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Skin Testing and Patch Testing in Non-IgE-Mediated Drug Allergy

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Abstract Drug skin tests can reproduce delayed hypersensitivity to drugs and entail a moderate reexposure of patients to offending drugs. Drug patch tests (DPTs) and prick tests can be done with any commercialized form of a drug. In non-severe delayed non-IgE-mediated reactions to drugs, intradermal tests (IDT) with delayed readings have a greater value, but their techniques lack standardization. A negative drug skin test does not exclude the responsibility of a drug, and the drug must be rechallenged in non-severe cases. DPTs are useful in maculopapular rashes, flexural exanthemas, and if done in situ, also in fixed drug eruption. Their best indication is in acute generalized exanthematous pustulosis or drug reaction with eosinophilia and systemic symptoms (DRESS). They should be carried out cautiously, following strict guidelines. Prick tests have a low value but they can sometimes be positive on delayed readings. In non-severe delayed reactions to drugs, intradermal tests with delayed readings are the most sensitive skin tests especially for beta-lactam antibiotics, radiocontrast media, heparins but also some biological agents. The value of patch testing varies according to the implicated drug and the non-immediate adverse drug reaction. In DRESS, DPTs have a good value in testing carbamazepine or proton pump inhibitors but remain negative in testing with allopurinol or salazopyrin. In toxic epidermal necrolysis, DPTs are safe but positive in only 9 to 23 % of the reported cases.

Keywords Drug patch tests · Intradermal tests · Maculopapular rashes · Fixed drug eruption · Acute generalized exanthematous pustulosis · Drug reaction · Eosinophilia · Systemic symptoms · Toxic epidermal necrolysis · Beta-lactam antibiotics · Radiocontrast media · Biological agents

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Introduction

In delayed hypersensitivity to drugs or non-IgE-mediated cutaneous adverse drug reactions (CADR), drug patch tests, prick tests, and intradermal tests (IDT) can be useful because beside clinical and chronological parameters, there is no standard complementary test to help in defining the cause of the adverse event. Since patients are often on multiple drug regimes, it is often difficult to identify the responsible agent solely on chronological criteria and pinpoint the relevant drug from history alone. Moreover, drug skin tests can aid in differentiating sensitization to the drug itself or to excipients and also in finding a replacement drug. However, while some drugs have been used widely and are standardized (e.g., beta-lactam antibiotics), many compounds are still not standardized for skin testing and their use remains experimental and should be interpreted cautiously.

Non-IgE-mediated drug allergies include non-severe CADR maculopapular exanthema (MPE), fixed drug eruption (FDE), and also severe cutaneous adverse drug reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

It is advised to perform drug skin tests at least 1 month after the resolution of the CADR and during the year following the CADR, as we do not know whether positive results will persist and whether some drug reactivity lasts longer, even if they seem remain positive many years after the onset of the adverse reaction.

Drug Patch Tests

Drug patch tests (DPTs) represent a method of diagnostic testing which is low-risk, as they can reproduce delayed hypersensitivity to drugs and entail only a moderate reexposure of patients to offending drugs. They can be done with commercialized products for DPTs at 10 % in

petrolatum. Unfortunately at the moment only a few drugs are available with standardized material for DPT (Chemotechnique laboratory, Velinge, Sweden). Commercialized preparations for drug patch testing can be bought in Europe but are not available in USA. In most of the cases, DPTs have to be prepared with the commercialized forms provided by the patients or pharmacy. Two sets of European guidelines have been published for clinicians to conduct DPTs using the drug in its commercially available formulation (pulverized tablet, syrup, solution, powder), with each drug diluted to 30 % according to the European Society of Contact Dermatitis (ESCD) [1] or 20 % according to the European Network for Drug Allergy (ENDA) [2]. Following these guidelines, it has to be kept in mind that the exact amount of the active ingredient in diluted commercialized forms of drug can vary a lot from one drug to another. The best vehicle to prepare drug patch test has not yet been determined. Petrolatum seems to be convenient in most of the cases [3, 4••]. Steroid hormones have to be tested diluted in alcohol as false negative results have been observed in testing estrogens diluted in water or petrolatum [1, 3]. Drug PT are applied on the upper back but in FDE, testing in the affected area is recommended [1, 3, 5]. The results of DPTs are reported according to the International Contact Dermatitis Research Group (ICDRG) criteria for patch test reading [6] with negative, doubtful, or positive (+, ++, +++) on day 2 and 4 [1, 2]. In cutaneous adverse drug reactions, the rate of positive results on DPTs varies from 11 to 44 % depending of the drugs tested and also their drug causality assessment [3].

To avoid false positive results, some drugs have to be tested at lower concentrations. The content of capsules of celecoxib in tablet should be tested at 10 % in petrolatum and not with any higher concentration [7]. Recently, 38 negative controls with celecoxib 100 mg tablets diluted at 1 % in petrolatum were reported [8••] (Table 1). Desloratadine has to be tested at 1 % in petrolatum [9]. Colchicine at 10 % in petrolatum induces false positive results; its threshold of specificity is unknown [10].

Testing with carbamazepine or pseudoephedrine has been reported to reinduce the CADR symptoms during patch testing [3]; therefore, it is recommended that patch tests are performed, first diluted at 1 % and, when negative, up to 10 %. Relapses of AGEP have also been reported with paracetamol [3] and pristinamycin [8••].

Drug Prick Tests

Performed to identify immediate reactions, prick tests are done on the volar forearm with the commercialized form of the drug and read at 20 min. In delayed reactions, they can be performed but read 24 h after the tests, because delayed positive results can occur also in prick tests in patients with drug-induced maculopapular rash (MPR) [3], AGEP, or DRESS [8••]. Thresholds for specificity in doing drug prick tests have been recently reviewed [4••].

Drug Intradermal Tests

The most sensitive skin test is the intradermal test (IDT) that must be done only with commercial products in an injectable form. IDTs are contraindicated in severe cutaneous adverse drug reactions. The ESCD guidelines [3] recommended an intradermal injection of 0.04 ml, while the European Academy of Allergy and Clinical Immunology (EAACI) guidelines [2] recommend injections of 0.02 to 0.05 ml. IDTs lack a sufficient degree of standardization due to variations in IDTs specificity thresholds from one center to another. At the moment, the European Network for drug allergies of EAACI is performing a multicenter study in order to standardize the method for IDTs. It is recommended to inject 0.02 mL, to note the name of the injected product, the site of injection (upper arm, forearm or back), and measure the diameter of the immediate injection papule (wheal). Read at 20 min, the IDT is considered positive only if there is a wheal of ≥immediate injection papule+3 mm and a surrounding erythema. On delayed readings, done at 24 h, IDTs are considered positive when there is an erythematous induration at the injection site, whatever the diameter measured. It can be necessary to do more delayed readings (3 days) in testing heparin derivatives or corticosteroids [3].

Some thresholds for specificity have been recently reported for IDTs [4••]. The main drug classes with delayed adverse reactions having been investigated with IDTs in a large number of patients are beta-lactam antibiotics, radiocontrast media (RCM), and heparins. Recommendations for maximal concentrations in testing beta-lactam antibiotics have been published [11]. Amoxicillin, amoxicillin–clavulanic acid, or ampicillin can be tested up to 20 mg/mL and cephalosporins up to 2 mg/mL. Among 326 cases of suspected reactors to beta-lactam antibiotics, 21 (6.4 %) had delayed positive results on IDTs [12•]. In the same study, 33/291 patients (11.3 %) with negative IDTs had a positive rechallenge.

Radiocontrast media can be tested at 1:10 dilution [13], and in plaque reactions or disseminated exanthema due to anticoagulants, heparin derivatives can be tested at 1:10 dilution [14] then. Read after 24 h and if negative later at 72 h. Attention has to be paid to avoid subcutaneously injecting too many heparin derivatives simultaneously, because it could induce anticoagulation. Considering biologicals, in severe injection site reactions to anti-tumor necrosis factor alpha agents, IDT could be of value and specific in testing infliximab up to 2 mg/mL, adalimumab up to 50 mg/mL, and etanercept up to 5 mg/mL [15•]. Recently, in patients with generalized exanthemas induced by interferon alpha, IDT up to undiluted drug

Table 1 Thresholds for specificity for drug patch tests.(according to Barbaud et al. [8••])

	Concentration and vehicle	Number of negative PTs in database
Acyclovir[a]	10 % pet.	4
Amoxicillin trihydrate[a]	10 % pet.	180
Amoxicillin–clavulanic acid 1,000 mg tablets	30 % pet.	177
Amikacin 250 mg injectable form	30 % pet.	15
Carbamazepine[a]	10 % pet.	10
Ceftriaxone injectable form	30 % pet.	180
Celecoxib 100 mg tablet	1 % pet.	38
Citalopram 20 mg	30 % pet.	3
Clindamycin 300 mg tablets	30 % pet.	6
Clobazam 10 mg tablets	30 % pet.	3
Dicloxacillin sodium salt[a]	10 % pet.	2
Diltiazem hydrochloride[a]	10 % pet.	12
Enoxaparin 30 IU anti-Xa	undiluted	33
Esomeprazole 40 mg tablet	30 % pet.	32
Iodixanol 320 mg/mL injectable form	undiluted	245
Ioversol 350 mg/mL injectable form	undiluted	245
Lamotrigine 100 mg tablets	30 % pet.	6
Lansoprazole 30 mg tablet	30 % pet.	14
Olanzapine 10 mg tablet	30 % pet.	1
Pantoprazole 40 mg tablet	30 % pet.	22
Paracetamol 500 mg tablet,	30 % pet.	48
Pristinamycin[a]	10 % pet.	15
Pseudoephedrine[a]	1 % pet.	4
Pyrimethamine 50 mg tablets	30 % pet.	1
Ramipril 2.5 mg tablet	30 % pet.	9
Spironolactone 25 mg tablet	30 % pet.	5
Tetrazepam 50 mg tablets	30 % pet.	12
Vancomycin 1,000 mg injectable form	30 % pet.	26

These negative results were obtained from the Diamm-Toxiderm database for skin tests in Nancy, France

[a] Material commercialized for drug patch tests by Chemotechnique diagnostics with drug diluted at 10 % in pet.

concentrations have been reported as useful and specific for studying potential cross-reactivities between different interferons [16•].

Delayed non-specific false positive results can occur with IDTs done with flu vaccines [17]. Whereas IDTs with platinum salts have a good negative predictive value especially in immediate reactions [18], in delayed skin reactions occurring with these chemotherapies, IDT with platinum salts have to be considered with caution because they can induce delayed false positive results. This has been reported, in one case with cisplatin diluted at 0.1 and 1 mg/ml and with carboplatin diluted at 1 mg/ml [19].

In AGEP or DRESS, performing intradermal tests is highly debatable but it could be considered in a limited number of patients having developed their severe CADR with a multiple regimen of drugs, for absolutely necessary drugs without any possible substitution and having a low drug causality assessment, according to chronological criteria. Moreover, in DRESS, it could be suggested to consider IDT only when there is no virus reactivation, assessed by a negative polymerase chain reaction.

Drug Skin Tests in Maculopapular Rashes

From a European multicenter study, skin tests with RCM were positive in 37/98 (38 %) non-immediate reactors [13]. Patch tests were positive in 22/79 (28 %) patients, prick tests in 3/98 cases, and 31/98 patients had positive delayed IDT, among them nine had delayed positive IDT but negative patch tests. On the other hand, seven patients had negative results on IDT but positive DPTs. Among RCM, cross-reactivities are frequent and can be studied by skin tests. Among 259 adults with delayed reactions to penicillins, 94 (36.3 %) had positive DPTs or IDTs to the culprit penicillin [20]. Eight of them displayed delayed positive results on IDTs but had negative DPTs. Drug skin tests with delayed positive results were

obtained in 93/173 (53.7 %) patients with MPR. Among 105 subjects with histories of non-immediate reactions to cephalosporins, seven patients (6.6 %) had delayed positive skin tests [21••] and among them, five exhibited a MPR. Of the 86 subjects with negative results with cephalosporin skin who accepted challenges with the suspect cephalosporin, all tolerated them. Considering clinical features, 39/110 reactive episodes due to cephalosporins were of MPR type. All five patients having MPR with hypersensitivity had delayed positive IDTs with the culprit cephalosporin with positive DPTs in only three cases.

Among ten patients with MPR due to interferons, DPTs had a poor value but IDTs with delayed readings (positive with the responsible interferon in all seven patients tested) can be useful for managing patients, studying cross-reactivities, and guiding the choice of alternative treatments.

A negative drug skin test does not exclude the responsibility of a drug in a cutaneous adverse reaction, and the drug must be rechallenged in non-severe cases. In patients with MPR, 14/150 rechallenges (9.3 %) with the suspected drug were not tolerated [22]. Substitution tests (i.e., a drug belonging to the same class as the responsible drug, but with a different chemical structure) after negative skin tests were positive in 5/68 tests (7.3 %) done in patients with drug-induced MPR.

In Situ Drug Patch Tests in Fixed Drug Reactions

In situ DPTs have been recommended for a long time in investigating the responsible drug for FDE in order to avoid a provocation test, which remains the gold standard for the etiological diagnosis of this recurrent, localized, delayed adverse drug reaction [5]. There were many case reports with positive lesional DPTs in FDE especially with non-steroidal anti-inflammatory drugs or trimethoprim–sulfamethoxazole. In a retrospective French multicentre study, lesional DPTs were positive in 12/19 cases tested [23]. Positive DPTs were observed with carbocisteine, paracetamol, pefloxacin, piroxicam, pristinamycin, tenoxicam, and trimethoprim–sulfamethoxazole.

Recently, Andrade et al. [24••] reported that lesional DPTs confirmed the clinical suspicion and allowed the identification of the culprit drug in 21/52 patients (40.4 %) tested with FDE. In all the cases, non-intralesional DPTs were negative. In situ DPTs were positive in one case with cetirizine and in 20/47 (42.6 %) with NSAIDs (9/27 with nimesulide, 9/23 with piroxicam, and 2/3 with etoricoxib). None of the seven patients tested with trimethoprim–sulfamethoxazole, none of the eight tested with paracetamol, and none of the 15 cases due to other antibiotics had positive lesional DPTs. In a few patients, when in situ DPTs were negative, oral rechallenge tests were done and were positive in 5/7 cases.

Drug Skin Tests in Symmetrical Drug-Related Intertriginous and Flexural Exanthema

Recently, it has been proposed to classify flexural exanthemas and give similarities and differences between Baboon syndrome and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) [25•]. Systemic drug-induced SDRIFE is often an obvious diagnosis i.e., occurrence after exposure to systemic drugs, sharply demarcated erythema of the buttocks and/or V-shaped erythema of the thighs, involvement of at least one other flexural fold, symmetry, and the absence of systemic symptoms. According to this classification of flexural systemic cutaneous adverse drug reactions, SDRIFE can be due to a systemic exposure to the offending drug.

The rate of positive patch tests has not been evaluated in flexural exanthemas; it could be from 52 to 82 % [25•]. Positive patch tests have been reported with beta-lactam antibiotics, clindamycin, erythromycin, neomycin, RCM, 5-aminosalicylic acid, or pseudoephedrine [3]. Recently, a SDRIFE due to etonogestrel contained in a contraceptive intravaginal ring has been published with a positive DPT [26].

Drug Skin Tests in Acute Generalized Pustulosis

Recently, in a French multicentre study, DPTs were conducted on patients referred for AGEP, DRESS, or SJS/TEN within 1 year of their SCAR, in testing all drugs administered in the 2 months prior to and the week following the onset of the SCAR [8••]. Drug patch tests were done according to the ESCD guidelines [1] using the commercialized form provided by the patients themselves, with each drug diluted to 30 % (80 % of cases) or 10 % (20 % of cases) in petrolatum. Among the 134 patients included, positive DPTs were obtained for 24 different drugs and were positive in 76 of the 134 patients (57.5 %) with SCAR.

For AGEP, DPTs seem to be of value, as they were positive in 26 out of 45 cases (58 %) in the French multicentre study and in seven out of 14 cases reported by Wolkenstein et al. [27]. In the recent multicentre study, in AGEP, the most frequent positive results were observed in testing beta-lactam antibiotics (mainly amoxicillin), pristinamycin, RCM but also corticosteroids [8••]. In the literature, there have also been some individual cases of patients with AGEP and positive DPTs for allylisopropylacetylurea, bleomycin, carbimazole, celecoxib, ciprofloxacin, clindamycin, diltiazem, metamizole, methoxsalen, metronidazole, morphine, nimesulide, pseudoephedrine, ranitidine, and tetrazepam [3].

A flare up of AGEP can rarely occur from DPTs. There are some cases reported with pseudoephedrine, but in testing with pseudoephedrine at 1 % in petrolatum then if negative with higher dosages, no relapse was observed in the case tested in the multicentre study [8••]. A relapse can occur in testing

Table 2 the value of drug skin tests according to the clinical features of the cutaneous adverse drug reactions

	Patch tests	Prick tests	IDT
Maculopapular rash	Useful (positive in 10 to 40 % of the series)	+ Before IDT and can be positive with delayed readings at 24 h	With immediate but especially delayed readings at 24 h and later if negative
Localized eczema due to heparins	Can be positive	No value but done before IDT	With immediate but especially delayed readings at 24 h and later if negative (frequently positive only after 3 days)
SDRIFE and systemic drug-induced Baboon syndrome	Useful (maybe 52 % to 82 %?)	One case with delayed positivity with amoxicillin	Unknown value
FDE	Useful on the residual area (positive in 40 % of the cases)	Unknown value	Unknown value
AGEP	Useful (positive in 50 to 58 % of the cases)	Unknown value	Unknown value could be useful. Tolerance unknown
DRESS	Useful (positive in 32 to 64 % of the cases). Done at least 6 months after the disappearance of the rash and biological disturbances. With highly reactive drugs e.g., carbamazepine or pseudoephedrine begin with at 1 % then if negative continue with higher concentrations. Multiple drug reactivities to different drug classes may occur.	Unknown value, probably very low value, some cases with delayed reactions	Unknown value. Has to be cautiously applied (relapses have been reported) and done only for absolutely necessary drugs, with a low drug causality assessment.
SJS/TEN	Can be done but are rarely positive in 9 to 23.5 % of the cases.	No value	Could be dangerous (flare-up reactions)

SDRIFE symmetrical drug-related intertriginous and flexural exanthema, *FDE* fixed drug eruption, *AGEP* acute generalized exanthematous pustulosis, *DRESS* drug reaction with eosinophilia and systemic symptoms, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis

paracetamol and one case was observed with pristinamycin [8••].

Value and safety of IDTs in AGEP are unknown. Although it was not an objective of the French multicentre study, the results suggest that IDTs with delayed readings could be useful for determining the responsible drug in patients with AGEP and negative PTs, as five of six cases had delayed positive results (four cases with beta-lactam antibiotics and one with a synergistin antibiotic) with good tolerance.

Drug Skin Tests in DRESS

In order to avoid any virus reactivation, in DRESS, we recommend performing DPT at least 6 months after the disappearance of the ADR. Two recent studies have emphasized the value and safety of DPTs in investigating patients with DRESS [8••, 28] with positive results in 18 cases of 56 Portuguese patients (32 %) [28] and 46 of 72 French cases (64 %) [8••].

In the two studies, the ESCD guidelines for DPT were followed but inclusion criteria for patients and the drugs tested were different. Barbaud et al.'s study [8••] included probable and definite DRESS induced by a large variety of drugs, whereas Santiago et al.'s study [28] found positive DPTs mainly with carbamazepine (13 with positive DPTs out of 18 suspected cases) and reported patients with DRESS due to anticonvulsants in 59 % of their cases and to allopurinol in 34 %. Moreover, in the French study, maybe more drugs per patient were investigated as all drugs within 2 months prior to onset for DRESS, as well as those introduced in the week following onset, were tested.

Among 72 cases with DRESS, 46 (64 %) had positive DPTs. These were observed in response to the following antimicrobials: beta-lactams, vancomycin, pristinamycin, quinolones, and one case each amikacin, pyrimethamine, and acyclovir. Positive DPTs to non-antimicrobials included carbamazepine (11 positive DPTs out of 13 suspected cases), proton pump inhibitors (PPIs; five cases), fluindione (two cases), spironolactone (two cases), celecoxib (one case at 30 % in petrolatum), and olanzapine, citalopram, clobazam, corticosteroids, diltiazem, heparin, lamotrigine, RCM (iodixanol) and tetrazepam (one case each).

In previous case reports, other drugs have also been reported with positive DPTs in patients with DRESS due to abacavir [31] but also aspirin, anti-tuberculosis drugs, cyclins, phenytoin, 3-propylthiouracil, and topiramate [3, 8••].

The value of patch testing varies according to the implicated drug. Drug PTs appeared to be unhelpful in cases of DRESS due to salazopyrin (five cases) [8••] and allopurinol, not yielding any positive results. Drug PTs to allopurinol were negative in 19 cases of the study of Santiago et al. [28] corroborated by Barbaud et al.[8••], who did not have any positive results among eight such patients.

Many studies have reported positive DPTs with carbamazepine at 10 or 30 %, including 11 cases among 13 patients with DRESS possibly due to this anticonvulsant in the study of Barbaud et al. [8••], seven out of 10 suspected cases in the study of Lin et al. [29•] and 13 /18 cases tested at 20 % in petrolatum reported by Santiago et al. [28]. In fluindione-induced DRESS, DPTs performed in 10 cases, were positive in nine cases [30•].

In DRESS, hypersensitivity seems to be long-lasting. Positive results on DPTs could imply transient, non-specific reactivity to drugs due to strong immunostimulation induced by virus reactivation, but this cannot explain why DPTs would remain positive with carbamazepine and beta-lactam antibiotics 11 years after the disappearance of DRESS in one case reported by Barbaud et al. [8••].

Multiple drug reactivity (MDR) to different classes of drugs administered appears more frequently in DRESS, reported in 13/72 cases (18 %) of DRESS [8••], whereas in the same country in non-severe cutaneous adverse drug reactions, MDR was found in only seven of 1,925 cases [32]. In vitro, using lymphocyte activation tests, this MDR has also been demonstrated in five patients with DRESS [33]. No functional deficiency of Treg cells was observed; drug-reactive T cells from these MDR patients were found in the pre-activated T cell fraction (CD4+ CD25dim T cell fraction with enhanced CD38 and PD-1 expression). This could show a lower threshold for activation by drugs.

Two cases of delayed reactions on drug prick tests have been observed in patients with DRESS [8••].

Drug Patch Tests in Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

Drug PTs do not appear to be very sensitive for SJS/TEN, as only two of 22 patients tested by Wolkenstein et al. [27] and four of 17 tested in the Barbaud et al. study [8••] had positive DPTs. Nevertheless, in the literature, positive DPTs in SJS/TEN have been reported for beta-lactam and glycopeptide antibiotics, carbamazepine, lamotrigine, PPI, tetrazepam, trimethoprim–sulfamethoxazole, pseudoephedrine, and ramipril [3, 8••, 27, 29•]. The sensitivity of DPTs could be dependent on the drug, as Lin et al. [29•] obtained 10 positive DPTs for carbamazepine in 16 patients with SJS/TEN.

Unfortunately, in the Barbaud et al. study [8••], there was not any difference in testing skin areas that were or were not previously affected by necrolysis.

Conclusions

In conclusion, skin tests mainly DPT in all cases and in non-severe CADR, IDT with delayed readings is of value and safe for investigating delayed non-IgE-mediated reactions to

drugs. During the last 5 years, owing to studies enrolling a large number of patients, we have improved our knowledge on the value and safety of these in vivo tests.

Rejected for a long time, because they were supposed to be dangerous, DPTs may have their best indication in SCARs such as AGEP or DRESS. Of course, they should be carried out cautiously, following the up to date recommendations summarized in Table 2. Prick tests have a low value in non-immediate drug reactions but they can be positive on delayed readings in a few cases. In non-severe delayed reactions to drugs, intradermal tests with delayed readings are the most sensitive skin tests especially for beta-lactam antibiotics, radiocontrast media, heparins but also some biological agents.

In the future, it will be necessary to better standardize our methods of skin tests in order to compare results in larger multicentre studies and determine thresholds of concentrations to avoid false positive results.

Compliance with Ethics Guidelines

Conflict of Interest Annick Barbaud declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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