ERN | EuroBloodNet

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Diagnosis and Management of VEXAS: Guidance Summary from an International Expert Panel

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European Reference Network | Hematological Diseases (ERN EuroBloodNet)

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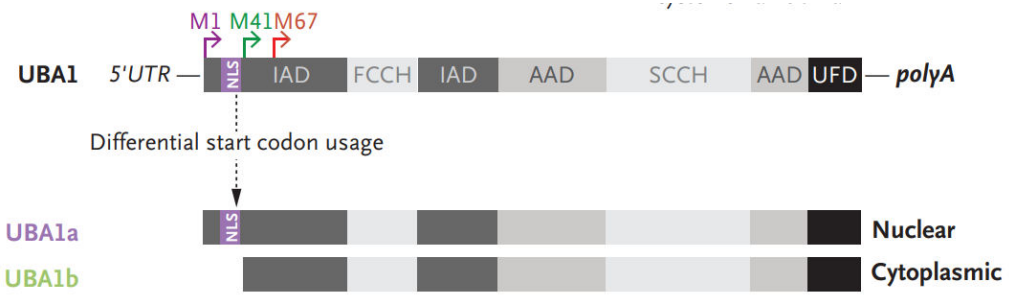
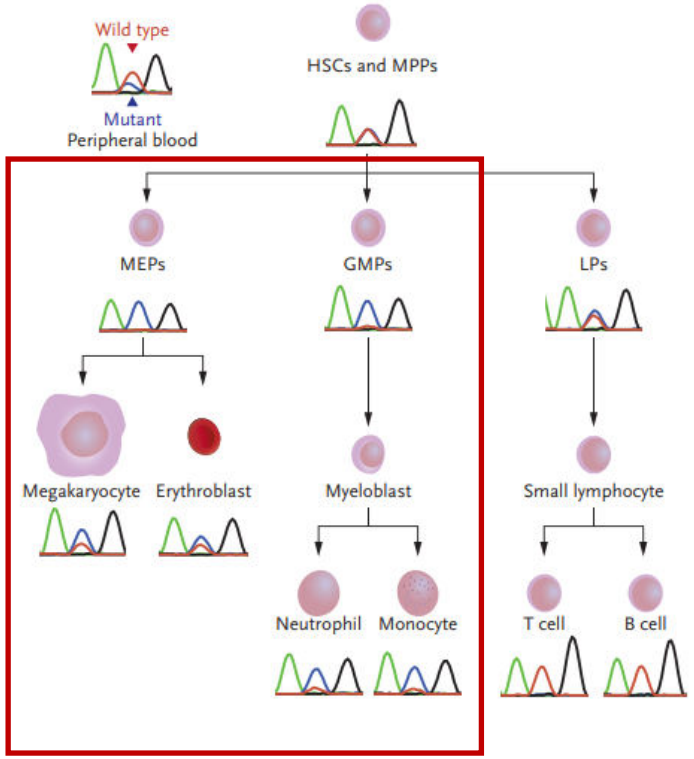
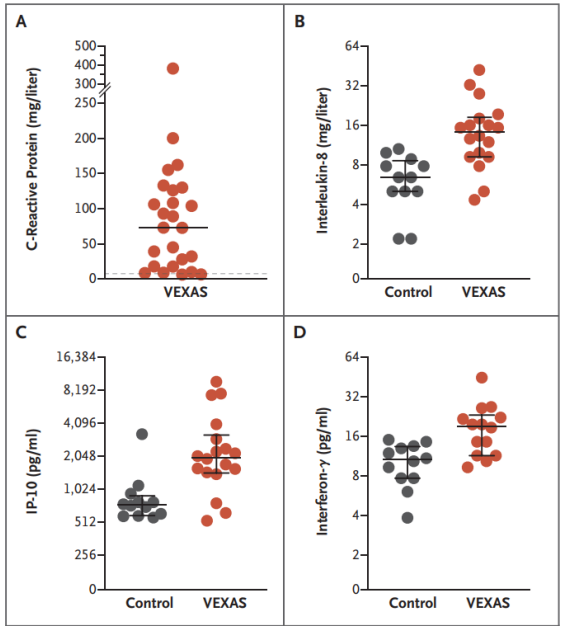
Vacuoles, E1 enzyme, X-linked, Autoinflammatory Syndrome (VEXAS, MIM #301054)

- "Genotype-first" strategy
- Mutations in *UBA1* (met41) exon 3
  - Altered synthesis of cytoplasmic UBA1b
  - P.M41T > p.M41V > p.M41L > splice mutations







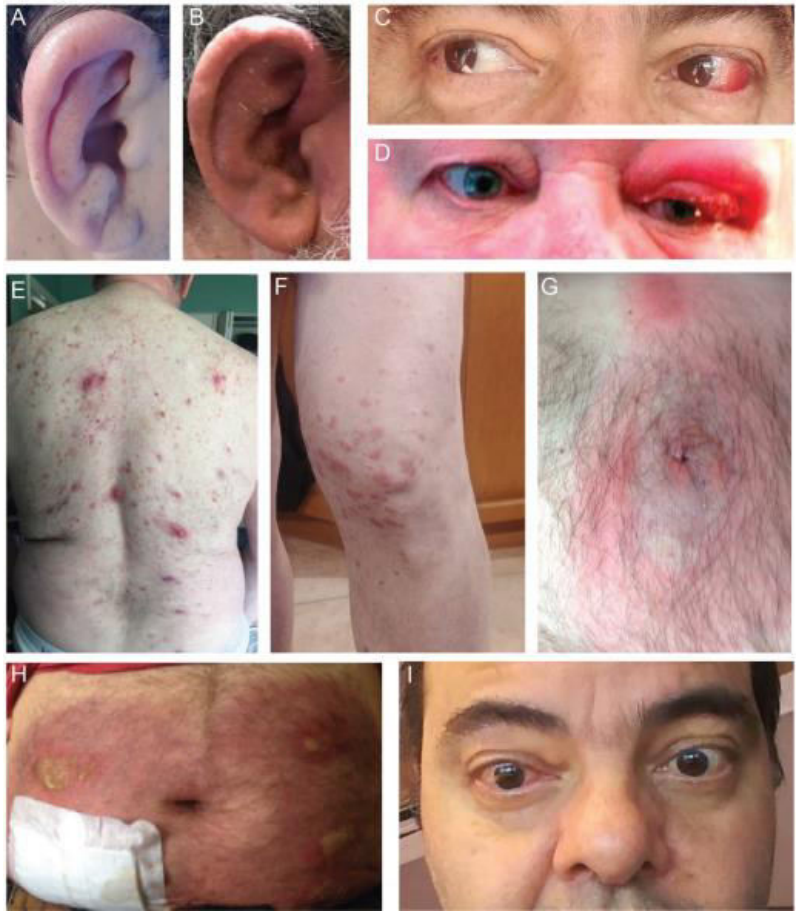
Cytokine levels in VEXAS patients

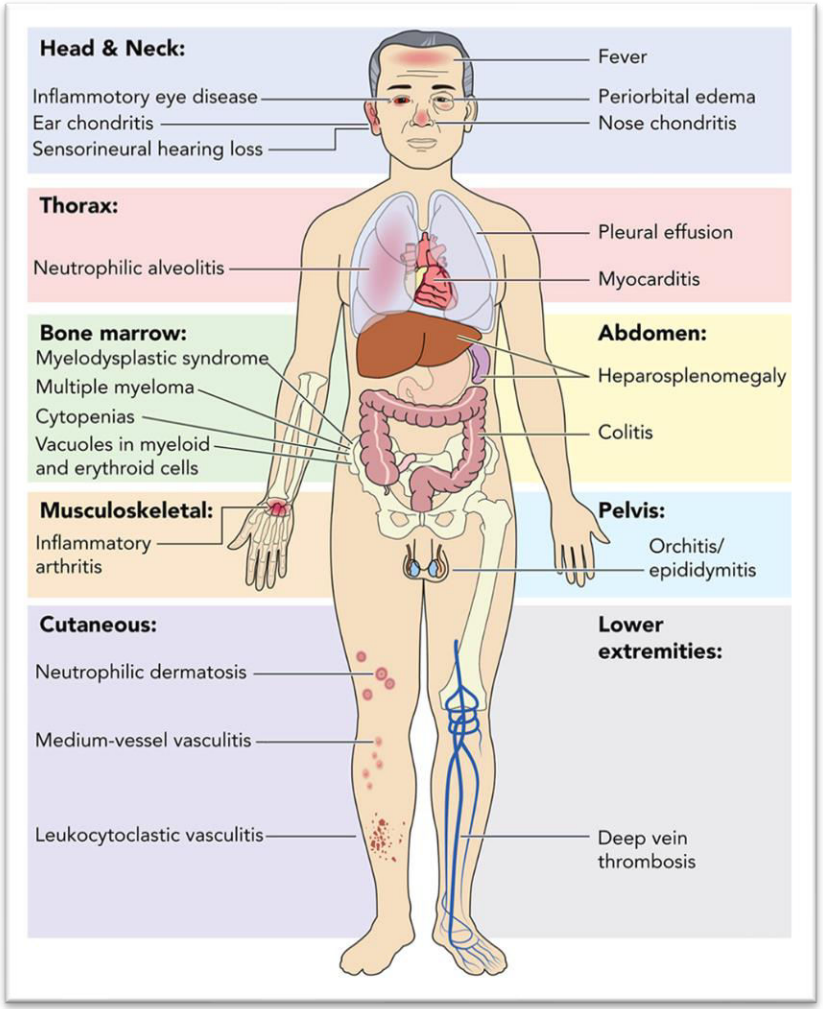
Beck *NEJM* 2020

The pleomorphic phenotype of VEXAS syndrome

Table 1. Demographic and Clinical Characteristics of Participants with the VEXAS Syndrome.*

Characteristic	Participants (N=25)
Demographic characteristics	
Male sex — no. (%)	25 (100)
Median age at onset (range) — yr	64 (45–80)
Died before the current study — no. (%)	10 (40)
Genetic characteristics	
Somatic *UBA1* (NM_003334.3) variant (p.Met41) — no. (%)	25 (100)
p.Met41Thr (c.122T→C)	15 (60)
p.Met41Val (c.121A→G)	5 (20)
p.Met41Leu (c.121A→C)	5 (20)
Key clinical features	
Fever — no. (%)	23 (92)
Skin involvement — no. (%)†	22 (88)
Pulmonary infiltrate — no. (%)	18 (72)
Ear and nose chondritis — no. (%)	16 (64)
Venous thromboembolism — no. (%)	11 (44)
Macrocytic anemia — no. (%)	24 (96)
Bone marrow vacuoles — no./total no. (%)	18/18 (100)
Laboratory findings	
Median C-reactive protein (IQR) — mg/liter	73 (18–128)
Median ESR (IQR) — mm/hr	97 (64–124)
Current or past treatment	
Glucocorticoids — no. (%)	25 (100)
Median no. of synthetic DMARDs (IQR)	2 (1–3)
Median no. of biologic or target synthetic DMARDs (IQR)	2 (0.5–3)
Diagnostic or classification criteria that were met — no. (%)	
Relapsing polychondritis	15 (60)
Sweet's syndrome	8 (32)
Myelodysplastic syndrome	6 (24)
Multiple myeloma or monoclonal gammopathy of undetermined significance	5 (20)
Polyarteritis nodosa	3 (12)
Giant-cell arteritis	1 (4)





Beck *NEJM* 2020; Ferrada *Blood* 2022

Diagnosis and Management of VEXAS: Guidance Summary from an International Expert Panel

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(I)Clinical features of VEXAS consensus statements

- **VEXAS is a hematoinflammatory disease characterized by a spectrum of rheumatologic, dermatologic, and hematologic features**
- **Persistently elevated inflammatory markers with a combination of skin, ocular, lung, or cartilage manifestations and/or cytopenia are suggestive of VEXAS**
- **Most cases of VEXAS have been reported in males older than 50 years**
- **Macrocytic anemia is a common hematologic abnormality in VEXAS but may not always be present**
- **Vacuoles present in early erythroid/myeloid precursors from bone marrow aspirates are suggestive of, but not diagnostic for VEXAS**
- **VEXAS is not a heritable disease**

(The main pathologic manifestations of VEXAS appear within hematologic features (HF) and/or inflammatory disease features (DF). The incorporated features in the diagnostic algorithm are not

Hematologic Features (HF):

- Macrocytosis[3] or Macrocytic Anemia
- MDS or Myelodysplasia
- Thrombocytopenia[4]
- Monocytopenia[5]

Major Disease Features (DF):

- Fever of Unknown Origin
- Auricular and/or nasal chondritis
- Neutrophilic dermatosis or neutrophilic urticarial dermatosis (Bx)
- Leukocytoclastic vasculitis (LCV) or leukocytoclasia (Bx)
- Non-infectious periorbital swelling
- Unprovoked or recurrent deep vein thrombosis
- Unprovoked or recurrent superficial thrombophlebitis
- Steroid dependency[6]

Minor Disease Features (DF):

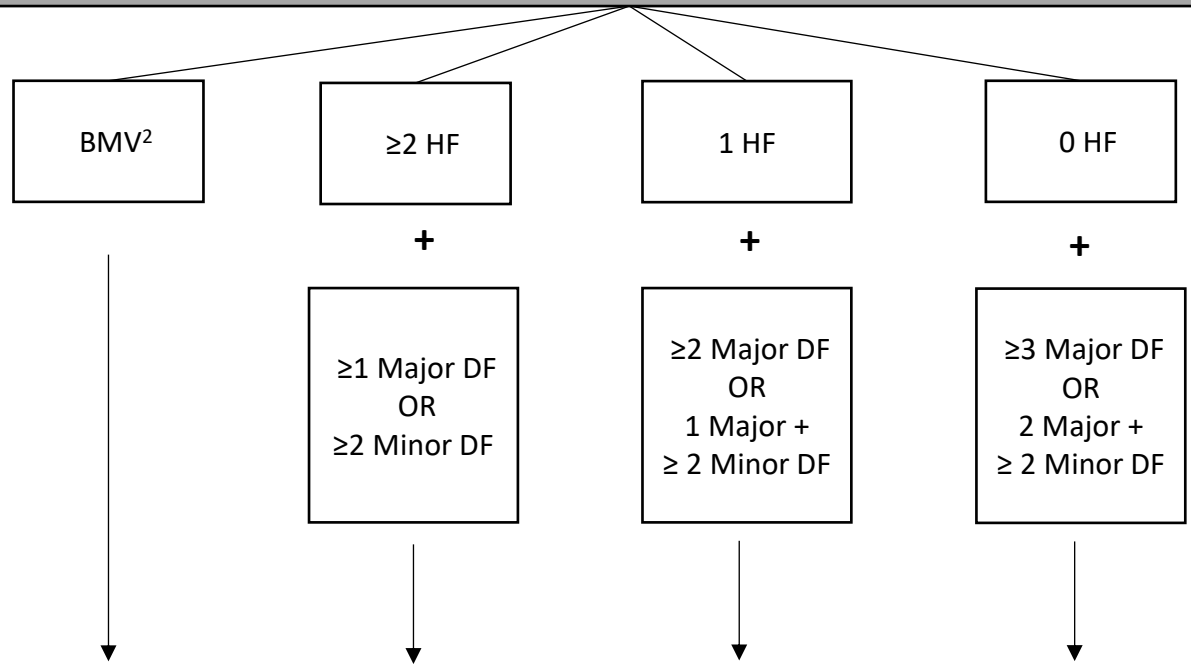
- Recurrent, non-infectious scleritis, episcleritis, uveitis
- Erythema nodosum (Bx)
- Recurrent urticaria / urticarial plaque
- Injection site reaction to anakinra
- Steroid responsive, non-infectious ground glass opacities
- Inflammatory arthritis
- Vasculitis (any size), relapsing / recurrent or with lack of response to SOC[7]
- Pericarditis / Myocarditis
- Nephrotic syndrome with renal amyloidosis (Bx)
- Interstitial nephritis (Bx)

BMV, bone marrow vacuolization; Bx biopsy confirmation required; CRP, C-reactive protein; MDS, Myelodysplastic syndrome; SOC, standard-of-care. (1) ≥ 2 occurrences of C-reactive protein (CRP) ≥ 20 mg/L; (2) Cytoplasmic vacuolization in erythroid and/or myeloid precursors for which copper deficiency, zinc toxicity, or alcohol abuse are not suspected as contributory causes. Quantitively significant cytoplasmic vacuolization most suggestive of VEXAS is ≥ 20% erythroid and/or ≥ 40% myeloid precursors (3) MCV ≥ 98 femtoliter on one or more occasions without associated folate or vitamin B12 deficiency (4) platelet count ≤ 100 x 10^9/L (5) monocyte count < 0.5 x 10^9/L (6) Requirement of ≥ 10 mg/day oral prednisone (or equivalent) for inflammatory syndrome symptomatic control (7) For patients utilizing skin biopsy with LCV as a major disease criterion, a different form of vasculitis must be present to consider additional inclusion of this minor criteria (e.g. large/medium vessel vasculitis or alternative form of small vessel vasculitis with biopsy findings of vasculitis on non-cutaneous sample, such as ANCA vasculitis).

When to consider testing for somatic *UBA1* variant

Pre-test probability is higher for MALES compared to FEMALES

Required: Age > 40 ↑CRP[1]



Testing strongly recommended

Consider testing if no alternative etiology present

(II)VEXAS diagnosis: UBA1 screening modalities consensus statements

- **The majority of patients with typical VEXAS have missense / splice site mutations at exon 3 of *UBA1***
- **A variety of sequencing methods can be used to diagnose VEXAS depending on resources and expertise**
- **Next-generation sequencing (NGS) has increased sensitivity to detect low level somatic variants with coverage of all coding/splice site regions**
- **Targeted testing for exon 3 variants can be used as an alternative to NGS with the understanding that such modalities may miss somatic variants with low VAF (Sanger sequencing) or variants outside of exon 3 (Sanger sequencing and digital droplet PCR (ddPCR))**
- **Active treatment may affect the accuracy of genetic testing by decreasing mutation level**
- **Somatic mutations defining VEXAS are detected in peripheral blood or bone marrow derived DNA**
- **If clinical suspicion is high and genetic testing for mutations in *UBA1* at exon 3 is negative in the peripheral blood, clinicians should ensure that testing covers the complete gene and consider testing a bone marrow sample**

Main additionnal informations provided by samples

1
- Hematopoiesis organization (maturation, atypia, dysplasia)
- Exclusion of other causes of cytopenia
- Evaluation and quantification of vacuoles in granulocytic and erythroid progenitors on BM smear

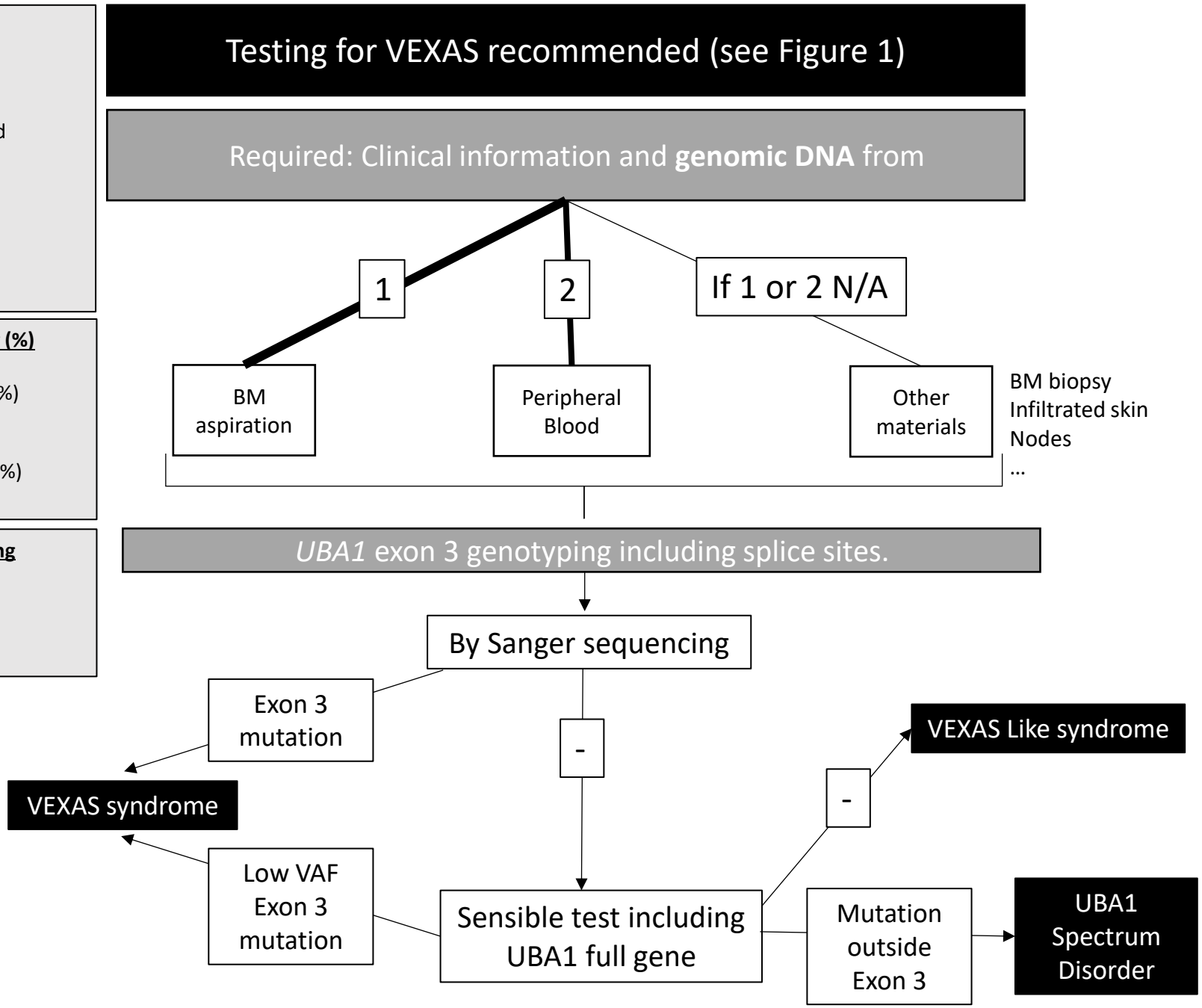
2
- Confirm macrocytic anemia with high CMV and RDW
- Circulating monocytes and platelets
- Allow acces to material to evaluate the inflammatory state

Available technics used for *UBA1* sreening with proposed sensitivity (%)

- Sanger Sequencing of exon 3 including hotspot and splice sites (10-15%)
- High Resolution Melting Analysis of exon 3 (1%)
- Droplet Digital PCR of exon 3 (1%)
- Targeted Next Generation Sequençing including full gene sequence (1%)
- WES (2-5%)

Additionnal approaches usefull in a context of UBA1 genetic testing

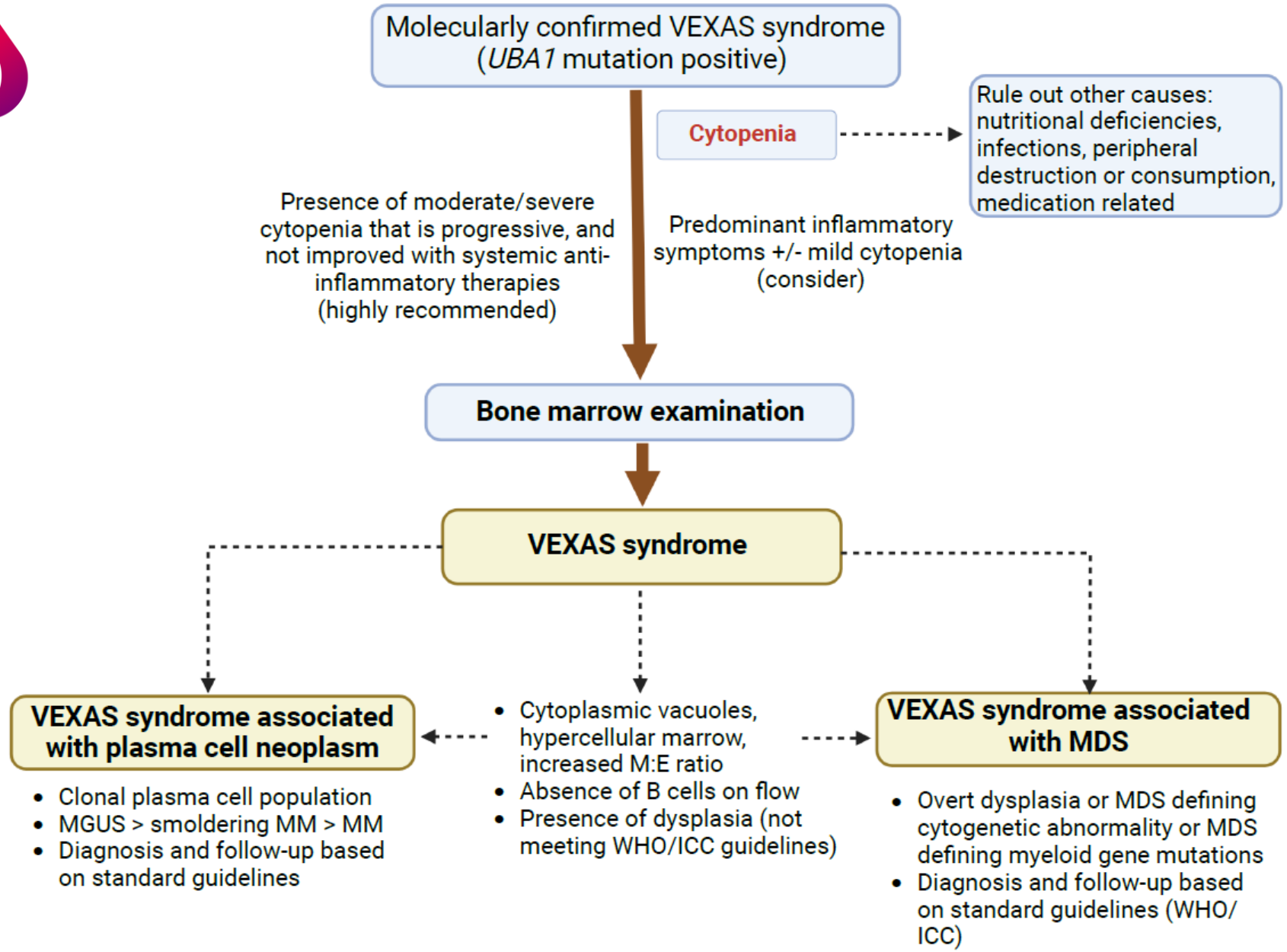
- Cytogenetic analysis
- Systematic biobanking (Blood plasma and serum, frozen cells…)
- Blood smear for future AI approaches



Group 2

(III)Diagnosis of MDS in patients with VEXAS consensus statements

- **Bone marrow examination is recommended in VEXAS patients with associated cytopenia to exclude an associated hematologic neoplasm**
- **Karyotype and next generation sequencing for co-existing somatic mutations should be performed with marrow examination**
- **Interpretation of bone marrow is challenging in VEXAS due to the frequent presence of signs of dysplasia, without meeting existing criteria for myelodysplastic syndrome diagnosis based on the WHO and ICC 2022 classifications**
- **The somatic clonal landscape in VEXAS is dominated by mutations in *DNMT3A* and *TET2*, generally without other driver mutations, but is to date difficult to discriminate from usual age related to more VEXAS specific signature**


Molecularly confirmed VEXAS syndrome (*UBA1* mutation positive)
Cytopenia
Rule out other causes: nutritional deficiencies, infections, peripheral destruction or consumption, medication related
Presence of moderate/severe cytopenia that is progressive, and not improved with systemic anti-inflammatory therapies (highly recommended)
Predominant inflammatory symptoms +/- mild cytopenia (consider)
Bone marrow examination
VEXAS syndrome
VEXAS syndrome associated with plasma cell neoplasm
• Clonal plasma cell population
• MGUS > smoldering MM > MM
• Diagnosis and follow-up based on standard guidelines
• Cytoplasmic vacuoles, hypercellular marrow, increased M:E ratio
• Absence of B cells on flow
• Presence of dysplasia (not meeting WHO/ICC guidelines)
VEXAS syndrome associated with MDS
• Overt dysplasia or MDS defining cytogenetic abnormality or MDS defining myeloid gene mutations
• Diagnosis and follow-up based on standard guidelines (WHO/ ICC)

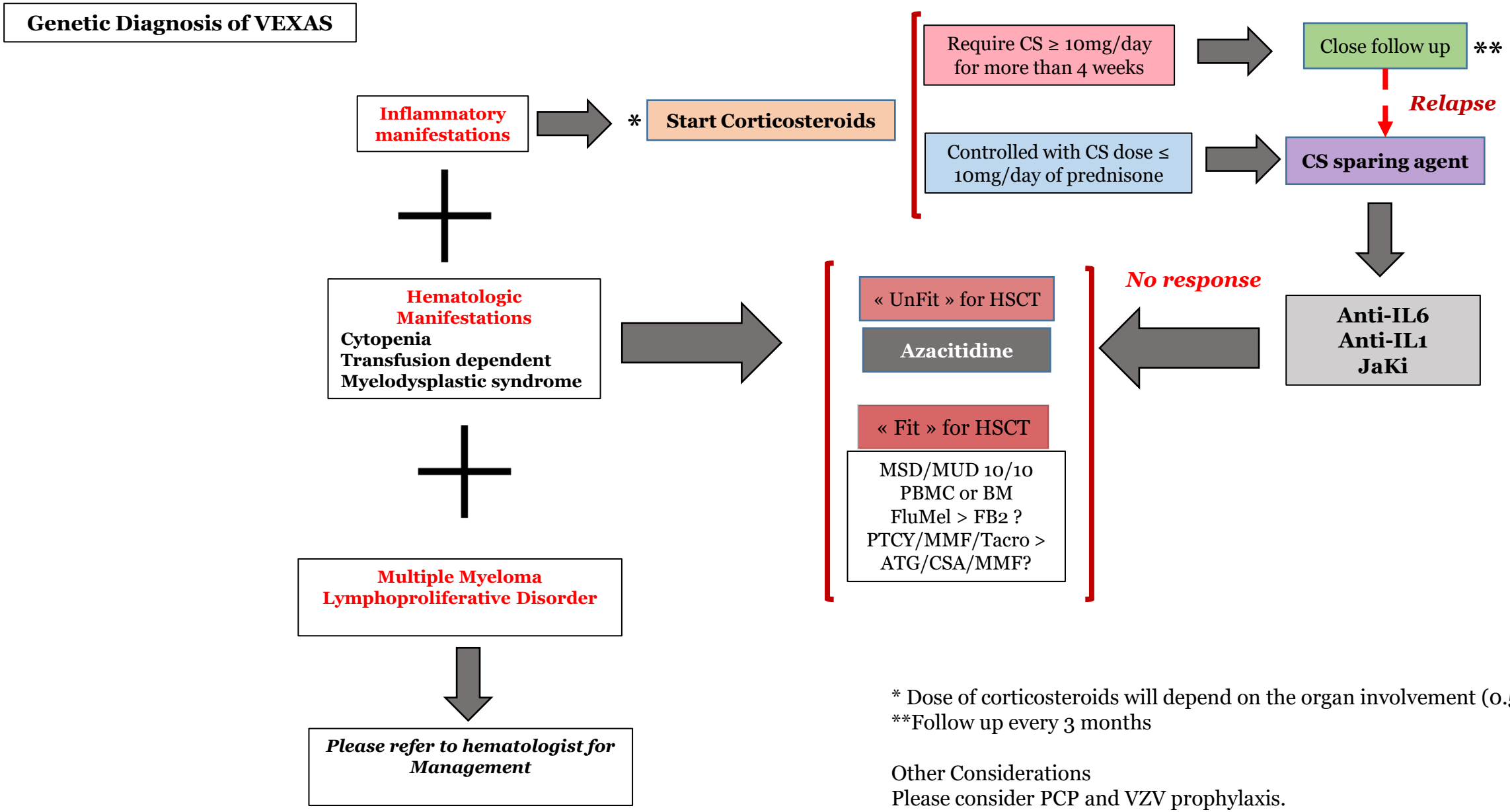
(IV)Outcome, prognosis, and management consensus statements (a)

- **Patients with VEXAS should be managed by a multi-disciplinary team with consideration of referral to an expert center when available**
- **Disease activity is defined by inflammation or worsening bone marrow failure**
- **The goals of treatment include controlling inflammation, preventing and treating bone marrow failure, preventing and treating secondary medical complications arising from implemented treatments and improving quality of life**
- **Infections, thromboembolic embolic disease, and treatment related co-morbidities are common in VEXAS and can mimic disease activity**
- **Flare of disease can be defined as recurrence of clinical or laboratory signs or symptoms of VEXAS**

(IV)Outcome, prognosis, and management consensus statements (b)

- **Glucocorticoids are usually needed to control inflammation in patients with VEXAS and should be tapered slowly to achieve the minimal dose required to control disease activity Future clinical trials will be needed to identify the best treatment for patients with VEXAS**
- **Medications that target inflammatory pathways (e.g. JAK inhibitors, IL-6 inhibitors) are more effective than conventional DMARDs (e.g. methotrexate, azathioprine) or B cell directed therapies (e.g. rituximab)**
- **Medications that reduce or eliminate the clonal burden of disease (e.g., azacitidine) can be an effective treatment in some patients with VEXAS**
- **Allogenic hematopoietic stem cell transplantation may be a curative treatment but should be reserved for select patients with VEXAS after a careful hematologic evaluation**
- **Prophylaxis against opportunistic infections, prevention of thromboembolic disease, and minimization of side effects related to chronic glucocorticoid therapy should be considered in all patients with VEXAS**
- **Future clinical trials will be needed to identify the best treatment for patients with VEXAS**

Treatment Algorithm For VEXAS Syndrome



* Dose of corticosteroids will depend on the organ involvement (0.5mg-1 mg/kg)
**Follow up every 3 months

Other Considerations
Please consider PCP and VZV prophylaxis.
** anticoagulation statement***

THANK YOU!

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