Dear Editors,

Gorlin syndrome (GS), or nevoid basal cell carcinoma syndrome, is caused by pathogenic variant in the PTCH1 tumor suppressor gene and characterized by basal cell carcinomas (BCCs), keratocystic odontogenic tumors of the jaw, medulloblastomas, and other cutaneous and skeletal features. GS is typically inherited but may be caused by a de novo mutation during development in 20 to 30% of cases. During their premenopausal years, affected women may develop ovarian fibromas (OFs), causing frequent urination, abdominal pain, and ovarian torsion. We aimed to evaluate the correlation of OF with cutaneous disease burden in females with GS.

A retrospective cross-sectional analysis was conducted using data from the national patient registry established by Gorlin Syndrome Alliance and Stanford University, which contains patient demographics, disease manifestations, and therapeutics received. Participants met clinical diagnostic criteria and/or were genetically confirmed. The registry consisted of 202 adults. Of 116 females, 51 (44.0%) reported OF (Table 1). The proportion of women with high BCC burden (250+ BCCs) was significantly greater in the OF group (P = .025) (Table 2). Median age at evaluation was comparable among cohorts. Median age of diagnosis was younger in the OF group (14 vs 18 years, Table 1). Jaw cysts, a common tumorigenic manifestation utilized as control, had no correlation with BCC burden (P = .624) (Table 2). The proportion of women with OF on vismodegib, a hedgehog signaling inhibitor used to treat aggressive cutaneous disease, was significantly higher than in women without OF (58.3% vs 33.3%, P = .009) (Table 1).

Our results demonstrate that women with OF have higher BCC burden are diagnosed younger and are more likely to be on systemic therapy. This association between OF and increased BCC burden was not specific, rather than a general reflection of increased tumorigenesis. We theorize patients with more deleterious mutations or those with de novo mutations occurring earlier in embryogenesis may be more likely to develop OF and greater BCC severity.

GS is a clinically heterogeneous disorder, with lifetime number of BCCs varying from less than 10 to over 2000.

What is known about this subject in regard to women and their families?

• There is a wide spectrum of disease severity in Gorlin syndrome (GS) patients.
• Some females with GS develop ovarian fibroma (OF), which may significantly impact quality of life by causing frequent urination, abdominal pain, and ovarian torsion.
• Few risk factors for cutaneous disease burden in GS have been identified. What is new from this article as messages for women and their families?
• GS females who have OF also appear to have more severe cutaneous disease burden, thus requiring closer dermatological monitoring and potentially warranting early initiation of systemic therapy.

Table 1. Demographics of adult patients participating in the Gorlin syndrome national patient registry established by Gorlin Syndrome Alliance and Stanford University

| Adult patients (n = 202) |
|------------------------|
| Gender                |
| Females 125 (61.9%)    |
| Males 77 (38.1%)       |
| Median age (range)     |
| Females with OF 54 years (19–75) |
| Females without OF 56 years (19–80) |
| Males 55 years (18–83) |
| Median age of diagnosis|
| Females with OF 14 years |
| Females without OF 18 years |
| Clinical manifestations|
| Ovarian fibroma (females, n = 116) 51 (44.0%) |
| Jaw cysts (n = 202) 92 (45.5%) |
| Treatments |
| Females with OF on systemic therapy 28 (58.3%) P = .009 |
| Females without OF on systemic therapy 20 (33.3%) |

*P value represents Chi-square analysis examining proportion of patients on systemic therapy (vismodegib) in females with OF vs females without OF. The P value is statistically significant at a threshold of .05.
burden and disease severity in women with GS. As OF onset in GS females is nearly two decades earlier than in the general population, recognizing its association with greater BCC number and aggressiveness in young women has significant clinical implication in disease surveillance and early intervention. Given the role of the hedgehog signaling pathway in OF and the increased likelihood of women with OF being on systemic therapy in our study, it would be important to further investigate the potential benefits of early initiation of a hedgehog inhibitor in GS females with OF both to manage increased BCC burden and as a tissue-sparing therapy to preserve fertility.

Conflicts of interest
None.

Table 2.
Lifetime number of BCCs in association Gorlin syndrome-associated tumors

| Lifetime BCCs* | OF | No OF | Jaw cyst | No jaw cyst |
|----------------|-----------------|-----------------|-----------------|-----------------|
| <10            | 3               | 10              | 7               | 6               |
| 250+           | 23              | 16              | 24              | 15              |

BCC, basal cell carcinoma; OF, ovarian fibroma.
*Number of female patients who reported either less than 10 or greater than 250 lifetime BCCs.
\( P = .025^a \)
\( P = .624^b \)

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Study approval
N/A

Author contributions
TW - Methodology, Analysis, Data Curation, Writing - Original Draft, Review & Editing.
DP - Methodology, Analysis, Writing - Review & Editing.
JT - Conceptualization, Writing - Review & Editing.

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