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. *Vaccine* **2024**.
141. Pan, K.M.; Baldwin, M.; Nguyen, J.; Gasset, M.; Serban, A.; Groth, D.; Mehlhorn, I.; Huang, Z.; Fletterick, R.J.; Cohen, F.E. Conversion of alpha-helices into beta-sheets features in the formation of the scrapie prion proteins. *Proceedings of the National Academy of Sciences* **1993,** 90, 10962–10966.
142. Langeveld, Jan P. M.; Wang, J.J.; Van de Wiel, Dick F. M.; Shih, Giles C.; Garssen, G.J.; Bossers, A.; Shih, Jason C. H. Enzymatic Degradation of Prion Protein in Brain Stem from Infected Cattle and Sheep. *The Journal of Infectious Diseases* **2003,** 188, 1782–1789.
143. Prusiner, S.B.; Groth, D.F.; McKinley, M.P.; Cochran, S.P.; Bowman, K.A.; Kasper, K.C. Thiocyanate and hydroxyl ions inactivate the scrapie agent. *Proceedings of the National Academy of Sciences* **1981,** 78, 4606–4610.
144. Race, R.E.; Raymond, G.J. Inactivation of Transmissible Spongiform Encephalopathy (Prion) Agents by Environ LpH. *Journal of Virology* **2004,** 78, 2164–2165.
145. Peretz, D.; Supattapone, S.; Giles, K.; Vergara, J.; Freyman, Y.; Lessard, P.; Safar, J.G.; Glidden, D.V.; McCulloch, C.; Nguyen, H.-O. B.; Scott, M.; DeArmond, S.J.; Prusiner, S.B. Inactivation of Prions by Acidic Sodium Dodecyl Sulfate. *Journal of Virology* **2006,** 80, 322–331.
146. Stroup, D.F.; Berlin, J.A.; Morton, S.C.; Olkin, I.; Williamson, G.D.; Rennie, D.; Moher, D.; Becker, B.J.; Sipe, T.A.; Thacker, S.B. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **2000,** 283, 2008–2012.
147. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Group, P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* **2010,** 8, 336–341.
148. Murad, M.H.; Montori, V.M.; Ioannidis, J.P.; Jaeschke, R.; Devereaux, P.J.; Prasad, K.; Neumann, I.; Carrasco-Labra, A.; Agoritsas, T.; Hatala, R.; Meade, M.O.; Wyer, P.; Cook, D.J.; Guyatt, G. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA* **2014,** 312, 171–179.
149. Gould, C.V.; Free, R.J.; Bhatnagar, J.; Soto, R.A.; Royer, T.L.; Maley, W.R.; Moss, S.; Berk, M.A.; Craig-Shapiro, R.; Kodiyanplakkal, R.P.L.; Westblade, L.F.; Muthukumar, T.; Puius, Y.A.; Raina, A.; Hadi, A.; Gyure, K.A.; Trief, D.; Pereira, M.; Kuehnert, M.J.; Ballen, V.; Kessler, D.A.; Dailey, K.; Omura, C.; Doan, T.; Miller, S.; Wilson, M.R.; Lehman, J.A.; Ritter, J.M.; Lee, E.; Silva-Flannery, L.; Reagan-Steiner, S.; Velez, J.O.; Laven, J.J.; Fitzpatrick, K.A.; Panella, A.; Davis, E.H.; Hughes, H.R.; Brault, A.C.; St George, K.; Dean, A.B.; Ackelsberg, J.; Basavaraju, S.V.; Chiu, C.Y.; Staples, J.E.; Yellow Fever Vaccine Virus, T.; Transfusion Investigation, T. Transmission of yellow fever vaccine virus through blood transfusion and organ transplantation in the USA in 2021: report of an investigation. *Lancet Microbe* **2023,** 4, e711–e21.
150. Yaqoob, I.; Salah, K.; Jayaraman, R.; Al-Hammadi, Y. Blockchain for healthcare data management: opportunities, challenges, and future recommendations. *Neural Computing and Applications* **2021,** 34, 11475–11490.
151. Musamih, A.; Salah, K.; Jayaraman, R.; Arshad, J.; Debe, M.; Al-Hammadi, Y.; Ellahham, S. A Blockchain-Based Approach for Drug Traceability in Healthcare Supply Chain. *IEEE Access* **2021,** 9, 9728–9743.
152. WHO, International Health Regulations (2005). 2nd edn. In World Health Organization: Geneva, 2008.
153. Bakanidze, L.; Imnadze, P.; Perkins, D. Biosafety and biosecurity as essential pillars of international health security and cross-cutting elements of biological nonproliferation. *BMC Public Health* **2010,** 10, (Suppl 1).
154. WHO, Global Covid-19 Vaccination Strategy in a Changing World July 2022 update. In World Health Organization: Geneva, 2022.
155. Wu, Y.C.; Chen, C.S.; Chan, Y.J. The outbreak of COVID-19: An overview. *J Chin Med Assoc* **2020,** 83, 217–220.
156. Beeckman, D.S.A.; Rudelsheim, P. Biosafety and Biosecurity in Containment: A Regulatory Overview. *Front Bioeng Biotechnol* **2020,** 8, 650.
157. Taylor, D.M. Inactivation of TSE agents: safety of blood and blood-derived products. *Transfus Clin Biol* **2003,** 10, 23–25.

 doi:10.20944/preprints202403.0881.v1

158. Klein, M.A.; Frigg, R.; Flechsig, E.; Raeber, A.J.; Kalinke, U.; Bluethmann, H.; Bootz, F.; Suter, M.; Zinkernagel, R.M.; Aguzzi, A. A crucial role for B cells in neuroinvasive scrapie. *Nature* **1997,** 390, 687–690.
159. Singh, S.; Kumar, A. Leukocyte depletion for safe blood transfusion. *Biotechnol J* **2009,** 4, 1140–1151.
160. Schmidt, A.; Refaai, M.; Kirkley, S.; Blumberg, N. Proven and potential clinical benefits of washing red blood cells before transfusion: current perspectives. *International Journal of Clinical Transfusion Medicine* **2016,** Volume 4, 79-88.
161. Cardigan, R.; New, H.V.; Tinegate, H.; Thomas, S. Washed red cells: theory and practice. *Vox Sanguinis* **2020,** 115, 606–616.
162. Palmqvist, M.; Von Schreeb, J.; Älgå, A. Autotransfusion in low-resource settings: a scoping review. *BMJ Open* **2022,** 12.
163. Guimaraes, L.E.; Baker, B.; Perricone, C.; Shoenfeld, Y. Vaccines, adjuvants and autoimmunity. *Pharmacol Res* **2015,** 100, 190–209.
164. Kaulen, L.D.; Doubrovinskaia, S.; Mooshage, C.; Jordan, B.; Purrucker, J.; Haubner, C.; Seliger, C.; Lorenz, H.M.; Nagel, S.; Wildemann, B.; Bendszus, M.; Wick, W.; Schönenberger, S. Neurological autoimmune diseases following vaccinations against SARS-CoV-2: a case series. *European Journal of Neurology* **2021,** 29, 555–563.