

ORIGINAL RESEARCH

Safety of assisted reproductive techniques in young women harboring germline pathogenic variants in *BRCA1/2* with a pregnancy after prior history of breast cancer

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Background: Knowledge is growing on the safety of assisted reproductive techniques (ART) in cancer survivors. No data exist, however, for the specific population of breast cancer patients harboring germline *BRCA1/2* pathogenic variants. **Patients and methods:** This is a multicenter retrospective cohort study across 30 centers worldwide including women diagnosed at ≤ 40 years with stage I-III breast cancer, between January 2000 and December 2012, harboring known germline *BRCA1/2* pathogenic variants. Patients included in this analysis had a post-treatment pregnancy either achieved through use of ART (ART group) or naturally (non-ART group). ART procedures included ovulation induction, ovarian stimulation for *in vitro* fertilization or intracytoplasmic sperm injection, and embryo transfer under hormonal replacement therapy. **Results:** Among the 1424 patients registered in the study, 168 were eligible for inclusion in the present analysis, of whom 22 were in the ART group and 146 in the non-ART group. Survivors in the ART group conceived at an older age compared with those in the non-ART group (median age: 39.7 versus 35.4 years, respectively). Women in the

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ART group experienced more delivery complications compared with those in the non-ART group (22.1% versus 4.1%, respectively). No other apparent differences in obstetrical outcomes were observed between cohorts. The median follow-up from pregnancy was 3.4 years (range: 0.8-8.6 years) in the ART group and 5.0 years (range: 0.8-17.6 years) in the non-ART group. Two patients (9.1%) in the ART group experienced a disease-free survival event (specifically, a locoregional recurrence) compared with 40 patients (27.4%) in the non-ART group. In the ART group, no patients deceased compared with 10 patients (6.9%) in the non-ART group.

Conclusion: This study provides encouraging safety data on the use of ART in breast cancer survivors harboring germline pathogenic variants in *BRCA1/2*, when natural conception fails or when they opt for ART in order to carry out preimplantation genetic testing.

Key words: *BRCA*, breast cancer, fertility, ART, pregnancy, survival

INTRODUCTION

Breast cancer is the most common cancer in women of reproductive age.¹ From the early 2000s, there have been growing research efforts on options for fertility preservation in patients with breast cancer and the safety of pregnancy following treatment completion.²⁻⁴ These topics are of major concern in young patients with breast cancer.⁵ Large multicenter studies have shown the safety of pregnancy after breast cancer treatments, for all histological subtypes,⁶⁻⁸ and, more recently, also for survivors bearing germline *BRCA* pathogenic variants.⁹

As reassuring evidence accumulates, current guidelines strongly recommend providers to discuss ovarian stimulation for oocyte and embryo cryopreservation before starting chemotherapy with all patients interested in future family planning.²⁻⁴ Breast cancer-tailored ovarian stimulation protocols have been developed to decrease serum estradiol concentrations during fertility treatment. Ovarian stimulation with letrozole for fertility preservation in women with newly diagnosed non-metastatic breast cancer can be considered safe when followed by chemotherapy.¹⁰ Regarding the specific safety question of this approach in *BRCA*-mutated breast cancer patients, the prospective non-randomized study of Kim et al.¹¹ reported a subgroup analysis of 26 patients harboring germline pathogenic variants in *BRCA1/2* who underwent fertility preservation compared with 21 who did not. No significant difference in relapse-free survival was observed ($P = 0.57$), although the exposed group had smaller tumor size than the non-exposed group ($P = 0.02$).¹¹

Despite numerous research efforts focused on studying efficacy and safety of fertility preservation strategies at breast cancer diagnosis and before starting anticancer therapies, poor evidence is currently available on the safety of fertility treatments in infertile breast cancer survivors following treatment completion.¹²⁻¹⁵ Therefore, further research is needed to improve the fertility management of breast cancer survivors, as some of them remain infertile or childless during oncology follow-up and may not have accessed prior fertility preservation strategies at diagnosis.

The presence of germline pathogenic variants in *BRCA1/2*, combined with the previous history of breast cancer, raises additional concerns on fertility-related issues in young women with breast cancer.^{16,17} *BRCA* status is often

not available when making decisions about fertility preservation. Since young age at diagnosis is a criteria for genetic testing,⁵ the result often becomes available when pursuing fertility treatments following remission.

To provide evidence on this important topic, we assessed the outcomes of a cohort of *BRCA*-mutated breast cancer survivors who had a pregnancy after prior history of breast cancer by comparing the population of patients who underwent assisted reproductive techniques (ART) to those who became pregnant naturally.

MATERIALS AND METHODS

Study design and patients

This analysis was conducted within a retrospective, international, multicenter study designed to assess the safety of pregnancy after breast cancer in young women with germline pathogenic variants in *BRCA1/2* (NCT02308085).⁹

Thirty centers worldwide provided clinical data of women diagnosed at ≤ 40 years with stage I-III invasive breast cancer between January 2000 and December 2012, harboring known deleterious germline pathogenic variants in *BRCA1* and/or *BRCA2* genes. Patients with the following characteristics were not eligible for inclusion: *de novo* stage IV breast cancer, germline *BRCA* variants of unknown significance, history of any previous invasive malignancy other than breast cancer, lack of oncological follow-up or information on post-treatment pregnancies. Datasets from countries with more than one participating center were cross-checked in order to exclude potential duplicated patients.

For the purpose of investigating the safety of ART, only women with a pregnancy after breast cancer were included. Among them, patients who developed a disease-free survival (DFS) event before having a pregnancy were excluded. The pregnancy cohort was divided into two groups, one including patients who had been exposed to ART to achieve the pregnancy (ART group) and the other including women who achieved the pregnancy naturally without the use of ART (non-ART group).

ART treatments

The following procedures were considered as ART treatments: ovarian stimulation for *in vitro* fertilization (IVF) or

intracytoplasmic sperm injection (ICSI) carried out after the completion of anticancer treatments, embryo transfer under hormone replacement therapy (HRT) following oocyte and/or embryo cryopreservation for fertility preservation at diagnosis, embryo transfer under HRT following oocyte donation, and ovulation induction for intrauterine insemination or planned intercourse.

Study objectives and endpoints

Our main objectives were to describe the occurrence of DFS and overall survival (OS) events in the ART and non-ART groups. Moreover, reproductive outcomes in the two groups were assessed.

DFS events were considered any of the following: locoregional recurrence, distant metastases, new contralateral or ipsilateral breast cancer, second primary malignancy, or death from any cause. OS event was defined as death from any cause.

Ethical approval

The study was coordinated and sponsored by the Institut Jules Bordet (Brussels, Belgium) that also acted as the central ethics committee. This study was approved by the ethics committees of all participating centers and participants provided written informed consent before inclusion, whenever requested by local regulations.

Statistical analyses

For continuous variables, median and interquartile range were reported. The baseline characteristics of patients in the two groups were compared, after excluding missing values, using the Fisher's exact test for categorical variables and the Mann–Whitney test otherwise. In order to assess survival events and reproductive outcomes, descriptive analyses were conducted.

RESULTS

Of 1424 patients registered in the study, 195 had a pregnancy following breast cancer. Among them, 19 developed a DFS event before pregnancy and for 8 patients, centers could not provide information about the use of ART, leaving 168 to be included in the present analysis. A total of 22 patients were exposed to ART treatment in order to achieve pregnancy (ART group) and 146 became pregnant without the use of ART (non-ART group).

In the ART group, 5 out of 22 (22.7%) patients had at least one pregnancy before breast cancer diagnosis, compared with 68 out of 168 (40.5%) in the non-ART group. Similarly, a smaller proportion of patients had at least one child in the exposed cohort [4 (18.2%) versus 56 (33.3%) in the non-ART group] (Table 1). ART-exposed patients were older at diagnosis than those in the non-ART group (median age of 33 versus 30.2 years). ART-exposed patients had lower-grade tumors, as 45.4% of them were diagnosed with a grade 1 or 2 tumor compared with 17.1% in the non-exposed cohort. Estrogen- and/or progesterone-positive tumors were

Table 1. Oncological characteristics at breast cancer diagnosis

	ART group (n = 22)	Non-ART group (n = 146)	P value ^a
Median age at diagnosis Years (IQR)	33.0 (30.0-36.0)	30.2 (28.0-33.0)	0.004
Parity at diagnosis			0.030
0	16 (72.7)	65 (44.5)	
≥1	4 (18.2)	56 (38.4)	
Missing	2 (9.1)	25 (17.1)	
Country of diagnosis, n (%)			0.049
Europe	14 (63.6)	117 (80.1)	
North America	0 (—)	8 (5.5)	
Latin America	0 (—)	3 (2.1)	
Israel	8 (36.4)	18 (12.3)	
Year at diagnosis, n (%)			0.840
2000-2004	4 (18.2)	35 (24.0)	
2005-2008	8 (36.4)	55 (37.7)	
2009-2012	10 (45.4)	56 (38.3)	
BRCA mutation, n (%)			0.473
BRCA1	14 (63.6)	108 (73.9)	
BRCA2	8 (36.4)	36 (24.7)	
BRCA1/2	0 (—)	2 (1.4)	
Histology, n (%)			0.113
Ductal carcinoma	19 (86.3)	121 (82.8)	
Lobular carcinoma	2 (9.1)	1 (0.7)	
Mixed ductal/lobular	0 (—)	2 (1.4)	
Other	1 (4.6)	12 (8.2)	
Missing	0 (—)	10 (6.9)	
Tumor grade, n (%)			0.008
1	1 (4.6)	4 (2.7)	
2	9 (40.8)	21 (14.4)	
3	11 (50.0)	114 (78.1)	
Missing	1 (4.6)	7 (4.8)	
Tumor size, n (%)			0.113
T1 (≤2 cm)	14 (63.6)	65 (44.5)	
T2-T4 (>2 cm)	8 (36.4)	80 (54.8)	
Missing	0 (—)	1 (0.7)	
Nodal status, n (%)			0.811
N0	14 (63.6)	96 (65.7)	
N1-N3	8 (36.4)	48 (32.9)	
Missing	0 (—)	2 (1.4)	
Hormone receptor status, n (%)			0.016
ER- and/or PR-positive	13 (59.1)	46 (31.5)	
ER- and PR-negative	9 (40.9)	100 (68.5)	
HER2 status, n (%)			0.079
HER2-negative	19 (86.4)	134 (91.8)	
HER2-positive	3 (13.6)	5 (3.4)	
Missing	0 (—)	7 (4.8)	
Breast surgery, n (%)			0.034
Conserving	18 (81.8)	81 (55.5)	
Radical	4 (18.2)	63 (43.1)	
Missing	0 (0.0)	2 (1.4)	
Chemotherapy, n (%)			0.204
None	1 (4.5)	0 (0.0)	
Anthracycline- and taxane-based	11 (50.0)	88 (60.3)	
Anthracycline-based	5 (22.7)	41 (28.1)	
Taxane-based	0 (0.0)	3 (2.0)	
Other	1 (4.5)	4 (2.7)	
Missing	4 (18.2)	10 (6.9)	
Endocrine therapy, ^b n (%)			1.000
No	1 (7.7)	5 (10.9)	
Yes	12 (92.3)	41 (89.1)	
Median duration of endocrine therapy in months (IQR)	48.5 (24-60)	50 (25-60)	0.517
Missing	4	15	

ART, assisted reproductive techniques; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; PR, progesterone receptor.

^a Excluding missing values, Fisher test for categorical characteristics, Mann–Whitney test otherwise.

^b Percentages in this case were calculated including only patients with hormone receptor-positive breast cancer.

diagnosed in 59.1% of ART-exposed patients versus 31.5% of neoplasms in the non-ART group (Table 1).

The most common ART technique that was used in order to achieve a pregnancy following anticancer treatment completion was ovarian stimulation for IVF/ICSI (seven patients, 31.8%). Embryo transfer under HRT following oocyte donation was the second most used approach (five patients, 22.7%). A total of four (18.2%) patients obtained their pregnancy by embryo transfer following oocyte and/or embryo cryopreservation for fertility preservation carried out at the time of breast cancer diagnosis. Only one patient (4.5%) became pregnant after ovulation induction. ART treatment was not specified in five survivors (22.7%) (Table 2).

Reproductive outcomes in the ART and non-ART groups are reported in Table 2. In the ART group, survivors were older at conception, compared with those in the non-ART group (39.7 versus 35.4 years old, respectively). Patients in the ART group tended to conceive later from breast cancer diagnosis compared with patients in the non-ART group (5.4 versus 3.5 years after breast cancer diagnosis, respectively). In the ART group, more patients experienced delivery complications than in the non-ART group (22.7% versus 4.1%, respectively), with no apparent difference in the other obstetrical complications.

Patients in the non-ART group had a longer median follow-up from conception compared with the patients in the ART group (5.0 versus 3.4 years; Table 3). In the ART group, 2 patients (9.1%) experienced a DFS event (specifically, a locoregional recurrence) compared with 40 patients (27.4%) in the non-ART group. No apparent difference in type of first DFS events was observed between the ART versus non-ART groups (Table 3). One patient that suffered from a locoregional recurrence was treated with ovulation induction, while the other one underwent an embryo transfer under HRT using her own cryopreserved oocyte/embryo. No patient from the ART group experienced an OS event, compared with 10 (6.9%) in the non-ART group.

DISCUSSION

The risk of infertility is one of the most feared consequences of oncological treatments.¹⁸ A growing number of young breast cancer patients are childless at the time of diagnosis, due to the steady rise in the age at the birth of the first child.¹⁹ We also know that pregnancy after breast cancer treatment does not increase the risk of relapse,⁶⁻⁸ including among survivors harboring germline pathogenic variants in *BRCA1/2*.⁹ The main approach to prevent infertility in young patients with breast cancer is fertility preservation using oocytes and/or embryo freezing before starting anticancer therapies, as endorsed by oncological and fertility guidelines.²⁻⁴ As some patients are not offered these procedures or will need further fertility interventions in order to conceive, it is important to investigate the safety of ART in breast cancer survivors, particularly for those bearing known deleterious germline pathogenic variants in *BRCA1* and/or *BRCA2* genes, for whom there is currently no

Table 2. Reproductive outcomes after breast cancer treatment

Reproductive outcomes	ART group (n = 22)	Non-ART group (n = 146)
Median age at the time of pregnancy, years (IQR)	39.7 (35.3-41.4)	35.4 (32.7-38.0)
Median time from breast cancer diagnosis to conception, years (IQR)	5.4 (2.4-6.7)	3.5 (2.3-5.2)
Pregnancy outcomes, n (%)		
Live birth	18 (81.8)	113 (77.4)
Ongoing	1 (4.6)	4 (2.7)
Induced abortion	0 (0.0)	13 (8.9)
Miscarriage	3 (13.6)	15 (10.3)
Unknown	0 (0.0)	1 (0.7)
Timing of delivery, n (%)		
At term (≥ 37 weeks)	11 (61.1)	84 (74.3)
Preterm (< 37 weeks)	3 (16.7)	7 (6.2)
Unknown	4 (22.2)	22 (19.5)
Pregnancy complications, n (%)		
None	10 (45.5)	82 (56.2)
Delivery complications	5 (22.7)	6 (4.1)
Congenital abnormalities	1 (4.5)	3 (2.0)
No. missing	6 (27.3)	55 (37.7)
Breast feeding, n (%)		
Yes	2 (9.1)	28 (19.2)
No	8 (36.4)	43 (29.4)
Unknown	12 (54.5)	75 (51.4)
Median duration (years)	0	1
Type of ART, n (%)		
Embryo transfer under HRT following oocyte and/or embryo cryopreservation at diagnosis	4 (18.2)	Not applicable
Embryo transfer under HRT following oocyte donation	5 (22.7)	
Ovarian stimulation for IVF/ICSI after cancer treatment	7 (31.8)	
Ovulation induction	1 (4.5)	
Unknown	5 (22.7)	

ART, assisted reproductive technologies; HRT, hormonal replacement therapy; ICSI, intracytoplasmic sperm injection; IQR, interquartile range; IVF, *in vitro* fertilization.

available data to refer to. Our multicenter international retrospective study is the first to analyze the impact of ART on oncologic and obstetrical outcomes in a population of young *BRCA*-mutated breast cancer survivors having a pregnancy following their breast cancer treatment.

Oncofertility counseling for patients harboring a germline pathogenic variant in *BRCA1/2* remains challenging considering the limited and conflicting knowledge that is currently available on the effects of these defects on fertility. Specifically, over the last 10 years, preclinical and clinical studies have focused on a diminished fertility potential due to an impaired DNA repair ability, especially in case of DNA double strand breaks. Recent literature provides evidence on a diminished ovarian reserve, especially in case of germline *BRCA1* pathogenic variants, both in healthy women as well as in breast cancer patients.¹⁶ These data could explain a potential reduced effectiveness of fertility preservation in breast cancer patients.²⁰ Moreover, extensive literature exists on a possible increased susceptibility to ovarian aging, although more severe ovarian damage in case of gonadotoxic exposure has not been clearly established.²¹⁻²⁴ Furthermore, new and specific treatments are now in use for breast cancer patients when a *BRCA1/2* pathogenic variant is found, such as poly (ADP-ribose) polymerase (PARP) inhibitors^{25,26} and platinum

Table 3. Oncological outcomes		
	ART group (n = 22)	Non-ART group (n = 146)
DFS event, n (%)		
No	20 (90.9)	106 (72.6)
Yes	2 (9.1)	40 (27.4)
DFS type, n (%)		
Locoregional recurrence of primary invasive breast cancer	2 (9.1)	7 (4.8)
Distant recurrence (with or without locoregional recurrence) of primary invasive breast cancer	0 (–)	10 (6.9)
Second primary breast cancer	0 (–)	19 (13.0)
Second primary malignancy	0 (–)	4 (2.7)
Death without recurrence	0 (–)	0 (–)
Death, n (%)		
No	22 (100.0)	136 (93.1)
Yes	0 (–)	10 (6.9)
Median follow-up from breast cancer diagnosis, years (IQR)	7.5 (6.5-10.5)	8.8 (6.8-11.8)
Median time from breast cancer diagnosis to DFS event, years (IQR)	7.5 (6.5-10.5)	7.9 (5.6-10.5)
Median follow-up from conception, years (IQR)	3.4 (1.1-5.5)	5.0 (2.8-7.7)
Median time from conception to DFS event, years (IQR)	3.4 (1.1-5.3)	3.7 (2.0-6.1)

ART, assisted reproductive techniques; DFS, disease-free survival; IQR, interquartile range.

agents.²⁷ In mouse experiments, olaparib has shown to have a gonadotoxic potential, although it did not increase the gonadotoxic effect of other chemotherapy agents when used in association.²⁸ Unfortunately, no clinical data in terms of reproductive outcomes are available on the added effect of olaparib or platinum agents in exposed breast cancer patients, adding uncertainty to an already nebulous patient counseling. Moreover, a growing number of otherwise healthy women discover that they harbor a *BRCA1/2* pathogenic variant and demand access to ART for preimplantation genetic testing (PGT), adding specific concerns on its safety and efficacy.¹⁷ Furthermore, breast cancer survivors who aim to conceive demand to be treated with ART for infertility and/or in order to prevent the transmission of the pathogenic variant to offspring through PGT.

Recently, few studies have tried to address the safety of ART in breast cancer survivors following completion of anticancer therapies. Three retrospective multicenter studies,^{12,14,15} and one registry study,¹³ did not find any increased relapse risk in the survivors exposed to ART. None of these studies focused on breast cancer survivors harboring germline pathogenic variants in *BRCA1/2*.

In most of the above-mentioned studies, patients exposed to ART had favorable oncological characteristics (low tumor stages, negative nodes, and hormone receptor-positive disease in the majority of the patients). Similar to prior studies, we also observed that patients in the ART group had favorable oncological characteristics. A total of 63.6% of the patients had T1 stage, 63.6% node-negative disease, 45% grade 1-2 tumors, and 59.1% hormone receptor-positive breast cancer. Moreover, as in prior reports,^{12,14} most of the patients underwent chemotherapy (77.4%). These data suggest that oncologists and fertility specialists are probably concerned about the safety of ART in breast cancer survivors, supporting mainly patients with

favorable oncological characteristics to undergo these options.

Additionally, patients aiming to conceive through ART were more often childless at diagnosis (72.7%) and older (median age of 33 years). Survivors who conceived naturally were pregnant at a younger age, most probably in relation to their earlier age at diagnosis, but we might also hypothesize complementary reasons such as a lower prevalence among these patients of a hormone receptor-positive breast cancer and a possible shorter time to conceive because ART was not required. Among the 22 patients in the ART cohort, the most commonly used approach in order to obtain a pregnancy was embryo transfer under HRT in 40.9% of cases (embryos were cryopreserved at breast cancer diagnosis or obtained from oocyte donation/cryopreserved oocytes), followed by IVF/ICSI in 31.8% of cases. These results are in line with the previous study in breast cancer survivors obtaining a pregnancy through ART: 44% became pregnant following embryo transfer from oocyte donations and 36% became pregnant following ovarian stimulation.¹² Similarly, in another study taking into account all ART procedures carried out in breast cancer survivors, 51.7% of cycles consisted of ovarian stimulation for IVF/ICSI (107/207) and 30.9% were embryo transfer under HRT (64/207).¹⁴ Embryo transfer under HRT exposes patients to a physiologic serum estradiol concentration and, for those using oocyte donation, it allows avoiding the transmission of the *BRCA* pathogenic variant. Through the use of ovarian stimulation for IVF/ICSI, which was the second most frequent technique in our study (seven patients, 31.8%), patients could be exposed to higher values of estradiol levels. However, this technique allows access to PGT for *BRCA1/2* pathogenic variants, which might be highly valued from a survivor's perspective. Unfortunately, data on the attempts of PGT in our cohort were not available. Data on

ART were missing for five patients (22.7%), indicating a need for better communication between oncology and fertility centers.

Patients in the ART cohort experienced more delivery complications compared with those who became naturally pregnant (22.7% versus 4.1%, respectively). It is known that the exposure to ART,²⁹ and older age at conception,³⁰ lead to an increased obstetrical risk.

DFS events tended to be less frequent in the ART cohort (9.1% in the ART cohort versus 27.4% in the non-ART cohort). This tendency could be related to a shorter median follow-up in the ART group (3.4 years for the ART cohort versus 5.0 years in the non-ART cohort) and to the higher prevalence of hormone receptor-positive (59.1% in the ART group versus 31.5% in the non-ART group) and low-grade tumors (50% of grade 3 tumors in the ART cohort versus 78.1% in the non-ART cohort). Although the ART cohort of our study is rather small, no apparent alarming prognostic signals have been observed for survivors bearing *BRCA* pathogenic variants exposed to ART in order to obtain a pregnancy. Notably, it is the first study reporting ART outcomes in the population of *BRCA*-mutated breast cancer survivors achieving a pregnancy following anticancer treatment completion, with one of its major assets being its multicentric nature with 30 centers worldwide. These encouraging data can help physicians when counseling *BRCA*-mutated breast cancer survivors on the safety of ART following completion of anticancer therapies.

The main limitations of our study are its size and its retrospective nature reporting mostly descriptive analyses. Moreover, the ART and non-ART groups were characterized by some differences in baseline and post-treatment characteristics. However, it is important to elicit that only ~12% of young breast cancer patients bear a *BRCA1/2* pathogenic variant,^{31,32} and that only a minority of breast cancer patients achieve pregnancy.^{33,34} As a result, even though 30 centers participated worldwide in this study with a total of 1424 patients who were registered, 22 patients could be included in the ART cohort for the purpose of this analysis.

In conclusion, our study showed that in breast cancer survivors bearing germline *BRCA* pathogenic variants, the use of ART does not appear to increase the risk of relapse. However, it is important to underline that there is a great need for an international registry which could be promoted and endorsed by international oncology and fertility societies. This tool would allow to increase our knowledge and give more solid answers on this subject of great interest to many women.

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DISCLOSURE

EdA has acted as a scientific advisory board member and has received honoraria from Roche/Genentech, Novartis, Seattle Genetics, Zodiacs, Libbs, Pierre Fabre, and Lilly; has received travel grants from Roche/GNE and GlaxoSmithKline (GSK)/Novartis; and has received research grants through his institution from Roche/GNE, AstraZeneca, GSK/Novartis, and Servier, outside the submitted work. FAP has acted as consultant for Ipsen, Roche Diagnostic, and Merck outside the submitted work. CRJ has acted as a scientific advisory board member and her institution has received honoraria from Bristol Myers Squibb (BMS), Theramex, and Roche; and her institution has received speaker's fees from Theramex and BMS, outside the submitted work. AS has acted as a consultant for Eli Lilly, Pfizer, Novartis, and Roche; has received speaker's fees from Teva, Roche, Pfizer, and Novartis; has received travel grants from Neopharm, Celgene, and Medison; and has received grant support from Novartis and Roche, outside the submitted work. CVG has acted as a consultant, as a scientific advisory board member, and has received speaker's fees from Roche, Novartis, Pfizer, Lilly, and Merck Sharp & Dohme (MSD); and has received research funding from AstraZeneca, Roche, and Pfizer, outside the submitted work. OCC has acted as a scientific advisory board member for Ascires Sistemas Genómicos; and has received grant support from Roche Diagnostics, Neomedic, and Takeda, outside the submitted work. KP has acted as a scientific advisory board member for AstraZeneca, Eli Lilly, Gilead Sciences, MSD, Novartis, Pierre Fabre, Roche, Teva, and Vifor Pharma; has acted as a consultant for AstraZeneca, Novartis, Pfizer, and Roche; has received speaker's fees from Eli Lilly, Medscape, MSD, Mundi Pharma, Novartis, Pfizer, and Roche; has received travel grants from AstraZeneca, Novartis, Pfizer, PharmaMar, and Roche, outside the submitted work. FP has acted as a scientific advisory board member and has received speaker's fees from Amgen, AstraZeneca, Daichi-Sankyo, Eisai, Eli Lilly, Ipsen, MSD, Novartis, Pierre-Fabre, Pfizer, Roche, Seagen, and Takeda; has received travel grants from Celgene, GlaxoSmithKline, and Roche; and has received research funding from AstraZeneca, Eisai, and Roche, outside the submitted work. ARF has received honoraria from Bayer, Daiichi Sankyo, Novartis, and Roche; and has received travel grants from Roche, outside the submitted work. JB has acted as consultant for AstraZeneca and Pfizer outside the submitted work. ID has acted as a scientific advisory board member and received grant from Roche; has received speaker's fees from Novartis; and has received travel grants from Theramex and Ferring, outside the submitted work. ML has acted as a consultant for Roche, Lilly, AstraZeneca, Exact Sciences, and Novartis; and has received honoraria from Sandoz, Roche, Lilly, Pfizer, Novartis, Ipsen,

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