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ORIGINAL CONTRIBUTION

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Monitoring chemotherapy-induced alopecia with trichoscopy

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Summary

Background: Chemotherapy-induced alopecia (CIA) ranks among the psychologically most devastating effects of cancer treatment for oncological patients, with an overall incidence of 65%. Nowadays trichoscopy is largely employed in the diagnosis of alopecia, but no description of CIA trichoscopic pattern is present in literature.

Aims: We want to create an organic description of CIA trichoscopic aspects.

Methods: Oncological patients candidate to chemotherapy drugs, afferent to our trichological outpatient were studied. Anamnesis, clinical exam, clinical global photography, pull test, trichogram, and trichoscopy were conducted at the different moments of therapeutic treatment.

Results: A definite trichoscopic pattern in the different phases of treatment was observed. After the first 3 weeks of chemotherapy rare and scattered black dots, broken hairs, flame hairs and pohl pinkus appeared. At the end of chemotherapy besides the features described above, numerous thin hair in regrowth were detected, together to rare terminal hair, scattered black dots and circle hair. Three months after chemotherapy a progressive increase of follicular units and elongation of the existing hair were visible.

Conclusions: We propose an description of CIA trichoscopic pattern and its evolution during the different phases of chemotherapy.

KEYWORDS
alopecia, chemotherapy, hair loss, skin reactions, trichoscopy

1 | BACKGROUND

Chemotherapy-induced alopecia (CIA) ranks among the psychologically most devastating effects of cancer treatment for oncological patients. It negatively influences body image, sexuality, and self-esteem, so that up to 8% of patients are referred to refuse chemotherapy for the risk of hair loss.[1]

Nevertheless to date no fully satisfactory cure for CIA is at hand.[2] Its Overall incidence is estimated to be 65%, but its prevalence and severity are related to the category and the number of the administered drugs. It is more frequent with poly-chemotherapy if compared to monotherapy.[3]

Hair-shaft shedding may occur few days after starting chemotherapy or, more often, after 2 weeks (anagen effluvium). If hair loss takes place months after the beginning of the therapy, a stop of anagen occurs with the induction of catagen and consequent telogen (telogen effluvium).

The mitotic activity of the hair follicle in the moment of the insult is probably the most important among factors that may influence the shedding pattern.[3] Up to 90% of scalp hairs are normally in anagen phase, that explains why it is the most frequent affected area, unlike beard, lashes, eyebrown, axillary, and pubic hair that are usually less involved. Chemotherapy accelerates the normal transition from late anagen phase, characterized by a lower mitotic rate, to telogen. Catagen and telogen are mitotically inactive phases and are typically not interested.[3, 4]

The affected areas seem to be selective, and frontal or occipital hairlines are more frequently involved. Most of all alopecia is

reversible with a complete regrowth in 3-6 months, even if texture and color may be different after the regrowth.[5] Although, rare cases of permanent alopecia (about 20% of CIA) are reported, and it is probably the consequence of a damage of hair-follicle stem cells.[3, 4, 6]

What exposed before is related to "classic" better known anti-cancer drugs. Nowadays several molecularly targeted anti-cancer drugs have been developed. Hair loss associated to these new drugs has an overall incidence of 14.7%, but its characteristics and mechanism are different and poorly understood.[4, 7]

Trichoscopy is an effective, noninvasive and nonexpensive method for scalp evaluation.

A manual dermoscope (×10 magnification) or a videodermoscope (up to × 1000 magnification) may be used to enhance the diagnosis of many types of alopecia. This method besides to be simple, quick, and easy to perform, allows to make a certain diagnosis and it is useful for monitoring treatment and follow-up. Using trichoscopy a lot of scalp biopsy could be avoided, making this technique well accepted by patients.

Even if trichoscopy is actually largely employed in the diagnosis of any type of scalp diseases, no description of CIA trichoscopic pattern are present in literature.

Nevertheless trichoscopy plays a crucial role in CIA management; it is useful for the individuation of specific features before, during and after chemotherapy. Before the treatment trichoscopy, together to trichogram, may help to evaluate the presence of a latent or prior scalp disease.

Trichogram allows us to instantly evaluate anagen/telogen ratio. This data associated to therapeutic protocol (molecule, number of drugs, dose, timing, and methods of administration) let us to estimate the onset of hair loss and the pattern of presentation. During chemotherapic treatment, in particular after 2/3 weeks, trichogram and trichoscopy may show follicular unit damage.

Our aim is to describe CIA trichoscopic pattern, and their modifications during the different phases of chemotherapy.

2 | MATERIALS AND METHODS

In order to describe CIA trichoscopic pattern, we studied oncological patients candidate to chemotherapy with "traditional" drugs afferent to our trichological outpatient.

We selected 12 women between 35 and 70 years old, affected by breast cancer that would have been treated with 4-6 cycles of FEC protocol (5-fluorouracile, epirubicine, and cyclofosfamide). Women with other cancer localization simultaneously and/or other chemotherapeutic drugs were excluded.

Our evaluation consisted in anamnesis with particular attention to the presence of previous scalp diseases and the drug protocol that was established; clinical exam; pull test; clinical global photography and trichoscopy using Fotofinder trichoscan®; trichogram.

All these evaluations were conducted at the following times: before the beginning of chemotherapy (T_0), 3 weeks after the first administration (T_1), every month during chemotherapy and every 3 months after the end of the therapy until 1 year (T next to T_1).

3 | RESULTS

All patients completed the treatment and the evaluations.

3.1 | T_0 evaluations

No patients referred previous scalp diseases, pull test was negative in the 100% of patients. Trichogramm showed anagen hair >90%.

Seventy per cent had a normal trichoscopic pattern, but in the 30% of patients, trichoscopy showed anisotrichya, hair miniaturization, and density reduction.

3.2 | T_1 evaluations

Pull test was positive with hair in dystrophic anagen phase. Trichogramm showed 70%-100% dystrophic anagen bulb hair.

Rare and scattered trichoscopic signs appeared. They consisted in black dots (67% of patients), broken hairs (8% of patients), exclamation marks (42% of patients), flame hairs (56% of patients) and pohl pinkus (56% of patients), a certain grade of miniaturization was present in 100% of patients (Figures 1 and 2).

3.3 | $T > 1$ evaluations

Pull test was positive. Trichogramm showed 70%-100% dystrophic anagen bulb hair.

Trichoscopic evaluations during the following months showed sporadic yellow dots and yellow 3D dots (75% of patients), some thin, depigmented and scattered regrowing hair (100% of patients), in the form of circle hair (33% of patients), pigtail (42% of patients), vellus-like hair (92% of patients; Table 1).

At the end of chemotherapy besides the features described above, numerous thin hair in regrowth with variable length and caliber and variously pigmented were detected. Rare terminal hair could be seen, and scattered black dots may remain, but circle hair was the most characteristic feature (Figure 3).

Three months after the end of chemotherapy trichogram showed an increase in anagen hair, a reduction or disappearance of dystrophic anagen hair and absence of telogen hair.

Trichoscopy showed a progressive increase in active follicular units (that were previously empty) and elongation of the existing hair was visible with trichoscopy. At the emergence from follicular ostia regrowing hair is usually nonpigmented; we observed that after few millimeters in length hair begins to be pigmented, assuming a bicolor appearance, being white at the tips and variously pigmented at the basis (Figure 4).

Eight percent of patients' new hair appeared different than before, becoming hyperpigmented and thicken (56%) or thinner (44%), a different pigmentation was observed in the 80% of cases (Figure 5).

These changes normally last just until one year after the end of the treatment, after this time they come back to prechemotherapy aspect.

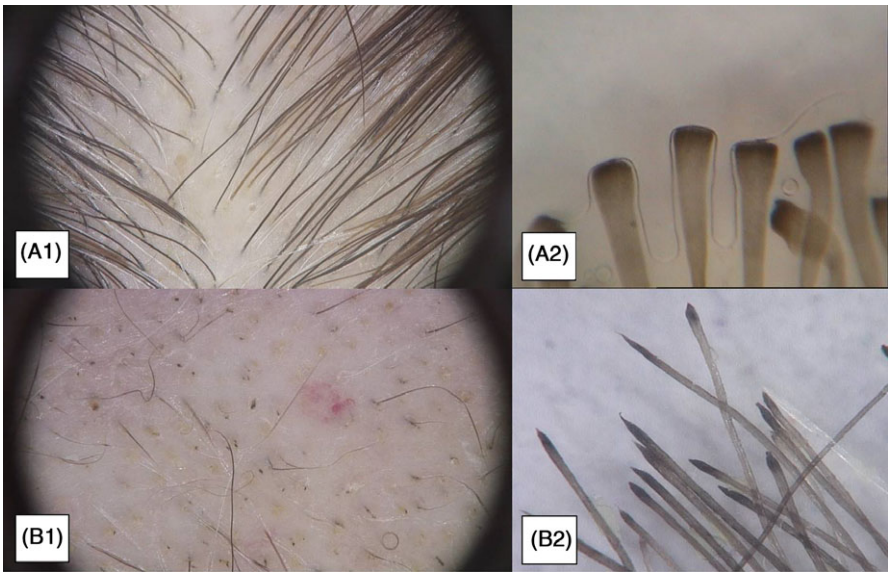

FIGURE 1 Trichoscopy and trichogram of the same patient before (A1, A2) and during (B1, B2) chemotherapy. Image A1: normal trichoscopic pattern. Image A2: anagen hair. Image B1: Black dots, broken hairs, sporadic yellow dots, pohl pinkus and a circle hair could be observed. Image B2: dystrophic anagen hair

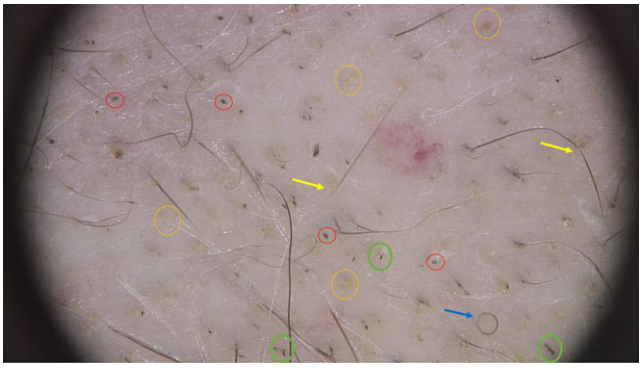

FIGURE 2 A trichoscopic image during chemotherapy administration. Black dots (red circles), broken hairs (green circles), sporadic yellow dots (yellow circles), pohl pinkus (yellow arrow), and a circle hair (blue arrow) could be observed

Nevertheless about 20% of all patients, reported a reduction in the distribution of follicular units and the persistence of vellus hair if compared with the T_0 state. The 50% of these subjects had anisotrichya, hair miniaturization and density reduction at the time of the first evaluation, but another 50% had a normal trichoscopy.

4 | DISCUSSION

At the best of our knowledge no complete description of CIA trichoscopic pattern are present in literature. Just isolated trichoscopic feature are reported to be present in patients with CIA and they are not differentiated on the basis of the chemotherapy phase.

Miteva and Tosti reported the presence of flame hair in 100% of 6 cases of chemotherapy induced hair loss, described as a type of hair residue resulting from severe external injury to the hair shaft.[8]

TABLE 1 Patients' trichoscopic findings at T_2 evaluation

Patients	Circle hair	Pohl pinkus	Exclamation marks	Black dots	Flame hair	Density reduction	Empty follicles	Miniaturization	Yellow dots	Vello-like hairs	Pigtail hairs	Broken hairs
1	0	1	1	1	1	0	1	1	1	1	0	0
2	0	1	0	1	1	1	1	1	1	1	1	0
3	1	0	0	0	0	0	0	1	0	1	1	0
4	0	1	0	1	1	1	1	1	1	1	0	0
5	0	0	0	0	0	0	0	1	0	1	0	0
6	0	0	1	1	1	1	1	1	1	1	0	0
7	1	1	0	1	1	1	1	1	1	1	1	1
8	1	1	1	1	1	1	1	1	1	1	1	1
9	1	0	0	0	0	1	0	1	0	0	0	0
10	0	1	1	1	1	1	1	1	1	1	0	0
11	0	1	0	1	1	1	1	1	1	0	1	0
12	0	0	1	0	0	1	1	1	1	1	0	0
	33%	58%	42%	67%	67%	75%	75%	100%	75%	92%	42%	8%

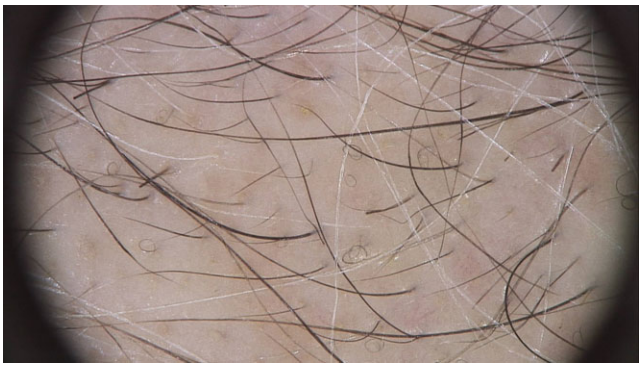

FIGURE 3 This figure shows the phase of regrowth: a lot of circle hair and vellus hair are observed

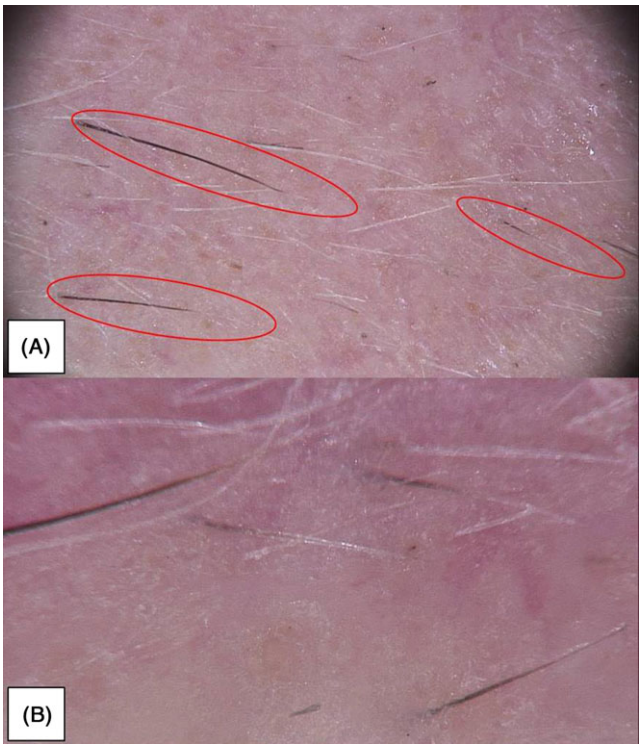

FIGURE 4 The figure shows several "black and withe hair" (A, lower magnification; B, greater magnification). They are the sign of progressive recovery of the damaged follicular melanocytes

Kowalska-Oledzka et al[9] reported black dots in 2 of 5 patients with CIA as sign of cytotoxic and antiproliferating effects of chemotherapeutic agents in anagen phase.

Pirmez et al[10] reported the presence of exclamation marks, coudability hairs, Pohl-Pinkus constrictions, black dots, yellow dots, and color changes in six patients affected by miscellaneous tumors, but no precise times of observation were indicated.

No other feature seems to be reported.

We have conducted an organized study with the aim to evaluate trichoscopic alterations of CIA, and to establish observation times. Trichoscopy may indicate the grade of alopecia during the chemotherapy, but what in our opinion is more important is

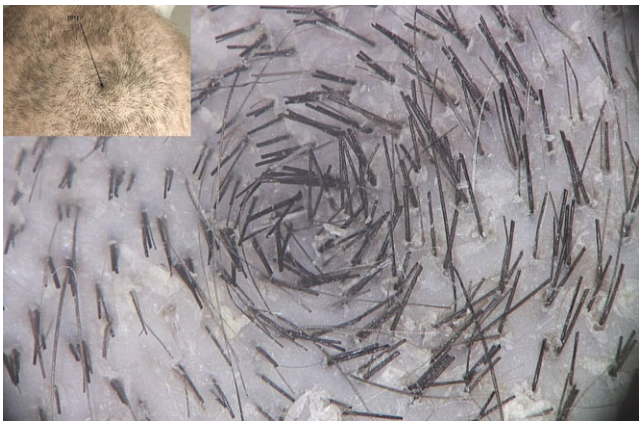

FIGURE 5 This figure shows a case of a regrowth characterized by hyperpigmented and thicken hair with a follicular encumbrance

pretreatment scalp evaluation that lead to individuate hair alteration and allows treating them. The presence of anisotrichya and rare scattered yellow dots may indicate the presence of androgenetic alopecia. A reduction of hair density with together terminal and regrowing hair suggests a diagnosis of telogen effluvium. If alopecia areata (AA) is present, we will find yellow dots, exclamation mark hairs, black dots, and broken hairs. Finally in case of alopecia areata incognita a diffuse hair density reduction, yellow dots cluster and scattered short hypopigmented regrowing hairs will be detached.

The previous presence of these diseases may influence the regrowth after chemotherapy. This influence may be explained with different mechanisms. Concerning AGA, if follicular units are already fibrotic, they couldn't be recovered even when the drug insult is over. Telogen effluvium could be paradoxically protective, because telogen hair is less vulnerable to drug toxicity. AA mechanism is more difficult to explain, but we can hypothesize that an already damaged follicle and the loss of the immunological privilege could be more easily stricken from chemotherapy. Moreover knowing the T_0 condition could avoid a misdiagnose of permanent alopecia caused by chemotherapy.

Among the trichoscopic pattern we observed, there are some that deserve a particular attention and discussion (Figure 6).

Broken hairs, detected at the beginning of chemotherapy, mimic exclamation marks that are usually associated to AA. But these ones are shorter, signal of an hair damage just after the emergency from the follicular ostium.

Exclamation marks are present in the same phase. They are expression of a progressive reduction of follicular mitotic activity without ongoing in telogen. This is an important difference with exclamation marks present in AA, which are associated to the beginning of telogen phase.

Flame hair, also observed by Miteva and Tosti[8] results from the disruption, fragmentation, and multifocal pigmentation of the hair shaft at the emergency of the follicular ostium.

The specific trichoscopic pattern of flame hair could be explained if we consider that the melanin-producing and transporting pigmentary unit is one of the principal targets of chemotherapy toxicity.

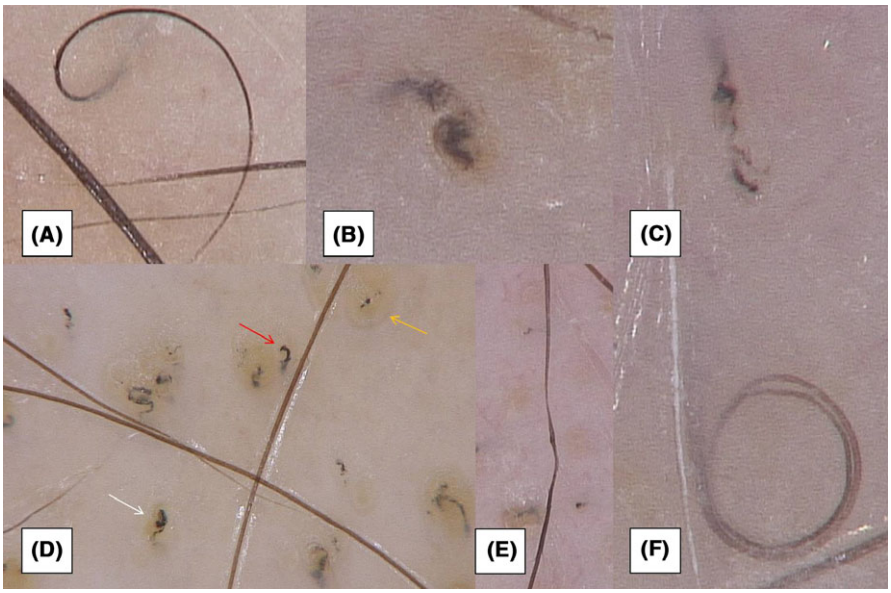

FIGURE 6 Some of the most typical CIA trichoscopical findings: pig tail hair (A), ingrown circle hair (F), flame hair (B, C, and D white arrow), comma hair (D, red arrow), yellow 3D dot (D, yellow arrow), pohl pinkus (E)

This lead to abnormal transfer of pigment granules to ectopic hair pigmentary bulb locations, extrafollicular melanin incontinence, disrupted formation of melanosomes, and inhibition of melanosome transfer into precortical keratinocytes.[11, 12]

In our opinion, these alterations could explain the trichoscopic image of flame hair as a dispersion of melanin around the damaged hair follicle because of a morphological cortical disorganization associated to a laxity of hair medullar cells. This leads to a structural disruption of hair shaft, which appears fray, producing the flame image.

It is interesting to distinguish flame hair observed in CIA, due to the direct cytotoxic effect of the drugs on the matrix cells, from the same sign frequently detected in trichotillomania, which is associated to a mechanical injury to anagen hair. Moreover, flame hair of trichotillomania has a pulled-back aspect, while in CIA it appears fray.[8]

Pohl pinkus is consequence of the alternation of reduction and increase in keratinocyte proliferation activity, which leads to the development of constrictions and expansions along the hair shaft. Which means that hair follicle is not destroyed by drug toxicity. This feature is present all along the treatment phases. It remembers pseudomoniletrix present in patients with AA, but here the internodal tract is longer. Its pathogenesis is similar to the one of exclamation marks, but in this case, the damage is not too severe to arrest follicular mitotic activity, so that after a period of reduced proliferation, it is able to regrow.

Scattered yellow dots appear after the first weeks of chemotherapy, and they are the expression of a retarded anagen phase. In other words, they represents the delayed return in anagen of the hair that were in catagen or in telogen at the moment of the drug insult.

Circle hair, pigtail, and vellus-like hair are visible during a prolonged chemotherapy. They are expression of thin regrowing anagen hair. Circle hair differs from pigtail because it has the same caliber all along the hair shaft, so that it is able to form a complete circle. Whereas pigtail is thicker at the ostium, and it became more and more thin toward the tip.

Concerning postchemotherapy phase, about 3 months after the last drug administration, circle hair, vellus-like hair and some terminal hair are detachable, and these hairs will reconstitute the previous assets. Hair pigmentation results delayed, in fact as shown in Figure 4 at the emergence from the follicular ostia hair appeared white. After several weeks we detached bicolor hair (white at the tips and pigmented at the basis). We called these hairs "black and white hair." We hypothesize that this observation is the result of a reactivation of follicular melanocytes, which have been damaged, but not destroyed by drug insult. It is interesting to point out the differences with AA. Indeed it is characterized by the presence of with vellus-like hair during the recovering phase of the disease that are destined to complete the hair-cycle, to fall, and then to be replaced by pigmented terminal hair.[11–13] Differently in CIA it is not necessary a whole hair cycle to reestablish pigmentation.

After 6 months/1 year the number of terminal hair and follicular units increase. Twenty percent of all patients doesn't show this improvement and they still present circle hair, vellus-like hair, and just few terminal hair, in particular at the androgen-dependent scalp areas. The 50% of these patients had no sign at T_0 evaluation. In regards to this last observation, we hypothesize that some women who had no sign at T_0 could have a latent FPHL condition that was revealed after drug insult; another mechanism could be the damage of hair-follicle stem cells.[3, 4, 6]

Finally, we observed that at T_0 30% of patients presents with anisotrichya, hair miniaturization and density reduction, but at the end of our evaluation just 20% of patients had these trichoscopic signs. Among this 20%, just 50% of patients had trichoscopic alteration at T_0. Standing to this observation from 10% to 20% of subjects had a trichoscopic aspect better than the one before chemotherapy. The mechanism at the basis of this observation remains unknown, but a damage-response strategy development is reported in damaged hair follicles,[4] and we suppose that it could have a role. Obviously other observations and reports are needed.

5 | CONCLUSIONS

This study wanted to produce an description of CIA trichoscopic pattern and its evolution during the different phases, in order to indicate which are the most important moments that have to be monitored. Prechemotherapy evaluation showed a normal trichoscopical aspect in the 70% of patients. During chemotherapy black dots, broken hairs, exclamation marks, flame hairs, pohl pinkus, circle hair, pigtail, and vellus-like hair were detached with different times of presentation. After chemotherapy administration 80% of patients presented a complete hair regrowth. More studies have to be conducted to better characterize this type of hair loss, and continuous attention must be paid to the effects of new but also old drugs.

CONFLICT OF INTEREST

All the authors disclose any financial, consulting, and personal relationships with other people or organizations that could influence (bias) the author's work. We also disclose any scientific writing assistance, any grant support and numbers (including NIH/Wellcome-funded papers), and any statements of employment.

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