Protocol Version 1.3

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1. Title:

Research protocol for organ transplantation from HIV+ donors into HIV+ recipients under the Final HIV Organ Policy Equity (HOPE) Act.

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3. Background and purpose:

The advent of effective antiretroviral therapy (ART) in the mid-1990s for treatment of individuals infected with HIV transformed a rapidly fatal disease into a well-controlled chronic illness. Currently, the life expectancy of individuals infected with HIV and receiving ART early in the course of their disease approaches that of individuals without HIV infection (Wada, 2013, 2014). In this era of greater longevity, liver failure, end-stage renal disease, and cardiovascular disease have emerged as important causes of morbidity and mortality in patients with HIV infection (Neuhaus, 2010).

Organ transplantation prolongs survival and improves quality of life for individuals with end-stage organ disease (Matas, 2014; Kim, 2014). Until recently, however, organ transplantation was unavailable to those infected with HIV due to concerns that pharmacologic immunosuppression to prevent organ rejection would hasten the progression from HIV infection to AIDS, leading to increase rates of opportunistic infections, concerns about disease transmission, and reluctance to allocate organs to a

population whose outcome was unpredictable (Blumberg, 2009, 2013a, 2013b; Mgbako, 2013; Taege, 2013).

Nevertheless, a few transplant programs accepted HIV-positive patients on their transplant waiting lists and accumulated data showing kidney or liver transplantation could be done safely in these patients (Roland, 2002, 2003a, 2003b, 2003c; Blumberg, 2009; Stock, 2010; Yoon, 2011; Terrault, 2012). Subsequently, a prospective, multicenter clinical trial of kidney and liver transplantation in 275 patients demonstrated that, among HIV-positive kidney and liver transplant recipients, patient and graft survival rates were acceptable and within the range of outcomes currently achieved among non-infected transplant recipients.

However, the rate of kidney rejection was unexpectedly high, demonstrating that the immune dysregulation resulting from HIV infection, HCV co-infection, and antirejection drugs is complex and incompletely understood. Some of the challenges encountered in that study remain relevant for clinical sites offering organ transplantation to HIV-positive individuals today (e.g., management of drug interactions and toxicities when combining complex medical regimens, management of combined morbidities of two or more active diseases, and the need for ongoing collaboration among medical professionals from different specialties) (Frassetto, 2007, 2014; Locke, 2014). Despite the complexities, this study and others (Ragni, 1999; Frassetto, 2009; Huprikar, 2009; Stock, 2010; Touzot, 2010; Cooper, 2011; Duclos-Vallee, 2011; Reeves-Daniel, 2011; Fox, 2012; Terrault, 2012; Grossi, 2012; Gomez, 2013; Harbell, 2013) demonstrate that kidney and liver transplantation are appropriate in HIV- positive individuals with liver or kidney failure, although gaps in knowledge and many research questions remain. There is much less experience with heart (Calabrese, 2003; Bisleri, 2003; Pelletier, 2004; Uriel, 2009, 2014; Castel, 2011a, 2011b; Durante-Mangoni, 2011 and 2014; Madan 2019) and lung (Mehta, 2000; Humbert,2006; Petrosillo, 2006; Bertani, 2009; Kern, 2014a, 2014b) transplantation in HIV-positive recipients, or mechanical circulatory assistance (Brucato, 2004; Fieno, 2009; Mehmood, 2009; Sims, 2011) as a bridge to transplantation. However, case reports, small case series, and our own institutional experience with four heart transplant recipients with HIV suggest acceptable outcomes are possible with selected patients at experienced centers with the appropriate expertise.

Prior to the passage of the HOPE Act, U.S. law required that all U.S. transplants for HIV-positive recipients utilize organs from HIV-uninfected donors. (See 42 U.S.C. 273(b)(3)(C), 274(b) and 18 U.S.C. 1122, all prior to amendment by the HOPE Act). The potential for increasing the pool of available organ donors for all recipients by allowing the use of organs from donors infected with HIV for transplantation into recipients infected with HIV (hereinafter referred to as ‘‘HIV-positive to HIV-positive transplantation’’) is recognized (Boyarsky, 2011, 2015; Mgbako, 2013; Mascolini, 2014; Kucirka, 2015; Richterman, 2015). It is estimated that an additional 500 organ donors per year might be available if HIV-positive individuals were accepted as organ donors for HIV-positive recipients (Boyarsky, 2011). The first published experience with HIV-positive to HIV- positive SOT at this time came from Muller et al from the University of Cape Town in South Africa. Initially, Muller et al (2010) reported 100 percent patient and graft survival in a four-patient pilot study. Subsequently, the same group reported an additional 10 HIV-positive to HIV-positive renal transplants (Muller, 2012). All patients were restarted on ART early postoperatively in the immunosuppressive setting of T- cell-depleting induction therapy,

tacrolimus, mycophenolate mofetil, and prednisone. One to 4 years after transplantation, outcomes remained excellent and all patients had undetectable viral loads (Muller, 2012). The cumulative University of Cape Town experience of 27 HIV-positive to HIV-positive transplant procedures was recently summarized in the New England Journal of Medicine (Muller, 2015). The 1- and 5-year death-censored graft survival was 93 and 84 percent, respectively, and 1- and 5-year patient survival was 83 and 74 percent, respectively. Of note, the South African HIV-positive deceased donors were ART-naive, without history of opportunistic infection or proteinuria, and had normal pre-transplant renal biopsies. While renal function has remained normal in the recipients, three have had routine post-transplant renal biopsies demonstrating new changes typical of early HIV-associated nephropathy that were not present in baseline biopsy specimens. The long- term significance of these findings remains unknown and awaits longer follow-up. All patients had undetectable plasma HIV viral loads after transplantation. Graft rejection rates were 8 percent at 1 year and 22 percent at 3 years.

The HOPE Act permits HIV-positive to HIV-positive organ transplantation under IRB-approved research protocols conforming to the Final Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV, which were developed as directed in the HOPE Act. Patients receiving HIV-positive kidneys from deceased HIV-positive donors in South Africa (Muller, 2015) had survival rates of 84 percent and 74 percent at 1 and 5 years, respectively; however, there is presently no evidence for the safety, efficacy, and effectiveness of HIV-positive to HIV- positive transplantation in North America. The Final Safeguards and Research Criteria are meant to support the acquisition of new clinical knowledge and mechanistic insights about HIV-positive to HIV-positive organ transplantation in the United States. The results of this research will be evaluated by the Secretary of HHS and the OPTN to determine whether and how the OPTN standards for organ transplantation shall be revised to address HIV-positive organ donors.

The research protocol described below was drafted in accordance to the Final Safeguard and Research Criteria for Transplantation of HIV-positive donor organs in HIV-positive recipients as published by the HHS through the NIH that establishes the criteria for conducting research in HIV-positive to HIV-positive organ transplantation in the United States. The criteria address the minimum safety and data requirements of clinical research in HIV-positive to HIV-positive transplantation. As mandated by the HOPE Act, the Secretary, together with the OPTN, is charged with reviewing the results of scientific research conducted under these criteria to determine whether the OPTN's standards of quality should be further modified and whether some HIV- positive to HIV-positive transplants should proceed outside the auspices of research conducted under such criteria (see attached the original document).

Montefiore Medical Center and the Montefiore-Einstein Center for Transplantation meet the institutional standards and requirements to carry on a research protocol on HIV-positive to HIV-positive kidney transplantation with a collective experience of over 15 kidney transplants on HIV positive recipients since 2008. In terms of liver transplantation, the physicians of the Montefiore Transplant Center have been involved in the care of 5 liver transplants in HIV positive recipients in the previous 4 years, as of February 2022. Similarly, the physicians of the Montefiore heart transplant program have been involved in the care of 5 cardiac transplants in HIV positive recipients in the previous 4 years, as of February 2022. The Montefiore AIDS Center for Positive Living provides care to over 2500 HIV positive

individuals in the Bronx. Potential transplant candidates, as per protocol, are evaluated by transplant ID clinicians with expertise also in HIV. The Center for Positive Living providers and the Montefiore infectious disease faculty practice follow these patients closely for the first year after transplantation. The majority of these patients have elected to remain at Montefiore for their HIV care. Multidisciplinary transplant protocols include management of HIV recipients and the outcomes of these cases have met the national standards without affecting our program-specific reports (SRTR reports).**As of February 2022, Montefiore Medical Center has performed three kidney transplants under the HOPE protocol, and the abdominal transplant and infectious diseases faculty meet regularly to discuss organ offers made under the study.**

4. Objectives and outcome measures

Montefiore's research in HIV-positive to HIV-positive transplantation will address questions related to HIV superinfection; incidence and severity of opportunistic infections (including transmission of occult OIs from donor to recipient); immunologic mechanisms contributing to the increased rate of kidney rejection observed in HIV-positive recipients and quality of life for recipients of HIV- positive to HIV-positive transplantation. To ensure that all nationwide studies of HIV-positive to HIV- positive transplantation can contribute to evaluation of the safety of the procedure, the following key donor and recipient characteristics and outcome measures must be incorporated into the design of all clinical trials of HIV- positive to HIV-positive transplantation.

Wait List Candidates

- HIV status
- CD4+ T-cell count
- Co-infection (HCV, HBV)
- HIV viral load
- ART resistance
- Removal from wait list (death or other reason)
- Time on wait list

Donors (all)

- Type (deceased)*
- HIV status (HIV-positive new diagnosis, HIV-positive known diagnosis)
- CD4+ T-cell count
- Co-infection (HCV, HBV)
- HIV viral load

- ART resistance
- Pre-transplant donor allograft biopsy

*Living Donors will be excluded from this protocol

Transplant Recipients

- Rejection rate (annual up to 5 years)
- New Opportunistic Infections
- Failure to suppress viral replication (persistent viremia)
- HIV-associated organ failure
- Malignancy
- Graft failure
- Acquisition of resistant viral strain
- Death

5. Methods:

- Donor Eligibility

Montefiore Einstein Center for Transplantation has decided to exclude living donors from this research protocol. HIV- positive deceased donors of organs for transplantation into an HIV-positive recipient must fulfill applicable clinical criteria in place for HIV-uninfected organ donors.

One concern about the consequences of transplanting an organ from an HIV-positive donor to a HIV-positive recipient is the acquisition of a resistant strain with subsequent poor viral control and decreased responsiveness to antiretroviral therapy (ART). Adverse consequences could range from transient loss of viral suppression, necessitating a change in antiretroviral regimen to a worst-case scenario in which the new infecting strain of HIV is unresponsive to available antiretroviral treatment and subsequently the recipient develops progression of their HIV infection and the development of opportunistic infections or HIV related malignancies (Redd, 2013).

Information relevant to understanding the known or potential extent of antiretroviral resistance in the strain of HIV infecting the organ donor may be incomplete for many reasons:

- There may be inadequate virus in donor specimens for antiretroviral resistance testing;
- If the specimen is adequate, there may not be enough time within the decision-making evaluation window to fully assess antiretroviral resistance before the clinical deterioration of the donor, organ procurement, and implantation;
- The donor's history of antiretroviral treatment may be unknown or incomplete;
- Results from prior antiretroviral resistance testing may be unavailable.

These issues might be especially challenging when considering organ donation from deceased donors whose HIV infection is first identified during donor evaluation. As of 2011, an estimated 1 in 6 U.S. adults living with HIV infection were undiagnosed (Prevention, 2013) and an estimated 16 percent of newly diagnosed, untreated individuals were infected with virus resistant to at least one class of antiretroviral drug (Kim, 2013; Megens, 2013).

It is anticipated that the risk of transmission of resistant HIV strains may be lower from deceased donors with a well-documented history of adherence to antiretroviral treatment, undetectable viral load at demise. However, to impose this as an eligibility criterion would limit the pool of suitable donors. In addition, it will not be possible in all cases to obtain viral loads and/or antiretroviral resistance profiles in the time available for donor evaluation. Transplant teams evaluating a donor must review all available donor and recipient information available and if necessary, be able to propose an antiretroviral regimen that will be safe, tolerable, and effective for the recipient after transplantation as the regimen in place in the recipient before transplantation. If there is doubt about the ability to suppress viral replication after transplantation, the transplant must not move forward. Fortunately, with the development of newer antivirals, including integrase strand transfer inhibitors (INSTI), acquisition of resistance is much less likely. In the HOPE pilot study involving the care of 75 renal transplants, there were no cases of donor derived drug resistance. (Durand, et al Am J transplantation 2021a;21:1754-1764)

Donors co-infected with hepatitis are not excluded from HIV-positive to HIV- positive transplant; however, careful consideration must be given when evaluating a donor co-infected with HBV and/or HCV (Terrault, 2012; Miro, 2012; Moreno, 2012; Sherman, 2014; Chen, 2014). Although HCV therapeutic strategies are rapidly evolving (Liang, 2013), it is possible that mixed genotype HCV infections may influence post- transplant treatment of HCV in the recipient. Prior antiretroviral treatment of the donor and/or recipient with agents active against HBV (i.e., lamivudine, emtricitabine, adefovir, and tenofovir) has the potential for inducing or uncovering archived HBV drug resistance in the recipient (Dieterich, 2007; Soriano, 2009; Pais, 2010).

HIV-positive transplant candidates who are listed for a transplant in the context of a research study of HIV- positive to HIV-positive transplantation must have the same opportunity as other transplant candidates to receive an organ from an HIV-negative donor, should one become available for them.

1.1 HIV-Positive Donor Eligibility Criteria

The HIV-specific donor eligibility criterion for deceased donors is listed (Table 1). Co-infection with HBV and/or HCV is not an exclusion criterion.

1.1.1 HIV-Positive Deceased Donors

When evaluating HIV-positive deceased donors, it is understood that limited medical history may be available and/or known at the time of the donor evaluation. The OPO must make reasonable efforts to obtain prior medical history so that a transplant center team may best determine the suitability of the potential donor based on the information available. A complete history of antiretroviral regimens and a history of viral load tests and resistance testing are especially valuable for evaluating the likelihood of donor HIV resistance to antiretroviral regimens. A history of OIs or cancers is also of high importance,

due to the increased risk for both attributable to HIV, and the additional difficulty of treating some infections and neoplasms in a post-transplant setting. It is possible that deceased donors with lower CD4+ T-cell counts may pose an increased risk of harboring transmissible diseases (e.g., opportunistic infections or neoplasms) that may be difficult to detect during organ harvest and transplantation; teams conducting transplants under the HOPE Act are urged to assess donors with low CD4+ T-cell counts (e.g., <200/mL) with special caution and to promptly inform IRBs and the PI of known or suspected disease transmission events.

Minimum eligibility criteria for all HIV-positive deceased donors:

i. Documented HIV infection using an FDA-licensed, approved, or cleared test device(s).

ii. No evidence of invasive opportunistic complications of HIV infection.

iii. Pre-implant donor organ biopsy to be stored, at a minimum, for the duration of the study (or at least 5 years); additional specimens may be obtained to support specific research goals.

Additional eligibility criteria for HIV- positive deceased donors with a known history of HIV and prior treatment with ART:

i. The study team must describe the anticipated post-transplant antiretroviral regimen(s) to be prescribed for the recipient and justify their conclusion that the proposed regimen will be safe, tolerable, and effective.

- Recipient Eligibility

A key consideration when evaluating potential HIV-positive transplant candidates is the ability to suppress HIV viral load post-transplant. This includes a thorough assessment by the transplant team of the candidate recipient's prescribed antiretroviral medications, HIV RNA levels while on medications, adherence to HIV treatment, and any available HIV resistance testing; a similar evaluation of the donor must also be carried out. A transplant should only take place if, after evaluating both recipient and donor, the team is confident they can define a post- transplant antiretroviral regimen that will be safe, tolerable, and effective. If there is any doubt on the part of the transplant team about the ability to suppress viral replication post- transplant, the transplant should not move forward. Concerns about transmitted drug resistance must be included in the recipient informed consent process for the research study. At the time of an organ offer, the recipient informed consent must address the transplant team's assessment of risk specific to the organ they are being offered.

2.1 HIV-Positive Recipient Eligibility Criteria

The following HIV-specific criteria must be met when screening for an HIV- positive to HIV-positive organ transplant (also refer to Table 1):

i. Last CD4+ T-cell count >200/mL (kidney, heart, lung). Patients with end stage liver disease may be lymphopenic due to cirrhosis and splenic sequestration, so a cutoff of 100 will be applied to them if

there is no history of opportunistic infection or malignancy. Potential liver transplant patients with a history of opportunistic infection or malignancy must have a CD4 positive T-cell count >200/uL unless the transplant team feels that an effective prophylactic strategy would make transplant safe in the CD4 100-200 range.

ii. HIV RNA less than 50 copies/mL and on a stable antiretroviral regimen.*+

iii. No evidence of active opportunistic complications of HIV infection.

iv. No history of primary CNS lymphoma or PML.

v. Concurrence by the study team that based on medical history and ART, viral suppression can be achieved in the recipient post-transplant.

*Patients who are unable to tolerate ART due to organ failure or who have only recently started ART may have detectable viral load and still be considered eligible if the study team is confident there will be a safe, tolerable, and effective antiretroviral regimen for the patient once organ function is restored after transplantation.

+Those patients on a protease based regimen will be evaluated prior to transplant by our HIV/Transplant infectious disease service to attempt transition to INSTI regimen

+ We enroll 100 HIV positive patients who are eligible for solid organ transplant.

TABLE 1—SUMMARY OF DONOR AND RECIPIENT ELIGIBILITY CRITERIA FOR HIV-POSITIVE SERO-CONCORDANT ORGAN TRANSPLANT PAIRS UNDER THE HOPE ACT

HIV-Related variables	Deceased donor	Living donor	HIV-Positive recipient
Current CD4+ T-cell count (T lymphocytes/μL)	No requirement	≥500 for 6 months prior to organ donation.	If no history of OI • ≥200 (kidney, heart) • ≥100 (liver) If history of OI • ≥200 Last CD4+ T-cell count Prior to enrollment
Plasma HIV RNA viral load (copies/mL).	No requirement**	<50	<50*
Opportunistic infection	No invasive OI	No invasive OI	Currently, • No active OI Historically, no • CNS lymphoma • PML

* Organ recipients who are unable to tolerate ART due to organ failure or who have only recently started ART may have detectable viral load and still be considered eligible if the study team is confident there will be a safe, tolerable, and effective antiretroviral regimen to be used by the recipient once organ function is restored after transplantation.

** In deceased donors with a known history of HIV infection and prior treatment with ART, the study team must describe the anticipated post- transplant antiretroviral regimen(s) to be used by the organ recipient and justify their conclusion that the proposed regimen will be safe, tolerable, and effective.

- Transplant process and post-transplant considerations

Organ recovery, transplant procedure, handling and storage of donor organs/tissues, as well as management of solid organ transplant recipients are well described in our policies and procedures section (intranet), including the multidisciplinary management and immunosuppression protocols of HIV-positive recipients.

Waitlist acceptance criteria: Once an IRB- approved research protocol in HIV- positive to HIV-positive transplantation is finalized, the transplant center will inform the OPTN of additional organ-specific acceptance criteria for organs from HIV-positive donors. Those HIV-positive solid organ transplant candidates on the wait list willing to accept an HIV- positive organ must specify any additional acceptance criteria to the OPO.

Consent process and Independent HIV-Positive Recipient Advocate: One of Montefiore's senior transplant coordinators is actively collaborating with an NIH initiative to train and credential independent advocates for protecting and promoting the rights and interests of the HIV-positive recipient (or prospective recipient). The independent advocate for the HIV- positive recipient will:

i. Promote and protect the interests of the HIV-positive recipient (including with respect to having access to a suitable HIV-negative organ if it becomes available) and take steps to ensure that the HIV-positive recipient's decision is informed and free from coercion.

ii. Review whether the potential HIV-positive recipient has received information regarding the results of SOT in general and transplantation in HIV- positive recipients in particular and the unknown risks associated with HIV- positive to HIV-positive transplant.

iii. Demonstrate knowledge of HIV infection and transplantation.

Attached: -Informed consent for research

Post-transplant care

After discharge, patients are seen by the multidisciplinary transplant team according to the below schedule. During weekly morbidity and mortality meeting the post-transplant team meets and reviews the transplant recipients seen during the week to discuss patients, complications (infections, rejection, bleeding, readmission, re-surgery, malignancy, patient death, and graft loss), and allograft function. These events are stored in the transplant computerized database and communicated to the OPTN in accordance with regulations. Recipients are also assessed and contacted in respect to QAPI initiatives to further improve patient care initiatives.

Adult Transplant Patients are generally evaluated according to the following schedule after abdominal transplantation:

First month: twice a week labs (kidney) or once a week labs (liver), once a week clinic visit

2-3 months: once a week labs and every other week clinic visit

4-5 months: every other week labs and one month clinic visit

6-12 months: once a month labs and every other month clinic visit

Second year: every 2 months labs and 4 months clinic visit

3-5 years every 3 month labs and 6 months clinic visit

> 5 years every 3 months labs and once a year clinic visit

During each clinical visit, bloods and vital signs are obtained, a physical exam is performed and medications are reviewed with each patient. Medical and surgical problems will be addressed on an ongoing basis and appropriate referrals are made to specialists. Pharmacist, nutritional and social service support is available at each clinic. The Transplant Patient will receive specific instructions from the Transplant Multi-Disciplinary Team as to their follow-up care.

Additional transplant allograft biopsy will be performed either as clinically indicated (kidney, liver) or as per the standard post-transplant protocol (heart).

All patients will be assigned to one respective transplant clinician for outpatient follow-up. Patients will be seen at least once within a month after transplantation by a transplant surgeon.

In order to promptly detect viral breakthrough or possibility of viral superinfection, HIV viral loads should be performed at baseline and four weeks after transplantation, every three months for the first year post transplantation, and every 4-6 months in patients who have achieved sustained viral suppression. If viral breakthrough is detected on two consecutive assays, genotypic resistance studies will be sent. T cell subsets will be monitored every three months for the first year, and every 4-6 months in stable patient. A Montefiore transplant infectious disease provider will see the patient at the time of transplant, one month after transplantation and every three months for the first year post transplant. After the first year, should they wish, stable transplant patients may return to their outside provider. The Montefiore transplant ID attending will maintain close contact with the primary care provider, and also see the recipient twice a year for the duration of the study. To assist patients with urgent infectious disease issues the Montefiore AIDS center provides walk in services Monday through Friday, and 24 hour service coverage for established patients.

Transplant physicians will give 24 hour coverage service for post-transplant patients with any questions and complaints.

6 – Potential risks

Risk considerations and pertinent safeguards to potential recipients have been described in detail above under donor and recipient eligibility sections.

Prevention of Inadvertent Transmission of HIV

Although the use of HIV-positive organs may help alleviate transplant shortages and reduce patient waiting list times, there also are patient safety concerns to consider. Prevention or management of inadvertent transmission of HIV or exposure of an HIV-negative recipient to organs or tissues from an HIV-positive donor due to identification error is paramount (Ison, 2009, 2011a, 2011b). The transplant community, with regulatory oversight at multiple levels, has been able to achieve a high level of safety through routine procedures and clinical practice. The precautions taken with ABO compatible donor-recipient pairs and HCV-infected donor organs in HCV- infected recipients (Morales, 2010; Kucirka, 2010; Mandal, 2000; Tector, 2006) are existing models. However, vulnerabilities still exist, and mishaps still occur. For instance, the risks of error during manual transcription of information are well documented.

Montefiore Medical Center and the transplant center already count with an institutional biohazard plan for handling of HCV-positive organs and tissue disposal for HCV-positive recipients and ABO compatibility verification policies. HIV-positive status of donor organ, donor tissues and intended recipient will be added to the organ-to-recipient verification form.

7- Confidentiality and safeguards to minimize risks.

The research protocol was drafted in accordance to the Final Safeguard and Research Criteria for Transplantation of HIV-positive donor organs in HIV-positive recipients as published by the HHS through the NIH that establishes the criteria for conducting research in HIV-positive to HIV-positive organ transplantation in the United States (attached document and informed consent).

8- Study benefits

The potential for increasing the pool of available organ donors for all recipients by allowing the use of organs from donors infected with HIV for transplantation into recipients infected with HIV. It is estimated that an additional 500 organ donors per year might be available if HIV-positive individuals were accepted as organ donors for HIV-positive recipients. Preliminary data nationally suggest earlier access to transplantation in patients with HIV who accept organs from donors with HIV (Durand 2021a; Durand 2021b).

9- Data Safety Monitoring Board

A DSMB comprised of three physicians (not involved in the study) will continue to be assembled every 12 months to review safety data.

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