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Transplantation programs facing lack of empirical evidence on SARS-CoV-2 vaccination: A society recommendation consensus update

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Abstract

Background: Since phase III trials for the most prominent vaccines excluded immunocompromised or immunosuppressed patients, data on safety and efficacy of SARS-CoV-2 vaccines for recipients of solid organ transplantations are scarce.

Aims: Our study offers a synthesis of expert opinions aligned with available data addressing key questions of the clinical management of SARS-CoV-2 vaccinations for transplant patients.

Method: An online research was performed retrieving available recommendations by national and international transplantation organizations and state institutions on SARS-CoV2 vaccination management for transplant recipients.

Results: Eleven key statements were identified from recommendations by 18 national and international societies, and consensus for the individual statements was evaluated by means of the Society Recommendation Consensus score. The highest consensus level (SRC A) was found for prioritized access to vaccination for transplant patients despite anticipation of a weakened immune response. All currently authorized vaccines can be considered safe for transplant patients (SRC A). The handling of immunosuppressive medication, the timely management of vaccines, and other aspects were aligned with available expert opinions.

Conclusion: Expert consensus can be determined for crucial aspects of the implementation of SARS-CoV-2 vaccination programs. We hereby offer a tool for immediate decision-making until empirical data becomes available.

Abbreviations: ABM, Biomedical Agency, France; AST, American Society of Transplantation; COVID-19, coronavirus disease 2019; CST, Canadian Society of Transplantation; DSO, German Organ Transplantation Foundation; DTG, German Society of Transplantation; HR, hazard ratio; JST, Japan Society for Transplantation; mRNA, messenger ribonucleic acid; NHS, National Health Service; NTS, Dutch Transplant Foundation; OR, odd's ratio; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SRC, Society Recommendation Consensus; TSANZ, Transplant Society of Australia and New Zealand; TTS, The Transplant Society

KEYWORDS
COVID-19, SARS-CoV-2 vaccination, solid organ transplantation

1 | INTRODUCTION

Since the first emergency use authorizations of SARS-CoV-2 vaccines, large vaccination campaigns have been launched worldwide. However, transplantation programs are faced with a dramatic lack of data to guide the implementation of such campaigns with regard to transplant recipients and patients awaiting transplantation. The phase III trials for the most prominent vaccines - BNT162b2 mRNA vaccine (Pfizer/BioNTech), mRNA-1273 vaccine (Moderna), ChAdOx1-nCoV-19 chimpanzee adenovirus (ChAd) vector vaccine (AstraZeneca/University of Oxford) - demonstrated a high level of efficacy in preventing coronavirus disease (COVID-19) as well as a corresponding high safety profile. All three trials explicitly excluded immunocompromised or immunosuppressed patients.[1–3] Faced with the inevitable lack of empiric guidelines, our study offers a synthesis of expert opinions extracted from recommendations and statements made by national and international transplantation societies in the context of available data. It is our aim to provide a tool for the clinical management of SARS-CoV-2 vaccinations within solid organ transplantation (SOT) programs.

2 | METHODS

An online research was performed retrieving available publications by national and international transplantation organizations and state institutions concerning recommendations on SARS-CoV-2 vaccination management for transplant recipients and patients on transplant waiting lists. Transplantation societies or institutions were included for which published statements or recommendations concerning transplant patients or waitlisted patients and SARS-CoV-2 vaccinations were available via online research. The retrieval of relevant statements and recommendations was performed by two independent researchers. Medically trained translators were consulted when necessary. Statements were included if recommended by more than two independent societies. The wording was validated by agreement of all researchers. Consensus for the individual statements was evaluated by means of the Society Recommendation Consensus (SRC) score.[4] Accordingly, all consenting recommendations were represented by one point and added up. Dissenting recommendations were subtracted (value of -1) from the number of societies supporting the recommendation. Partial consent or a recommendation for a case-by-case decision was marked as "partial agreement" and represented by 0 points. Missing comments of individual societies on a specific topic were marked as "not available (n.a.)" and represented by 0 points. A "strong" recommendation was defined as consensus within >50% of society recommendations (SRC A) and "medium" and "low" recommendation as consensus of >25% and <25% of retrieved recommendations (SRC B and C). No ethical approval was necessary as all information is accessible online.

3 | RESULTS

Recommendations or statements by 18 national and international societies were retrieved (Table 1 for according sources and links). Eleven key statements were defined and are listed in Table 2. The statements were then categorized according to the SCR-category A (strong consensus), B (medium consensus), and C (low consensus). Details of the SRC score calculation are provided in Figure 1. Individual statements are discussed hereafter.

3.1 | Recommendations with strong consensus (SCR A)

3.1.1 | Donors with prior SARS-CoV-2 infection can be considered for donation after clearance of infection

A strong consensus was found that prior SARS-CoV-2 infection does not constitute a contraindication for organ donation. The American Society of Transplantation (AST) requires a timely delay of 21 days between initial COVID-19 symptoms in addition to repeated negative PCR testing.[5] Additionally, the German Organ Transplantation Foundation (DSO) requires the absence of clinical symptoms and no radiologic signs of pulmonary manifestation of COVID-19.[6] The Canadian Society of Transplantation (CST) suggests a 4-week period after the first positive PCR test.[7] The British National Health Service demands a case-by-case decision after moderate and severe COVID-19 (defined as need for hospitalization) assuming chronic end-organ damage.[8] In contrast, the Chinese government issued a statement that prior SARS-CoV-2 infection is to be considered a contraindication and negative antibody results (IgG and IgM) are required before organ retrieval.[9] With regard to the vaccination of potential organ donors The Transplant Society states that the vaccination of the donor does not - under any circumstance - represent a contraindication for organ retrieval.[10]

3.1.2 | Prioritized access to COVID-19 vaccinations is recommended for patients who received an organ transplant or are awaiting transplantation

Unanimous consensus was found for prioritized access to SARS-CoV-2 vaccinations. A high hospitalization and mortality rate were shown for SOT recipients (OR 2.7 and 4.2). A particularly high risk of severe COVID-19 and mortality was shown for kidney transplant (HR 4.6 and

TABLE 1 Overview of web sources for individual society recommendations and statements

Institution/Society	Link to recommendation	Last update	Date of access
Transplant Society of Australia and New Zealand (TSANZ)	https://tsanz.com.au/information/covid-19.htm	14.04.2021	27.04.2021
Belgian Transplantation Society / Superior Health Council, Belgium	https://www.health.belgium.be/fr/avis-9618-la-priorisation-des-groupes-risque-pour-la-vaccination-contre-le-sars-cov-2-phase-ib	05.02.2021	06.04.2021
Brazilian Organ Transplantation Society	https://site.abto.org.br/blog/informacoes/transplante-para-orgaos-solidos-e-vacina-para-covid-19/ https://site.abto.org.br/wpcontent/uploads/2020/12/recomendacao_coint_vacinacao.pdf	22.02.2021	10.04.2021
Canadian Society of Transplantation / Canadian Blood service	https://profedu.blood.ca/sites/msi/files/20210224_covid-19_consensus_guidance.pdf https://www.cst-transplant.ca/COVID-19_Information.html	18.05.2021	22.05.2021
Minister for Health, People's Republic of China	http://www.organtranspl.com/cn/article/doi/10.3969/j.issn.1674-7445.2020.06.001	12.04.2021	16.04.2021
Biomedical Agency, France	https://www.agence-biomedecine.fr/IMG/pdf/mise_a_jour_recommandations_abm_020321-2.pdf https://www.agence-biomedecine.fr/IMG/pdf/bulletin_covid_no46.pdf	19.04.2021	06.05.2021
German Organ Transplantation Foundation	https://www.d-t-g-online.de/index.php/covid-19; https://www.infektionsschutz.de/coronavirus/schutzimpfung	26.04.2021	27.04.2021
National Health Service, Great Britain	https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/21654/dat3911.pdf https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/22862/inf1559.pdf	09.04.2021	16.05.2021
Ministry of Health, Italy/Italian Society of Organ Transplant	http://www.trapianti.salute.gov.it/trapianti/dettaglioComunicatiNotizieCnt.jsp	30.03.2021	10.04.2021
Japanese Transplantation Society	https://www.kansensho.or.jp/uploads/files/guidelines/2102_covid_vaccine_2.pdf https://square.umin.ac.jp/jst-covid-19/images/guidance4.1.pdf https://square.umin.ac.jp/jst-covid-19/images/vaccine0201.pdf	26.02.2021	05.04.2021
Dutch Transplant Foundation	https://lci.rivm.nl/handleiding-covid-19-vaccinatie-van-immuungecompromitteerde-patienten https://www.transplantatiestichting.nl/medisch-professionals/covid-19-en-transplantaties/covid-19-en-vaccinatiebeleid	26.03.2021	10.04.2021
Portuguese Institute for Blood and Transplantation	http://ipst.pt/files/TRANSPLANTACAO/CircularNormativaConjunta_2_IPST_DGS_1atualizacao_2.pdf	24.03.2021	10.04.2021
Scandiatransplant	http://www.scandiatransplant.org/members/prevention-of-transmission-of-infectious-diseases/InfectionGroup_Guidelines_with9.March2021_addendum.pdf	09.03.2021	18.04.2021
Swisstransplant	https://www.swisstransplant.org/fileadmin/user_upload/Infos_und_Material/Fachpersonen/Corona/COVID-19_vaccination.pdf	31.01.2021	18.04.2021
Federation of Scientific Medical Societies, Spain	https://www.asociacionasaco.es/wp-content/uploads/2021/02/20210128-FACME-trasplante-organos-solidos-2801.pdf	28.01.2021	10.04.2021
American Society of Transplantation	https://www.myast.org/sites/default/files/2021%2003%2018%20COVID19%20VACCINE%20FAQS_update.pdf	07.05.2021	18.05.2021
The Transplantation Society	https://tts.org/index.php?option=com_content&view=article&id=749&Itemid=140	01.03.2021	16.04.2021
The International Society of Heart and Lund Transplantation	https://ishlt.org/ishlt/media/documents/SARS-CoV-2_Guidance-for-Cardiothoracic-Transplant-and-VAD-center.pdf	01.02.2021	16.04.2021

TABLE 2 Individual statements with calculated Society Recommendation Consensus (SRC)

Statement	Recommendation with strong consensus (SRC A)	Consens US*
1	Donors with prior SARS-CoV-2 infection can be considered for donation after clearance of infection.	13/18
2	Prioritized access to SARS-COV-2 vaccinations is recommended for patients who received an organ transplant or are awaiting transplantation.	13/18
3	All currently authorized vaccines can be considered safe for SOT recipients.	11/18
4	Immunosuppressed patients may exhibit a weakened response to SARS-CoV-2 vaccines.	11/18
5	Transplantation should not be postponed due to vaccination schedules.	10/18
	Recommendation with medium consensus (SRC B)	
6	Vaccination respecting a timely delay of 2 weeks prior to transplantation and 4 weeks after transplantation should be favored.	9/18
7	SARS-CoV-2 antibody testing is not recommended for clinical decision-making	8/18
8	In case of T-/ or B-cell depleting immunosuppression, a delay of 3 months until vaccination can be recommended.	8/18
9	A delay of 2 weeks between SARS-CoV-2 vaccination and other vaccinations can be recommended.	5/18
	Recommendation with low consensus (SRC C)	
10	Immunosuppression should not be suspended or reduced during the process of vaccination.	4/18
11	After treatment of an acute rejection, a delay until vaccination can be recommended.	3/18

*Number of societies which support the statement (dissenting expert opinions were subtracted from the number of supporting opinions).

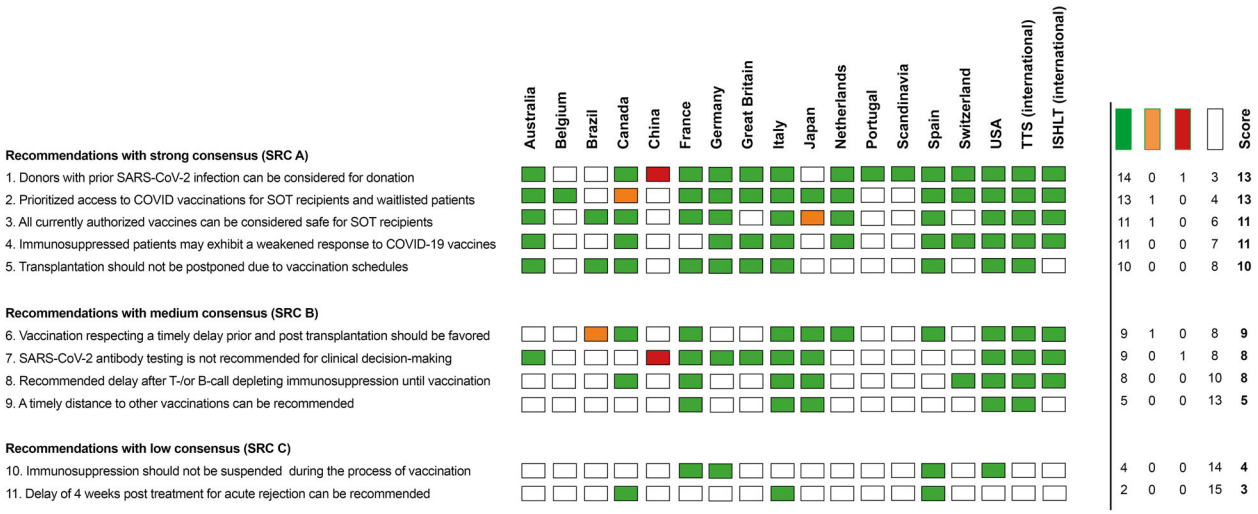

FIGURE 1 Positions of individual societies were defined as "consenting" (mark-up: green, attributed value: +1), "dissenting" (mark-up: red, attributed value: −1), "case-by-case decision/partial agreement" (mark-up: orange, attributed value: 0), or "not discussed" (mark-up: white, attributed value: 0). SRC categories were defined as strong = A (>50% of the societies support the statement); medium = B (25%–50% of the societies support the statement), low recommendation = C (<25% of the societies support the statement)
Abbreviation: SCR, Society Recommendation Consensus.

7.1; 30-day mortality rate: 23%) and lung transplant recipients (HR 3.5 and 6.2).[11] For liver transplant recipients, a comparable COVID-19-related mortality but a higher rate of intensive care admission was found compared to the general population. Enhanced social distancing is discussed as a protective mechanism.[12] Furthermore, chronically ill patients awaiting SOT are at higher risk for severe courses of COVID. For a cohort of 197 SARS-CoV-2 infected waitlisted patients, a mortality of 10.2% was shown.[13] Classification of SOT recipients and waitlisted patients within the high-risk group is thus justified. Vaccination of household members with the aim to counterbalance an estimated lower efficacy of the vaccine is discussed, but no recommendation consensus can be deduced.[5,14–16]

3.1.3 | All currently authorized vaccines can be considered safe for transplant patients and patients awaiting transplantations

Merely 0.6% of the 100.000 participants included in the vaccines' clinical trials of Pfizer and Moderna presented preexisting liver or kidney disease (excluded in the AstraZeneca trial).[12] Immunocompromised or immunosuppressed patients were excluded by all three vaccine trials. A first cohort study including 187 SOT recipients describes mild vaccine-related reactions as expected and no episode of acute rejection, COVID-19 outbreak, or other severe secondary reactions.[17]

Faced with insufficient evidence, a strong expert opinion consensus can be found to classify all currently authorized vaccines (mRNA and adenovirus vector based) as safe for use in immunosuppressed patients. Vaccines based on inactivated coronaviruses (e.g., CoVaxin, Bharat Biotech; BBIBP-CorV, Sinopharm) are proposed to be contraindicated for immunosuppressed patients, but currently no vaccine of this group gained emergency use authorization.[18]

As discussed by the Japanese Transplantation Society, merely 5% of the phase III trial population is of Asian ethnicity leaving an uncertain risk of a non-representative cohort even for the general population.[14]

3.1.4 | Immunosuppressed patients may exhibit a weakened response to SARS-CoV-2 vaccines (SRC A)

For a first cohort of 436 vaccinated transplant recipients, a detectable antibody titer at 20 days after the first injection was detected in 17% of participants.[17,19] A recent study that compared the antibody response of 34 SOT (kidney and heart transplantations) and 116 health care workers found a significantly lower response rate of 58.8% versus 100% (median titers: 1370 vs. 11710, $p < 0.001$).[20] Anti–metabolite immunosuppression (AMI) therapy (33% in those receiving AMI vs. 79%) and high dose corticosteroids in the last 12 months were found to be associated with low antibody response.[20,21] A second study (136 kidney recipients and 25 health controls) confirms a lower response rate (37% vs. 100% with a lower anti-spike level.[21] Several transplant societies (e.g., NTS, Netherlands) favor the use of RNA-based vaccines as a higher efficacy for elderly people - with presumed lower immunogenicity - was shown and to avoid the theoretical risk of replication of the vector virus - *per se* replication deficient - in a (strongly) immunosuppressed patient.[6,22] Attenuated immune response for cirrhotic patients is well described,[23] but the high risk of severe COVID-19 may nevertheless justify prioritized vaccination of immunosuppressed patients and patients awaiting transplantation.

3.1.5 | Transplantation should not be postponed due to vaccination schedules (SRC A)

Furthermore, a strong consensus was found with regard to prioritizing transplantation over vaccination. The absence of a vaccination should not contraindicate or delay a transplantation.[22] Excluding patients from transplantation after vaccination with a live attenuated vaccine is discussed in Germany.[6] Up-to-date, no SARS-CoV-2 vaccine of this category gained authorization.

The *Pan-London Transplant Collaborative Ethics Group* discusses handling of individuals that refuse SARS-CoV-2 vaccination - potentially up to 40% of the population[24] - stating that, in case of additional risk factors for severe COVID-19 infections and as long as transmission rates are high, it may not be appropriate to perform transplantation in the absence of vaccination.[25]

3.2 | Recommendations with medium consensus (SCR B)

3.2.1 | Vaccination respecting a timely delay of 2 weeks prior to transplantation and 4 weeks after transplantation should be favored

Consensus was found for respecting a delay of 2 weeks prior to transplantation (if transplantation date is foreseeable) and 4 weeks post-transplantation, in analog to recommendations for other vaccines.[26]

A longer time stretch since (kidney) transplantation was shown to correlate with seroconversion after SARS-CoV-2 vaccination compared to the non-seroconverted group (15.4 vs. 5.8 months).[27] Furthermore, anti–metabolite maintenance immunosuppression was associated with a low seroconversion rate. Clear evidence on the effects of specific immunosuppression regimens of vaccine response is pending.

Reduced vaccine immunogenicity after liver transplantations is well evaluated for hepatitis A and B virus, and pneumococcal and influenza vaccines.[28] Likewise, prioritized vaccination of patients on transplant waiting lists should be considered.

3.2.2 | SARS-CoV-2 antibody testing is not recommended for clinical decision-making

Up to now, the correlation between antibody titers and clinical immunity against COVID-19 remains uncertain. Two publications describe a less frequent antibody response of transplant recipients after SARS-CoV-2 vaccination (10.8% for kidney transplant recipients and 17% for a heterogenous transplant cohort at 20 days after injection of the first dose),[17,19] but as stated by the Dutch Transplant Foundation (NTS), the correlation of clinical immunity with a certain antibody titer is not yet defined.[29] In addition, the influence of the T cell-mediated immune response remains unclear and is not necessarily correlated with SARS-CoV-2 antibody titers.[30] Furthermore, the amplitude and duration of vaccine response as well as the duration of the response after transplantation remain to be assessed. As described above and in opposition to a strong consensus, the Chinese transplantation program demands negative antibody testing before organ retrieval.[9]

In contrast to the clinical use of antibody testing, clinical and biological monitoring and empirical evaluation of immune response rates is defined as a crucial task by the DSO.[6]

3.2.3 | In case of T-/ or B-cell depleting immunosuppression, a delay of 3 months until vaccination can be recommended

Consensus was found in anticipating a drastically reduced immunogenicity after T- or B-cell depletion and therefore shifting the benefit and risk of a vaccination. A delay of 3 months (AST, US) up to 6 months (ABM, France) until vaccination can thus be recommended.[5,22]

The AST also postulates a reduction or loss of pretransplant immunity after transplantation especially after T-/B-cell depleting immunosuppression.[5] Further data are pending.

3.2.4 | A delay of 2 weeks between SARS-CoV-2 vaccination and other vaccinations can be recommended

Consensus was found for a 2-week delay between reception of a SARS-CoV-2 vaccine and other vaccinations including the seasonal influenza vaccine.[14,22] The pursuit of a complete SARS-CoV-2 vaccination is to be prioritized over the influenza vaccine.

3.3 | Recommendations with low consensus (SCR C)

3.3.1 | Immunosuppression should not be suspended or reduced during the process of vaccination

Plural transplant societies recommend to maintain immunosuppression during the process of vaccination. Even though immunosuppression and especially antimetabolites may be associated with lower antibody response after vaccination,[31,32] the data are widely insufficient to justify taking any risk of rejection and disturbed transplant function.

3.3.2 | After treatment of an acute rejection, a delay until vaccination can be recommended

Analogous to general vaccination recommendations, vaccination during active treatment for rejection should be avoided.[26] The CST proposes a 4-week delay until SARS-CoV-2 vaccination, the Spanish Society of Transplantation at least 2 weeks.[7,33]

No elevated risk of rejection post-SARS-CoV-2 vaccination is to be expected. Such concerns have previously been raised especially in the context of the 2009 H1N1 influenza vaccines containing ASO3 adjuvant but were discarded by reviews.[34]

4 | DISCUSSION

At the present time, SARS-CoV-2 vaccination seems to be the key in controlling the SARS-CoV-2 pandemic. Once again, the high dynamic of this outbreak raises medical questions which as of yet cannot be answered by evidence-based findings. Currently, the implementation of vaccination programs for the high-risk group of transplant patients constitutes a time-sensitive task. The concept of SRC was designed during the first wave of the COVID-19 pandemic to facilitate immediate decision-making when facing a lack of evidence-based guidelines. We hereby offer a temporary approach for addressing crucial questions concerning SARS-CoV-2 vaccines for SOT recipients until evidence becomes available.

Homogenous recommendations were found for several key questions, cf. Figure 1. A strong recommendation consensus (SRC A) was found for prioritizing transplant recipients in receiving SARS-CoV-2 vaccination and classifying mRNA- and vector-based vaccines as safe and efficient for immunosuppressed patients despite an assumed lower immunogenicity. Furthermore, the pursuit of organ transplantation in the absence of vaccination can be recommended (SRC A).

Interestingly, first findings indicate that the higher risk of severe COVID-19 within SOT recipients is rather associated with the profile of preexisting conditions rather than the transplantation itself or the intake of immunosuppressive medication.[35] Accordingly, a high mortality of patients on transplantation waiting lists of 25.8% has been reported.[13] Put in the context of the expert consensus anticipating lower immunogenity after transplantation, prioritized vaccination of waitlisted patients – as proposed by several expert societies[5,15,22] – seems highly beneficial.

Furthermore, vaccination of household members was proposed by several transplant societies and can serve as a mechanism to counterbalance a lower vaccination success rate.[5,14,15]

The role of immunosuppressive medication within the course of a SARS-CoV-2 infection and vaccination remains unclear, and further data are urgently needed.[35] According to the expert consensus, immunosuppressive medication should be continued during the vaccination process (SRC C).

The guiding principles provided for in this paper are severely limited by the nature of our approach. For in summarizing and comparing available expert opinions, even a high level of expert consensus (SRC A) corresponds only to the lowest level of scientific evidence. SRC C corresponds to a consensus of three or more transplantation or health care expert committees and thereby to the lowest group of SRC. While evidence-based clinical guidelines can serve as clinical directives and can provide a fundament for the standardized care, SRC can merely serve to collect and evaluate expert opinion and thereby help to put individual decisions in the context of available expert opinion.

The crucial question of whether current available SARS-CoV-2 vaccinations will suffice in controlling the pandemic remains unanswered. Recent concerns are raised following the observation of escape mutations gaining relevance in evading neutralizing antibodies[36] as well as the observation of COVID-19 infections after full vaccine-immunization.[37] In this context, special attention should be paid to the attenuated immune response of transplant recipients.

The current lack of evidence demands systematic scientific monitoring of safety and efficacy of performed vaccination of transplant recipients and patients awaiting transplantation.

AUTHOR CONTRIBUTIONS

Research design: Nora Nevermann and Paul Viktor Ritschl. Performance of research: Nora Nevermann, Leke Wiering, Helen Wu, Philipp Moroder, Andreas Brandl, and Paul Viktor Ritschl. Data analysis: Nora Nevermann, Brigitta Globke, Felix Krenzien, Nathanael Raschzok, Wenzel Schöning, Georg Lurje, Robert Öllinger, Moritz Schmelzle, Johann Pratschke, and Paul Viktor Ritschl. Paper writing: Nora Nevermann, Brigitta Globke, Felix Krenzien, Nathanael Raschzok, Wenzel Schöning, Georg Lurje, Robert Öllinger, Moritz Schmelzle, Johann Pratschke, and Paul Viktor Ritschl.

CONFLICT OF INTEREST

Moritz Schmelzle received funding from Merck Serono GmbH, Bayer AG, Amgen Inc., ERBE Elektromedizin GmbH, Johnson&Johnson Medical GmbH, Takeda Pharm. Lim., Olympus K.K., Medtronic GmbH, and Intuitive Surg. Inc. All other authors declare no conflict of interest.

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