Development of a Disease Activity Index for the Assessment of VEXAS Syndrome (VEXAS-DAI)

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Disclosure Information

KB: None; **HM**: Speakers Bureau: AbbVie, Novartis, Sobi, Eli Lilly, UCB; Consultant: Sobi; Paid Instructor: Sobi; **DH**: None; **SS**: Speakers Bureau: Pharming, Takeda; Consultant: Novartis, Sobi, Takeda, KalVista, Celldex, Phraming, CSL Behring, Phavaris; Grant: CSL Behring, Novartis; **YK**: Speakers Bureau: Novartis, Amgen; Consultant: Sobi, Novartis; **CG**: Grants: Alexion; Consulting fees: Genesis Therapeutics; **MH**: Consultant: BMS/Celgene, Blueprint, Servier, Jazz pharmaceuticals, ABBVIE, Astellas ; **TC**: Speakers Bureau: BMS, Novartis, Amgen, Abbvie, Griffols, CSL-B; Consultant: BMS, Novartis; Grants: Novartis; **AM**: None; **MMP**: Grants: Stem Line Pharmaceuticals, Kura Oncology, Polaris, Epigenetix, and Solu therapeutics; Advisory Board for Sobi, AstraZeneca; **LDW**: Consultant: Abbvie, Vertex, Sobi; **GH**: Consultant: Scilex Holding, Aclaris Therapeutics; **OC**: Speakers Bureau: Novartis, Jazz; **AA-H**: None; **SG**: None; **MAF**: None; **SG-L**: Consultant: Sobi, Novartis; **PG**: None; **EMG**: None; **BP**: None; **MS**: Consultant: Amgen; **SAB, BGH**: Employee: Sobi Inc.; **SG**: Employee (former): Sobi Inc.; **MJK**: Consultant: Amgen; **DBB**: Consultant: Sobi, GSK, Novartis, Alexion, Montage Bio.

VEXAS syndrome is a systemic hemato-inflammatory disease

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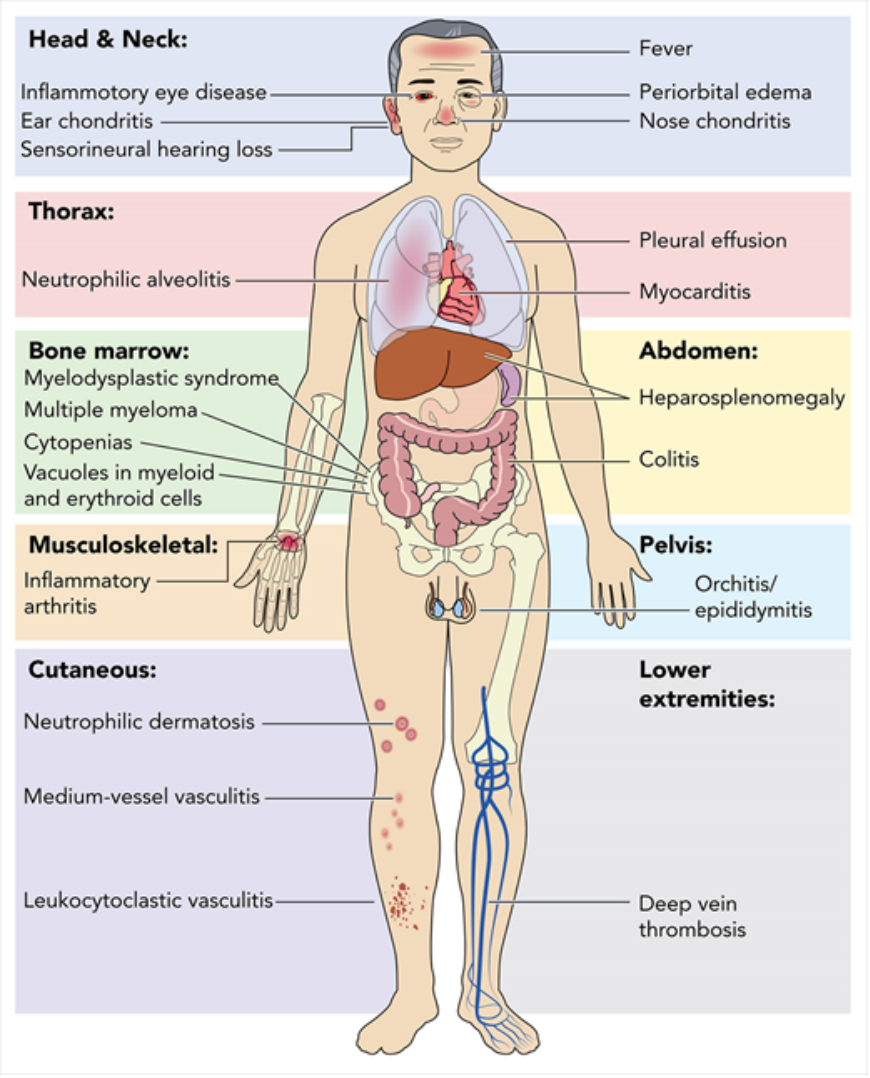
- Associated with somatic *UBA1* mutations in hematopoietic stem and progenitor cells.[1]
- Inflammatory manifestations can involve nearly every organ system, and severity can range widely between patients and over the course of disease.[1,2]
- Disease is chronic and progressive, characterized by inflammatory flares during which manifestations occur.[2]
- Standardized and validated disease activity indices (DAIs) are crucial for patient care and for advancing clinical research in multi-systemic inflammatory diseases.
- There is an unmet need for a validated DAI that captures VEXAS-related manifestations and scores disease activity based on the severity of each manifestation.



VEXAS, Vacuoles, E1 Enzyme, X-linked, Autoinflammatory, Somatic
[1] Beck et al. NEJM 2020. [2] Mekinian et al. Arthritis & Rheum 2025.
Figure source: Grayson, Patel, and Young. Blood 2021

DAI development: objective and methods

Objective

- To develop a comprehensive DAI to measure inflammatory activity and provide a standardized instrument for evaluation of treatment response.

Methods

Step 1: Instrument development

- Items / organ systems selected for inclusion based on systematic review and expert input.
- Severity grading for each manifestation adapted from Common Terminology Criteria for Adverse Events (CTCAE).
- The VEXAS-DAI was developed based on input from a multidisciplinary group of 18 expert Rheumatology, Hematology, and Immunology physicians using modified Delphi methodology.

Step 2: Instrument scoring

- Clinical vignettes composed corresponding to each type and severity of inflammation measured by the VEXAS-DAI.
- Physician experts rated the inflammation severity of each vignette based on a Physician Global Assessment (PGA).
- PGA scores provided a framework for DAI scoring.

Consensus achieved on items to be included in the VEXAS-DAI

- VEXAS-DAI finalized after 4 rounds of revision.
- Resulting instrument queries 13 organ systems, including a total of 31 items.
- Item grading assigned based on severity observed at the time of examination.

Domain	Items
Inflammatory-type rash	2
Chondritis	3
Periorbital involvement	1
Genitourinary involvement	1
Ophthalmologic involvement	5
Pulmonary involvement	3
Cardiovascular involvement	3
Neurologic involvement	5
Oral/gastrointestinal involvement	3
Renal involvement	1
New thrombosis/thromboembolism	1
Joint involvement	1
Constitutional symptoms	2
Total	**31 items**

Example domain: pulmonary involvement

Note: Non-inflammatory pulmonary processes, or sequela of resolved inflammation should not be considered in scoring. Pulmonary embolism should not be considered in scoring but should be considered separately in the Thrombosis and Thromboembolism domain. Chest imaging and/or upper airway visualization should be performed for diagnosis and follow-up of pulmonary findings to support severity grading, per standard practice.

Pneumonitis / Alveolitis
Current Severity (0-4): _____

Pleural effusion
Current Severity (0-4): _____

Upper airway involvement
Current Severity (0-4): _____

Pulmonary – Current Severity Score*

0	1	2	3	4
Not present	Asymptomatic, clinical or diagnostic observation only, no intervention indicated	Symptomatic but not requiring supplemental oxygen, medical or limited procedural intervention indicated	Resulting in respiratory distress or hypoxemia, requiring hospitalization	Life-threatening respiratory or hemodynamic compromise, urgent intervention indicated (e.g., non-invasive positive pressure ventilation or intubation with mechanical ventilation)

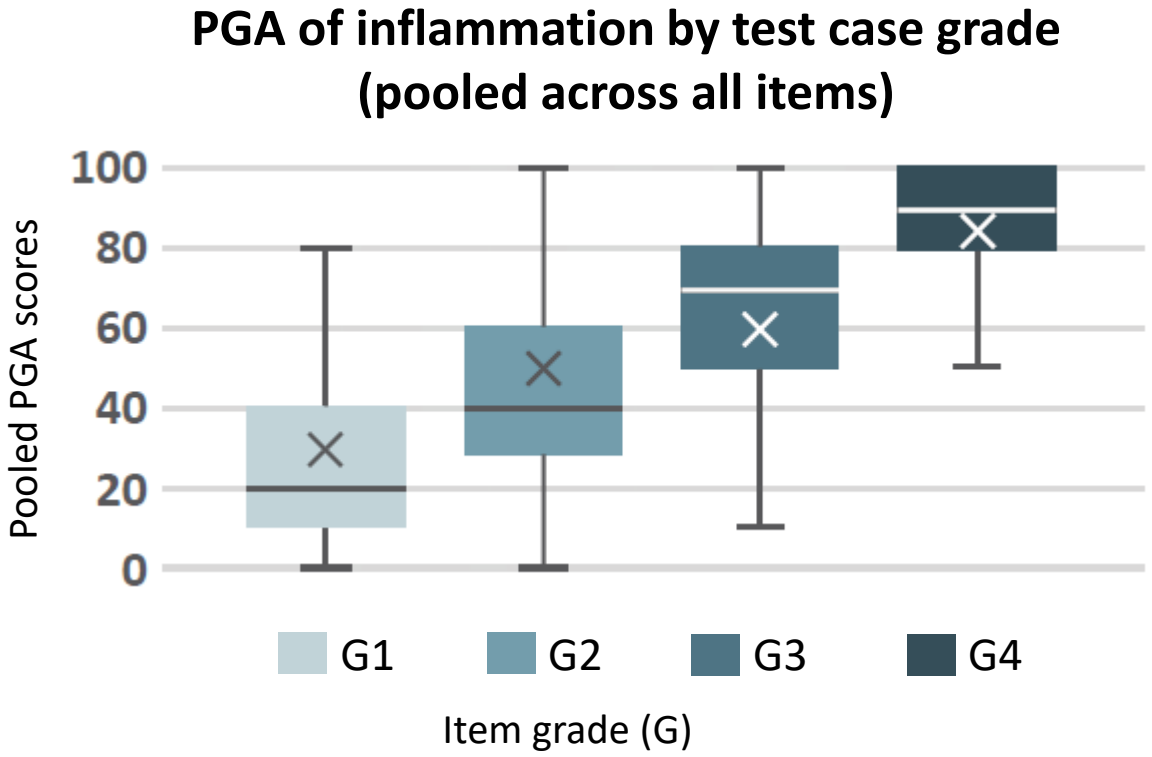
*A separate Severity Change score will also be captured for research purposes in the first version of the VEXAS-DAI. The Severity Change score is intended to be used as an anchor for instrument validation but will not contribute to instrument scoring.

Physician Global Assessment (PGA) of inflammation in clinical vignettes

- Test cases were created (one case per grade per item) for rating disease activity
- Physicians instructed to assume all manifestations directly related to VEXAS-associated inflammation.
- Scores (0-100) reflect level of inflammation, not medical seriousness.

Sample vignettes: pulmonary infiltrates severity grade 1-4, respectively
A patient has **asymptomatic** pulmonary infiltrates consistent with **pneumonitis** found incidentally on CT *Number must be between 0 – 100:* _____
A patient with **dyspnea** has pulmonary infiltrates on CT consistent with **pneumonitis** *Number must be between 0 – 100:* _____
A patient is **hospitalized** for **pneumonitis** and requires **supplemental oxygen** *Number must be between 0 – 100:* _____
A patient requires **intensive care** for severe **pneumonitis** requiring **intubation** *Number must be between 0 – 100:* _____

Across all items in all domains, PGA scores increase with increasing grade



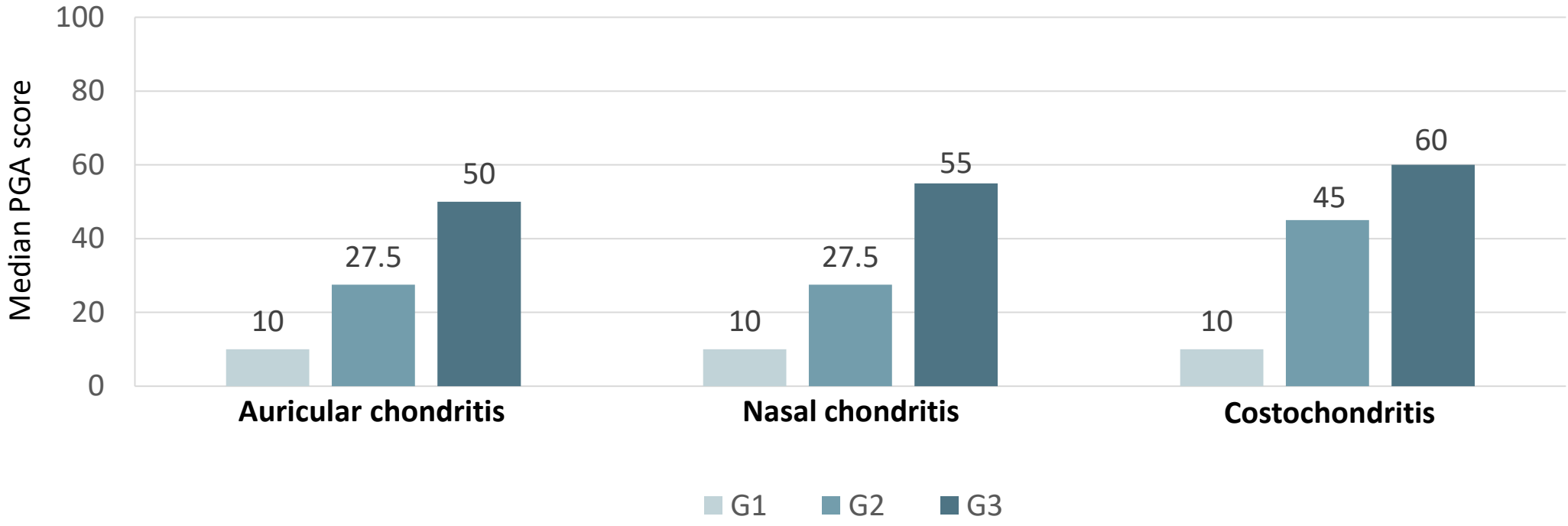
Legend
Boxes = interquartile range (IQR)
Whiskers = total range
X = mean
Line = median

- Grade 1 items elicited PGA ~20
- Grade 2 items elicited PGA ~40
- Grade 3 items elicited PGA ~70
- Grade 4 items elicited PGA ~90

Trend of increasing PGA with increasing grade provides justification for use of item grading to derive instrument scoring.

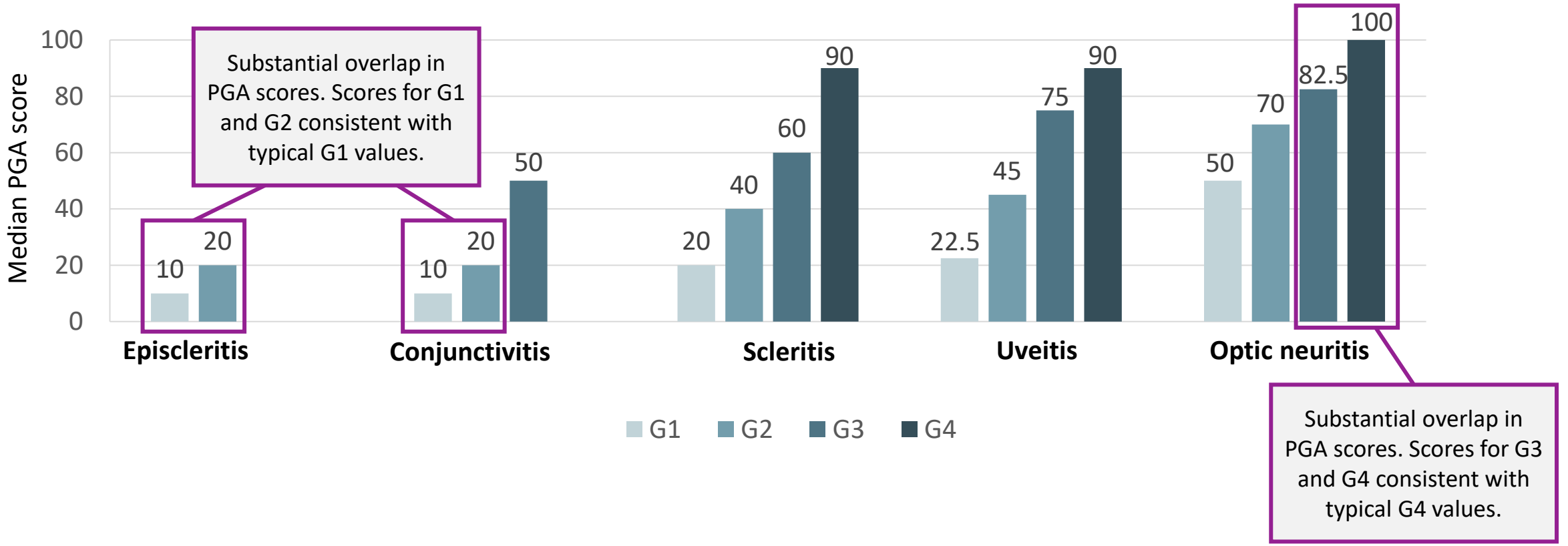
PGA results inform domain scoring
Example #1: chondritis

- Results justify scoring domain based on item severity grade, as grade (1-3) correlates with physician assessment of inflammation



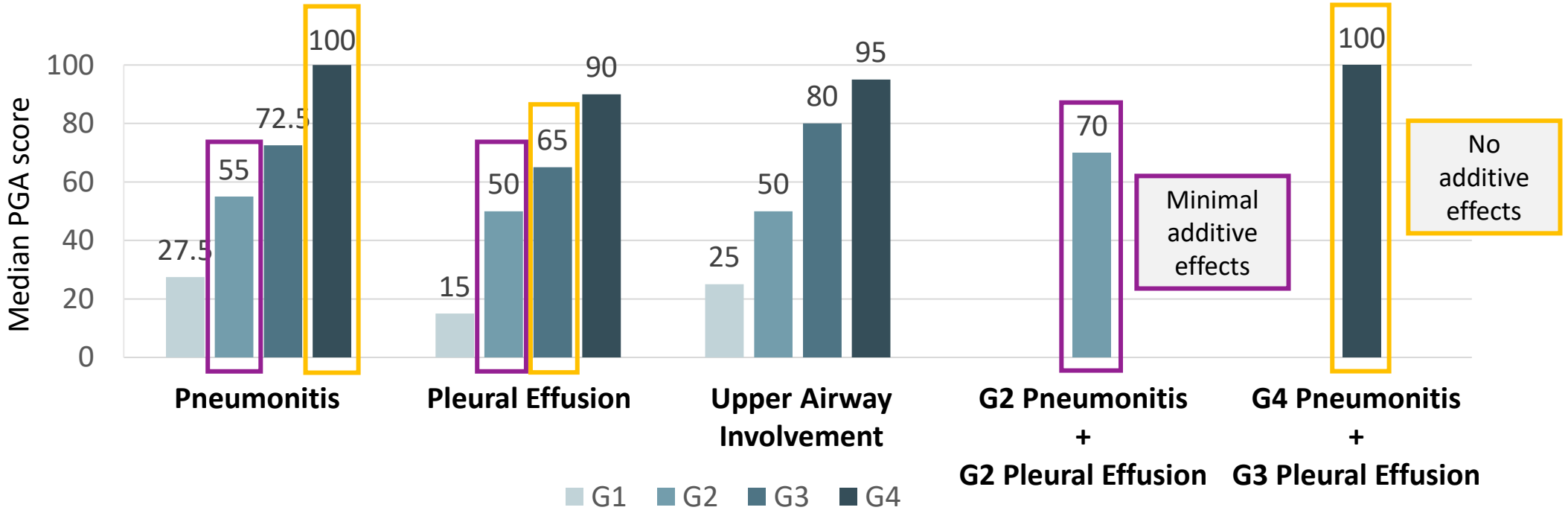
PGA results inform domain scoring
Example #2: ophthalmologic

- For episcleritis and conjunctivitis, G1 and G2 will be scored equally (both “1 point”)
- For optic neuritis, G3 and G4 will be scored equally (both “4 points”)



PGA results inform domain scoring
Example #3: pulmonary

- No / minimal additive effects observed when multiple manifestations co-occurred within the same domain
- Justifies having domain score be the worst score on any item (rather than adding item scores)



VEXAS-DAI scoring finalized based on PGA and expert committee review

- VEXAS-DAI total score is the sum of each domain score.
  - Total score ranges 0-40.
  - Higher scores indicate more active inflammation.
- Expert panel provided final input on instrument and scoring.
  - ‘New thrombosis / thromboembolism’ should not be scored, as isolated thrombosis may not be a reliable indicator of active inflammation.
  - ‘Joint involvement’ score should be based on presence or absence of arthritis in any joint.
  - ‘Inflammatory-type rash’ score should be based on type of rash (not body surface area).

Domain	Items	Max. Score
Inflammatory-type rash	2	4
Chondritis	3	3
Periorbital involvement	1	2
Genitourinary involvement	1	3
Ophthalmologic involvement	5	4
Pulmonary involvement	3	4
Cardiovascular involvement	3	4
Neurologic involvement	5	4
Oral/gastrointestinal involvement	3	4
Renal involvement	1	4
New thrombosis/thromboembolism	1	0
Joint involvement	1	2
Constitutional symptoms	2	2
Total	**31 items**	**40**

Conclusion: VEXAS-DAI validation

- VEXAS-DAI is designed to measure active inflammation in patients with VEXAS syndrome
  - VEXAS-DAI does not measure chronic damage or sequelae of resolved inflammation
- The VEXAS-DAI will be assessed and validated in the ongoing PAXIS study (NCT06782373; EUCT: 2024-516347-41-00; ACR 2025 Oral 2663)
- Once validated, the VEXAS-DAI may be a valuable instrument for use in clinical practice or as an efficacy endpoint in clinical trials

Acknowledgements

- VEXAS patients and caregivers
- Research collaborators

The authors would like to thank the Ministry of Health of the Czech Republic, grant nr. NU23-10-00160 and the Intramural Research Program of the National Heart, Lung and Blood Institute. The authors also acknowledge Kathleen York, CMPP from Sobi for publication coordination and Purvi Suthar from Sobi, Inc. for medical writing assistance. This presentation was created by the authors in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022). Sobi reviewed and provided feedback on the presentation. The authors had full editorial control of the presentation and provided their final approval of all content.

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2663: PAXIS: A Randomized, Double-Blind, Placebo-Controlled, Dose Finding Phase 2 Study (Part 1) Followed by an Open-Label Period (Part 2) to Assess the Efficacy and Safety of Pacritinib in Patients with VEXAS Syndrome

Date: **Wednesday, October 29**
Presentation Time: **11:30 AM - 11:45 AM**
Location**: W190A-B**