predict both clinical outcomes and therapeutic responses.

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CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES

It seems we are pulling at the same threads, given multiple phenotypes have been constructed, yet they have considerable overlap. There are opportunities to pull on new threads and unravel the complexity of HS through development of valid, reliable, and predictive phenotype schema.

Unraveling the Heterogeneity of Hidradenitis Suppurativa with Phenotype Schema
Joslyn S. Kirby

One of the major challenges faced with hidradenitis suppurativa (HS) is the variability in manifestations and treatment responses. Cazzaniga et al. (2020) conducted a cross-sectional study and latent class analysis to explain disease heterogeneity and formulate HS phenotypes. HS phenotypes might be useful for disease or treatment outcomes. Future studies should assess rater reliability and predictive validity for outcomes such as treatment response or disease progression.


“Nature uses only the longest threads to weave her patterns, so that each small piece of her fabric reveals the organization of the entire tapestry.” — Richard P. Feynman.

Hidradenitis suppurativa phenotypes: New approaches and existing schema
Hidradenitis suppurativa (HS) exhibits high variability in lesion morphology, body sites involved, and sometimes, unpredictable clinical responses to therapy (Canoui-Poitrine et al., 2009). This variability has spurred the search for patterns in the observed variables, or phenotypes, to help with prognostication and management.

Statistical analyses such as latent class (LC) and cluster analysis have been increasingly used to investigate the heterogeneity of diseases to identify phenotypes with combinations of clinical and laboratory findings. Performed either by hypothesis or data-driven methods, this approach has been shown to stratify entities with high clinical variabilities such as sarcoidosis, essential hypertension, and others (Guo et al., 2017; Park et al., 2019; Rubio-Rivas and Corbella, 2020).

For HS, a number of studies (Table 1) have proposed phenotypic subtypes (Canoui-Poitrine et al., 2009; Martorell-Calatayud et al., 2015; Naasan and Affleck, 2015). Some were based on expert opinion (Martorell-Calatayud et al., 2015; Naasan and Affleck, 2015; van der Zee and Jemec, 2015). Two studies utilized statistical analysis, namely LC analysis (LCA), to identify phenotypes that emerge from the data (Canoui-Poitrine et al., 2009; Cazzaniga et al., 2020). Regardless of methodology, phenotypes have some overlap because all of the classification schema take into account age, sex, and comorbidities.

This study by Cazzaniga et al. (2020) was conducted on a cohort of patients examined at 17 dermatologic centers that participate in the Italian Registry of HS. Overall, 965 patients were evaluated—a larger sample than the extant LCA study conducted with 618 French patients (Canoui-Poitrine et al., 2013).
Both studies included similar clinical variables; however, Cazzaniga et al. (2020) also included smoking status, Dermatology Life Quality Index score, the presence of excessive sweating, and a larger number of discrete body sites including the genital area but did not include detail on lesion morphologies, which were included in the study by Canoui-Poitrine et al. (2009). A three-class model best fit the data in both studies, indicating that there were three

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**Table 1. HS Phenotype Schema and Interrater Reliability**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Phenotype Schema</th>
<th>Interrater Reliability, $^1$ k (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cazzaniga et al. (2020)</td>
<td>Axillary–mammary–groin (LC1)/axillary–gluteal–groin (LC2)/axillary–groin (LC3)</td>
<td>—</td>
</tr>
<tr>
<td>Canoui-Poitrine et al. (2013)</td>
<td>Axillary–mammary (LC1)/folicular (LC2)/gluteal (LC3)</td>
<td>0.44 (0.39–0.48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.37 (0.32–0.42) $^2$</td>
</tr>
<tr>
<td>Naasan and Affleck (2015)</td>
<td>Typical/atypical</td>
<td>0.77 (0.76–0.79)</td>
</tr>
<tr>
<td>Martorell-Calatayud et al. (2015)</td>
<td>Follicular/nodular</td>
<td>0.81 (0.80–0.82)</td>
</tr>
<tr>
<td>van der Zee and Jemec (2015)</td>
<td>Regular/scarring folliculitis/frictional /conglobata/syndromic/ectopic</td>
<td>0.82 (0.80–0.83)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HS, hidradenitis suppurativa; LC, latent class.

$^1$From Frew et al. (2019)

$^2$From van Straalen et al. (2018)
pheno-phenotypes that best explained the data variabil-variability. Figure 1 shows that there is an overlap between the phenotypes identified in both LCA studies. Among the six phenotypes, there are similar probabilities for several of the variables and no single variable that defines phenotypic classification, which would make discrimination among them challenging.

Moving beyond description
Multiple groups have characterized HS phenotypes. However, there has been limited work to show that they are valid, reproducible, and with sufficient reliability to be applied. Two studies have evaluated the interrater reliability of phenotypes (Table 1). van Straalen et al. (2018) showed that the interrater reliability for the French LCA phenotypes was only fair. Frew et al. (2019) noted that the interrater reliability was fair for some and excellent for others. Phenotypic descriptions at a population level must be applicable at the individual level to be valuable. Frew et al. (2019) also described significant correlations among multiple phenotypes indicating significant redundancy between the schemas.

The cross-sectional design of all of the existing studies does not allow the validation of the phenotypes. We are not aware of any studies that validated extant phenotypic schema. Given the chronic but also waxing and waning nature of HS, it is also important to evaluate the stability of phenotypes. In the work by Cazzaniga et al. (2020), the LC3 phenotype had 45.3% of participants with HS for fewer than 5 years. This raises the possibility that this phenotype is seen in early disease but may not be stable or reproducible over time.

Next steps
From a practical perspective, it is crucial for these schemas (once valid and reliable) to be predictive of something that matters—HS progression, treatment response, etc. Only one study (Frew et al., 2019) investigated phenotype–genotype correlations, but few significant correlations were identified. I am not aware of any studies that evaluated the predictive validity of phenotype schema for treatment responses or disease progression. Returning to the opening quote by Feynman, this study provides an opportunity to ponder the tapestry that is HS. It seems that we are pulling at the same threads given that multiple phenotypes have been constructed, yet they have considerable overlap. There are opportunities to pull on new threads and unravel the complexity of HS through the development of valid, reliable, and predictive phenotype schema. First, there should be an effort to expand the variables used to construct phenotypes with more detail on clinical dermatologic assessment, extra-dermatologic findings on physical examination, or laboratory assessment, with the aim to generate phenotypes that decrease overlap and improve discrimination. Second, validation studies of phenotype schema with diverse patient populations should be conducted. Third, schema stability should be assessed because cross-sectionally defined subgroups may not reflect the temporal variability of the disease. Longitudinal trajectory was incorporated into an analysis for asthma and significantly improved schema stability and significantly predicted exacerbation (Park et al., 2019). Fourth, longitudinal data are also needed to evaluate the predictive validity for meaningful outcomes, such as reduction in disease severity, risk of disease progression, time to flare, or flare frequency.

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CONFLICT OF INTEREST
The author has received honoraria for work as a speaker for AbbVie and as a consultant for AbbVie, ChemoCentryx, Incyte, Janssen, Novartis, and UCB.

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