SUPPLEMENARY TABLE 1 Manifestations caused by, examinations, and differential diagnoses in patients with eosinophilia.

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
| **Hematological** | B-symptoms (weight loss, low grade fever, night sweats), lymph-adenopathy, hepato-/spleno-megaly, anemia with functional ischemic manifes- tations, bleeding, thrombosis, infec- tions, or acciden- tally discovered | Palpation of lymphadenophaty and organomegaly, hemorrhagic diathesis. Evaluation of skin changes, e.g. cutaneous lymphoma or mastocytosis  | Blood: INR, LDH, urate, creatinine, tryptase, IgA, IgG, IgE, IgM and M-protein  | Clonal analysis on blood, and/or bone marrow aspirate +biopsy from organ involvement, imaging (X-ray, US, CT, MRI, PET).iHES is a diagnosis *per exclusionem* in all manifestations  | Acute or chronic leucemia, MPN, MDS, myeloid / lymphoid eosinophilia, malignant lymphoma, GvHD, mastocytosis, histiocytosis | (65-67) |

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**Abbreviations:**

**Hematological**: CT computerized tomography; GvHD Graft-versus-Host Disease; Ig Immunoglobulin; iHES idiopathic hypereosinophilic syndrome; INR international normalized ratio (coagulation factor II,VII,X); LDH lactate dehydrogenase; MDS myelodysplastic neoplasm; MPN myeloproliferative neoplasm (Philadelphia negative); M-protein monoclonal protein; MRI magnetic resonance imaging; PET positron emission tomography; US ultrasonic imaging; X-ray ordinary imaging (e.g. chest, bone).

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
| **Dermatological** | Prurigo, urticaria, angioedema, erythroderma, macules, papules, plaques, nodules, mucocutaneous ulcers. Cutaneous vascular symp-toms including Raynaud, livedo reticularis, purpura, ulceration and necrosis. Nail splinters. Vesicles and bullaeB-symptoms.Symptoms from other organ systems | Dermatological evaluation including differential diagnosisEvaluation of organomegaly and lymph glands | Skin biopsy (+/- IF )CRP, ESR, ALAT, LDH, creatinine, Vitamin B12,IgA,IgG,IgM,IgE, tryptase | Depending on clinical suspicion: KIT D816V mutation peripheral blood, vasculitis screening, blood smearIf organ involvement see other sections | Eosinophilic dermatoses (Eosinophilic cellulitis (Wells syndrome), papulo-erythroderma of Ofuji, granuloma facialis)Atopic diseases including atopic dermatitisCutaneous drug reactions including DRESSVasculitis (Churg-Strauss) Immune dysregulation (e.g. Hyper IgE syndromes) Bullous pemphigoid, scabies, parasitic infections, Sezary Syndrome, mastocytosis,Gleich syndrome, GvHD | (68) |

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**Abbreviations:**

**Dermatological**: ALAT alanine amino transferase; CRP C-reactive protein; DRESS drug reaction eosinophilia systemic symptoms; ESR erythrocyte sedimentation rate; GvHD Graft-versus-Host Disease; IF immunofluorescence; Ig Immunoglobulin; LDH lactate dehydrogenase.

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
| **Cardiac** | Shortness of breath with activity or when lying down.Fatigue and weakness. swelling of the leg and/or abdomen, chest pain, cough, palpitations and embolic events | Cardiac murmurs, Dyspnea, oedema, rapid or irregular heart rhythm.Echocardiography (Löfflers endocarditis):LV/RV systolic dysfunction, endomyocardial thickening, with left and right apical mural thrombus formation and posterior mitral leaflet involvement.Progressive features with restrictive cardiomyopathy and atrioventricular valve regurgitation secondary to subvalvular damage (fibrosis) | ECG nonspecific changes. (ST elevation or non-ST elevation, T wave inversion, atrioventricular block, bundle branch block, ventricular arrhythmia, atrial fibrillation and supraventricular tachycardia).Biomarkers: Troponine, CK-MB, pro-BNP | Cardiac MRI (if possible with IV gadolinium contrast to improve diagnostic accuracy).Consider: coronary CT / coronary angiogram (to exclude coronary artery disease).Consider: endomyo-cardial biopsy (gold standard) | Heart failure. ischemic heart disease, valvular heart disease, other forms of myocarditis | (69, 70) |

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**Abbreviations:**

**Cardiac**: CK-MB creatine-kinase myoglobin binding; CT computerized tomography; ECG electrocardiogram; IV intravenous; LV left ventricle; MRI magnetic resonance imaging; pro-BNP pro-Brain Natriuretic Peptide; RV right ventricle.

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
| **Pulmonary** | Dyspnea, cough, fever, pleuritic pain, myalgia, hemoptysis, rhino-sinuitis, B-symptoms, (uncontrolled) asthma, nasal polyposis | Lung auscultation, lung physiology: spirometry with diffusioncapacity or bodypletymography, if asthma suspicion spirometry with reversibility testing and/or provocation tests, 6MWT, saturation, skin affection | Inflammation markers as descri-bed for infectious eosinophilic diseases*.* Aspergillus serology (separate table for parasitic causes).ANA, ANCA, Quantiferon/ T-spot/ Mantoux testRadiology: HRCT (detection of patho-gnomonic findings compatible with eosinophilic lung diseases) | BAL: Flowcytometry (detection of eosino-philia). Culture and microscopy for fungi, PCR for Pneumocystis Jirovecii, TB, NTMTissue: TBB or TBCB (detection of organ-related eosinophilia and pathognomonic histological findings) | Primary parenchymal eosinophilic lung diseases: iAEP, iCEP, HES, iHypereosinophilic BO, pulmonary EGPA (see “Rheumatological”)Primary airway-related eosinophilic lung diseases: Eosinophilic asthma, eosinophilic bronchitisSecondary airway-related eosinophilic lung diseases: Asthma, ABPA, ABPMSecondary parenchymal eosinophilic lung diseases: CPA, TB, NTM, PCP, HIV, drugs, IPF, lung cancer, PLCH | (71-73) |

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**Abbreviations:**

**Pulmonary**: ABPA Allergic bronchopulmonary aspergillosis; ABPM Allergic bronchopulmonary mycosis; ANA anti-nuclear antibodies; ANCA Anti-neutrophil cytoplasmic autoantibodies; BAL Bronchoalveolar lavage; BO Bronchiolitis obliterans; (C)OP (Cryptogenic) organising pneumonia; CPA Chronic pulmonary aspergillosis; EGPA Eosinophilic granulomatosis with polyangiitis; HES hypereosinophilic syndrome; HIV human immunodeficiency virus; HRCT high resolution computed tomography; iAEP Idiopathic acute eosinophilic pneumonia; iCEP Idiopathic chronic eosinophilic pneumonia; IPF Idiopathic pulmonary fibrosis; NTM Non-tubercolous mycobacteria; PCP Pneumocystis Carini (now Jirovecii) Pneumonia; PCR polymerase chain reaction; PLCH Pulmonary Langerhans cell histiocytosis; TB Tuberculosis; TBB Transbronchial biopsy; TBCB Transbronchial cryobiopsy; 6MWT six minute walking test.

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
| **Rheumatological** | B-symptoms. Myo-arthralgia. Uncontrolled asthma. Chronic rhinosinuitis and nasal polypose.Glomerulo nephritis. Pericarditis and cardiac rhythm abnormalities. Mononeuritis multiplex (sensory, motoric dysfunction)  | LymphadenopathyPalpable purpura or urticaria | Blood: albumin, CRP, IgG, IgA, IgM and IgE. ANCAUrine analysis with microscopic examination of urinary sedimentRadiology:X-ray of the chest and HRCTSinus-CT(Cardiac MRI)ECG, Echocardiography | Tissue biopsy with eosinophilic infiltration, granulomatosis and necrotizing vasculitis from e.g. Lung, SkinNasal or Kidney Nerve conduction and EMG  | EPGA – multiorgan system diseaseDifferential diagnosis are the other ANCA-associated vasculitis GPA and MPA | (74, 75) |

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**Abbreviations:**

**Rheumatological**: ANCA anti-neutrophil cytoplasmic antibodies; CRP C-reactive protein; CT computerized tomography; ECG electrocardiogram; EMG electromyography; EPGA Eosinophilic granulomatosis with polyangiitis; GPA granulomatosis with polyangiitis; HRCT high resolution computed tomography; Ig immunoglobulin; MPA microscopic polyangiitis; MRI magnetic resonance imaging; ; X-ray ordinary imaging (e.g. chest, bone).

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
| **Oto rhino laryngology** | Nasal obstruction, nasal secretion, Loss of sense of smell, pain and/or pressure over sinusEar pain/ earfullness | Test of nasal breathingNasal endoscopyTest of sense of smellOtoscopyExamination of the throat Symptom score using the PROM SNOT-22 | Biopsy of nasal polyps with count of eosinophilic cells Total IgE | CT-scanning of the nasal sinus | Chronic Rhinosinusitis with or without nasal polyposisEosinophilic GPACRS wNP is most often a type 2 inflammation in the nasal mucosa. In rare cases the disease is part of primary eosinophilia | (76, 77) |
| **Gastro- enterological and liver** | Dysphagia. Pain. Nausea and vomiting. Diarrhea. Weight loss. Obstruction. Abdominal distention, jaundice | No specific findings, or weight loss and signs of malnutrition.Signs of liver failure (ascites, icterus, spider naevi, palmar erythema) | Nutrition panel.Liver function tests. Autoimmune liver serology | Endoscopy with mucosal biopsies according to presenting symptoms. Imaging with US and CT Ascites cytology and liver biopsy. MRCP | Infection. Drug reaction. Inflammatory bowel disease.Toxic hepatitis. Autoimmune hepatitis. Sclerosing cholangitis | (78) |

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**Abbreviations:**

**Oto rhino laryngology:**  CRS wNP Chronic Rhinosinusitis with Nasal Polyposis; CT computerized tomography; GPA granulomatosis with polyangiitis; Ig immunoglobulin; PROM (Patient reported outcome measure) SNOT-22 ( Sino-Nasal Outcome Test 22 items).

**Gastroenterological and liver:** CT computerized tomography; MRCP magnetic resonance cholangiopancreatography; US ultrasound.

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
| **Neurological** | Cerebral throm-bosis, mostly arterial with paresis. Visual dysfunction. Encephalopathy, particularly cognitive and / or upper neuron paresis. Peripheral neuropathies, sym metric or not, sen sory or motoric or both. Mononeuritis multiplex | Consciousness, cranial nerve testing, neck stiffness, muscle function (paresis), deep tendon reflexes, sensibility, coordination of movements, cognitive testing, speech  | Blood glucose, ionized calcium, thyroid test, liver enzymes and INR, vitamin B6 and B12 CT cerebrum, lumbar puncture (incl cell counts, protein, microscopy and culture)  | MRI cerebrum and/or medulla spinalis. Electro diagnostic analysis of nerve and muscle function, EEG, Nerve or brain biopsy. Autoimmune anti bodies ANA and ANCA, CSF: oligoclonal bands in CSF and other specific tests as indicated | Apoplexia, disseminated sclerosis, Guillain-Barré syndrome, intoxication (alcoholism, medication, metal, metabolic), uncontrolled diabetes, infectious meningitis, increased intracranial pressure, tumor – malignant or benign, EGPA, other ANCA-associated vasculitis GPA and MPA | (79, 80) |

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**Abbreviations:**

**Neurological**: ANA Anti-nuclear antibody, ANCA anti-neutrophil cytoplasmic antibodies; CSF cerebrospinal fluid; CT computerized tomography; EEG electroencephalogram; EGPA Eosinophilic granulomatosis with polyangiitis; GPA granulomatosis with polyangiitis; INR international normalized ratio (coagulation factor II,VII,X); MPA microscopic polyangiitis; MRI magnetic resonance imaging.

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
| **Nephro-urological** | Pain (flank, lower abdominal), dysuria, hematuria, urine retention, symptoms of renal failure, fever | Abdominal palpation (pain-characteristics, mass) | Blood: creatinine, clearance, blood urea nitrogen, PSA in males; urine analysis (dipstick, quantitative protein and volume, eosinophils in urine), culture and microscopy for microorganismsImaging: US, CT, MRI, nuclear scan | Cysto-uretero-scopy, renal biopsy  | Glomerulopathy – autoimmune or infectious, acute tubular necrosis. EGPA, GPA, MPA, IgG4-related disease, Erdheim-Chester disease, sarcoidosis, DRESS, parasitic diseases, eosinophilic cystitis, dialysis-associated eosinophilia, renal malignancy | (81, 82) |

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**Abbreviations:**

**Nephro-urological**: CT computerized tomography; DRESS drug reaction eosinophilia systemic symptoms; EGPA Eosinophilic granulomatosis with polyangiitis; GPA granulomatosis with polyangiitis; ); Ig immunoglobulin; MPA microscopic polyangiitis; MRI magnetic resonance imaging; PSA Prostate Specific Antigen; US ultrasound.

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| **Manifestation** | **Variable symptoms** | **Objective clinical examinationa** | **Initial laboratory examinationsb** | **Confirmatory laboratory examinationsc** | **Differential diagnosesd** | **Ref.** |
|  **Congenital** **FE: IEI: inborn errors**  **Familial eosinophilia of immunity** | IEI: Atopy, recurrent infections (bacterial, viral, fungal), enteropathy, auto-inflammation/-immunity, failure to thriveFE: no specific symptoms, no increased infectious burden or findings consistent with atopy or immune dysregulation  | IEI: Familial predis-position, eczema, skin abscesses, adenopathy, eosinophilia, lympho-penia, elevated serum IgE, skeletal abnormali-ties, syndromic featuresFE: End organ damage due to eosinophilia not consistently observed | IEI: Red and white blood count, serum immunoglobulins, vaccination status, lymphocyte surface markersFE: persistent eosinophilia > 1.5 x 109/L, serum immunoglobulins, skin prick test, allergen specific IgE, and diagnostic work-up: e.g. infec-tious diseases, pul-monary, rheumato-logy, hematological | IEI: Genetic sequencing for monogenetic germline IEI variants associated with eosinophilia. Functional molecular/cellular studies, serum cytokinesFE: Genetic sequencing if available serum cytokines/ eosinophil granule proteins, eosinophil activation markers (CD25, CD69, HLA-DR). Classified as autosomal dominant disease, secondary to dysregulated IL-5 production  | IEI: DN STAT3 Job’s syndrome, AR DOCK8, XL WAS, Omenn syndrome (AR RAG1/2, XL IL2RG, AR/AD IL7R), AR IL6R deficiency, IPEX FOXP3, AD GOF JAK1FE: iHE or iHES, primary or secondary eosinophilia  | IEI: (83, 84)FE: (85, 86)  |

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**Abbreviations:**

**Congenital causes**: AD autosomal dominant; AR autosomal recessive; CD cluster of differentiation; DN dominant negative; DOCK8 dedicator of cytokinesis 8; FE familial eosinophilia; FOXP3 forkhead box P3; GOF gain-of-function; HLA-DR human leukocyte antigen – DR isotype; IEI inborn errors of immunity; Ig immunoglobulin; iHES idiopathic hypereosinophilic syndrome; IL2RG interleukin 2 receptor subunit gamma; IL5 interleukin 5; IL6R interleukin 6 receptor; IL7R interleukin 7 receptor; IPEX immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; JAK1 Janus kinase 1; RAG1/2 recombination activating 1/2; STAT3 signal transducer and activator of transcription 3; WAS Wiskott–Aldrich syndrome; XL X-linked.