

**Fig 1.** Hepcidin levels in patients with hidradenitis suppurativa (n = 113) across the disease severity. Hepcidin levels by anemia type: Serum hepcidin levels on log2 transformed y-axis across various anemia types (IDA, n = 4; ACD/IDA, n = 26; ACD, n = 7; not anemic, n = 64), with individual data points colored to reflect hidradenitis suppurativa physician global assessment score and shaped to reflect ferritin class. Total body iron stores were classified by ferritin class (0 for ferritin level of <20 ng/mL; 1 for  $20 \leq$  ferritin < 200 ng/mL; and 2 for ferritin level of  $\geq 200$  ng/mL). Black bars represent group medians. Significance was determined by Kruskal-Wallis analysis of variance with Dunn multiple comparisons test. ACD, Anemia of chronic disease; HS-PGA, hidradenitis suppurativa physician global assessment; IDA, iron deficiency anemia. \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ .

Reprints not available from the authors.

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#### Conflicts of interest

Dr Cohen is a principal investigator for Abbvie, Inc and on the advisory board of Abbvie, Inc and Verrica Pharmaceuticals. Dr Lowes has received fees for participating in the advisory boards of Abbvie, Janssen, and Viela Bio; has received consulting fees from Almirall, BSN, Incyte, Janssen, Kymera, and Xbiotech; and is a member of the board of the Hidradenitis Suppurativa Foundation. Authors Ghias, Johnston, Babbush, Kutner, Hosgood, and Gil have no conflicts of interest to declare.

#### REFERENCES

- Soliman YS, Chaitowitz M, Hoffman LK, Lin J, Lowes MA, Cohen SR. Identifying anaemia in a cohort of patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol.* 2020; 34(1):e5-e8.
- van Santen S, van Dongen-Lases EC, de Vegt F, et al. Hepcidin and hemoglobin content parameters in the diagnosis of iron deficiency in rheumatoid arthritis patients with anemia. *Arthritis Rheum.* 2011;63(12):3672-3680.
- Mecklenburg I, Reznik D, Fasler-Kan E, et al. Serum hepcidin concentrations correlate with ferritin in patients with inflammatory bowel disease. *J Crohns Colitis.* 2014;8(11):1392-1397.
- Miller IM, Johansen ME, Mogensen UB, Zarchi K, Ellervik C, Jemec GB. Is hidradenitis suppurativa associated with anaemia?: a population-based and hospital-based cross-sectional study from Denmark. *J Eur Acad Dermatol Venereol.* 2016;30(8):1366-1372.
- Ponikowska M, Matusiak L, Kasztura M, Jankowska EA, Szepietowski JC. Deranged iron status evidenced by iron deficiency characterizes patients with hidradenitis suppurativa. *Dermatology.* 2020;236(1):52-58.

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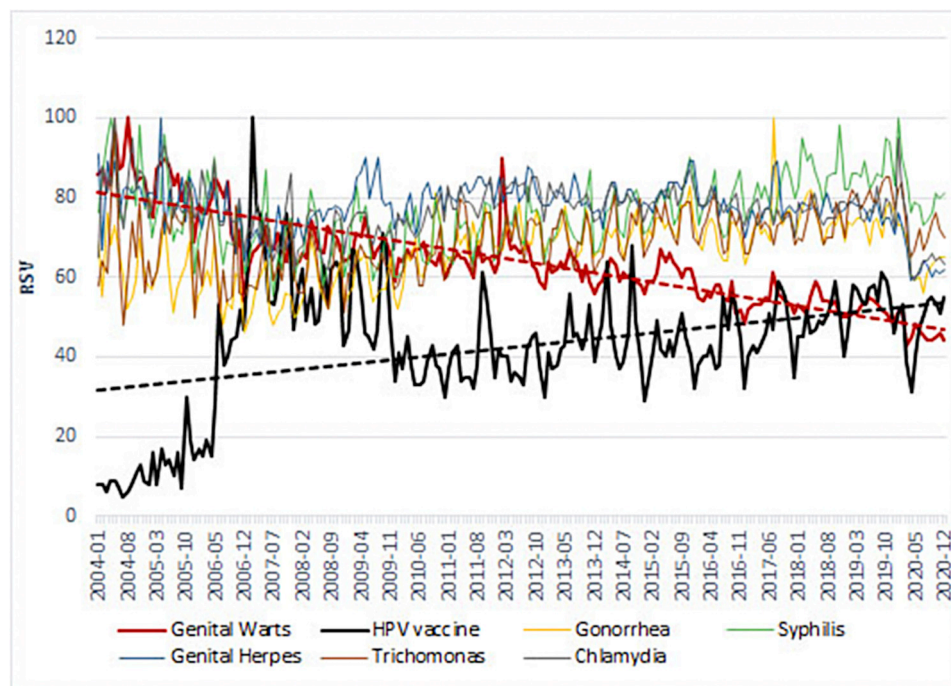
### Impact of human papillomavirus vaccine in reducing genital warts: A Google Trends analysis



*To the Editor:* In clinical trials and real-world settings, human papillomavirus (HPV) vaccination studies have shown very high protection rates against genital warts.<sup>1,2</sup> However, these traditional studies may have been affected by data quality issues, under-reporting of cases, reporting delays, or conflicts of interest, resulting in missed opportunities to respond to trends in disease prevalence. Google Trends is an online tracking system of internet search volumes that allows us to analyze “big data” collected worldwide in a certain amount of time,<sup>3</sup> offering an interesting tool to monitor public attention with regard to specific infectious diseases. In the present study, we investigated whether Google Trends could reflect the impact of HPV vaccination on genital warts.

We used the method recommended by Nuti et al.<sup>4</sup> Data from worldwide were obtained using topic queries during the period January 1, 2014, to December 31, 2020 and were aggregated based on the month (Fig 1). For this entire period, linear regressions of the relative search volume (RSV) index representing a normalized value, ranging from 0 (no searches) to 100 (for the peak of the search), were performed separately for several variables of interest. Their corresponding standardized beta coefficients reflect the strength of their relationship with the RSV.

This showed that the patients' interest in genital warts decreased (beta =  $-0.886$ ,  $P < .001$ ), while their interest in other common sexually transmitted infections increased (gonorrhea [beta =  $0.582$ ,  $P < .001$ ], syphilis [beta =  $0.355$ ,  $P < .001$ ], and trichomoniasis [beta =  $0.481$ ,  $P < .001$ ]) or remained relatively stable (chlamydia [beta =  $-0.134$ ,  $P = .056$ ]). The number of queries for genital herpes decreased but to a lesser extent than that



**Fig 1.** Regression analyses corresponding to searches for genital warts, HPV vaccine, gonorrhoea, syphilis, genital herpes, trichomoniasis, and chlamydia: Google Trends time data (17 years; 204 months). Inverse temporal evolution between the interest in HPV vaccination (beta = 0.395) versus that in genital warts (beta = -0.886). To compare the temporal evolution of the searches, data for each search were downloaded separately and presented as the RSV index. They do not represent the absolute search volume numbers but rather a normalized value, ranging from 0 (for no searches) to 100 (for the peak of the search). HPV, Human papillomavirus; RSV, relative search volume.

**Table I.** Top 5 countries for queries for genital warts, chlamydia, syphilis, trichomoniasis, genital herpes, and gonorrhoea

Genital warts	Chlamydia	Syphilis	Trichomonas	Genital herpes	Gonorrhoea
Iran <sup>‡</sup>	Cameroon <sup>‡</sup>	Zambia <sup>‡</sup>	Jamaica*	Jamaica*	Ghana <sup>‡</sup>
Serbia <sup>‡</sup>	Finland*	Paraguay*	Nicaragua <sup>‡</sup>	Trinidad-and-Tobago <sup>‡</sup>	Jamaica*
Taiwan <sup>‡</sup>	Norway*	Ghana <sup>‡</sup>	Honduras*	Puerto Rico <sup>‡</sup>	Panama*
Vietnam <sup>‡</sup>	Jamaica*	Panama*	Paraguay*	Panama*	Vietnam <sup>‡</sup>
Paraguay*	Puerto Rico <sup>‡</sup>	Tanzania <sup>‡</sup>	Moldavia <sup>‡</sup>	Paraguay*	Tanzania <sup>‡</sup>

\*HPV vaccine coverage between 50% and 79%.

<sup>‡</sup><50%.

<sup>‡</sup>HPV vaccine not introduced, according to Bigard et al.<sup>5</sup>

for genital warts (beta = -0.209, *P* = .003). The monthly RSV for genital warts (beta = -0.886, *P* < .001) was inversely correlated with the monthly RSV for HPV vaccine (beta = 0.395, *P* < .001) (Fig 1).

The top 5 countries where the queries for genital warts were the most popular were, with the exception of Paraguay, countries in which HPV vaccination is poorly available.<sup>5</sup> This was in contrast with the number of queries for other common sexually transmitted infections, essentially generated from Latin

American countries, where the HPV vaccination coverage is high (Table I).<sup>5</sup>

This study was limited by several factors: Google Trends provided only an RSV index, not the absolute search volume; an increase or decrease in online searches for health topics may have either mirrored epidemiological changes or reflected media coverage; the participant sample may have been biased toward internet users who use the Google search engine; a large amount of the data was not eliminated and may have amplified the sources of systematic error.

In conclusion, our data, generated from surveillance systems based on Google Trends, indicate the growing interest among the general public regarding common sexually transmitted infections, such as gonorrhoea, trichomoniasis, and syphilis. The number of queries for chlamydia remained stable. In contrast, the number of queries for genital warts decreased during the same period. These results are consistent with the expected impact of the HPV vaccine. The huge potential of surveillance systems based on Google Trends could be used in the immediate future as a support to the traditional surveillance systems.

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#### Conflicts of interest

None disclosed.

#### REFERENCES

1. Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ*. 2013;346(7907):f2032.
2. Baandrup L, Dehlendorff C, Kjaer SK. One-dose human papillomavirus vaccination and the risk of genital warts: a Danish nationwide population-based study. *Clin Infect Dis*. 2020:ciaa1067. [Epub ahead of print].
3. Google. Google trends Accessed January 17, 2021. Available at: [www.google.com/trends](http://www.google.com/trends)
4. Nuti SV, Wayda B, Ranasinghe I, et al. The use of google trends in health care research: a systematic review. *PLoS One*. 2014; 9(10):e109583.
5. Bigaard J, Franceschi S. Vaccination against HPV: boosting coverage and tackling misinformation. *Mol Oncol*. 2021;15(3): 770-778.

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### Three novel pathogenic *NEK9* variants in patients with nevus comedonicus: A case series



*To the Editor:* Nevus comedonicus (NC) (Mendelian Inheritance in Man: #617025) or comedo nevus belongs to the group of organoid epidermal nevi. NC is considered a hamartoma or nevoid malformation caused by a developmental defect in the pilosebaceous unit resulting in numerous dilated, keratin-filled comedones.<sup>1</sup> Etiologically, the affected pilosebaceous units tend to be unable to produce terminal hair, so the hair shaft itself is absent and the sebaceous glands are rudimentary.<sup>2</sup>

In 2016, Levinsohn et al<sup>3</sup> described somatic mutations in *NEK9* as the genetic cause of NC. However, confirmation of *NEK9* variants as the genetic etiology within an independent NC patient cohort remains insufficient in the literature.

Our patients presented with linearly arranged NC lesions in distinct body areas following Blaschko's lines, on the upper portion of the right arm, elbow, and forearm (patient 1, Fig 1), on the left side of the cheek (patient 2, Supplemental Fig 1, A available via Mendeley at <https://data.mendeley.com/datasets/9psknxmgfj/1>), in the left side of the cervical area (patient 3, Supplemental Fig 1, B), and in the left side of the temporal area of the scalp (patient 4, Supplemental Fig 1, C). None of the patients had extracutaneous manifestations, ruling out the syndromic form of NC. Next-generation sequencing analyses of DNA from all affected skin samples revealed pathogenic variants in the *NEK9* gene with low, variable percentages of the variants. A summary of the identified pathogenic variants and the mosaic percentages in affected skin is given in Table I (Supplemental Fig 2 available via Mendeley at <https://data.mendeley.com/datasets/9psknxmgfj/1>).

To date, pathogenic variants in 2 genes have been associated with NC and nevus comedonicus syndrome (NCS), namely variants in the genes *FGFR2* and *NEK9*. However, *FGFR2* pathogenic variants should be taken as historical errors because they were erroneously claimed as a cause for NC/NCS because of the confusion of Munro acne nevus with NC.<sup>4</sup> In contrast to the opinion of several authors, NC is neither related to Munro acne nevus nor to Apert syndrome.<sup>4</sup> Munro acne nevus is characterized by inflammatory acne lesions and represents the mosaic cutaneous manifestation of Apert syndrome, which is additionally characterized by craniosynostosis, syndactyly, and early epiphyseal closure.<sup>4</sup>

In 2016, Levinsohn et al<sup>3</sup> described a cohort of 3 patients with NC in whom they identified *NEK9* gene variants. Since then, only one very recent report also