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Hereditary alpha-tryptasemia – a potential cause of severe anaphylactic reactions and a modifier of mast cell diseases

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Summary

Hereditary alpha-tryptasemia (HAT) is an autosomal dominant genetic trait affecting 4% to 6% of the general population. Hereditary alpha-tryptasemia is caused by an excess of alpha tryptase encoding *TPSAB1* copy numbers on one parenteral allele, most often duplications or triplications, leading to elevated levels of basal serum tryptase. There might be a gene dosage effect between the number of additional *TPSAB1* copies, the level of basal serum tryptase and the severity of clinical symptoms, including atopic, cutaneous, gastrointestinal, musculoskeletal, autonomic and neuropsychiatric manifestations. Hereditary alpha-tryptasemia is a potential risk factor for severe anaphylactic reactions. The prevalence of hereditary alpha-tryptasemia is higher in patients with systemic mastocytosis. In the diagnostic workup of patients with anaphylactic reactions and symptoms of mast cell mediator release after measurement of basal serum tryptase, it is therefore essential to screen for both the *KIT* D816V activating point mutation and hereditary alpha-tryptasemia by droplet digital polymerase chain reaction. Such a diagnostic approach can identify patients with hereditary alpha-tryptasemia, which may allow the avoidance of further diagnostic workup with bone marrow examination. Moreover, it can identify patients at high risk of anaphylactic reactions. So far, no targeted therapy for hereditary alpha-tryptasemia is available. Treatment for symptom control consists of H1- and H2-blockers, leukotriene antagonists and cromoglicic acid. Urticaria and anaphylaxis are especially successfully treated with the monoclonal anti-IgE-antibody omalizumab in patients with hereditary alpha-tryptasemia. H1-blockers and steroids are sufficient in emergencies. As hereditary alpha-tryptasemia is a hereditary condition, first-degree relatives with anaphylactic reactions or symptoms of mast cell mediator release should be tested for hereditary alpha-tryptasemia after measurement of basal serum tryptase.

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A case illustrating the clinical problem

A 53-year-old gentleman was referred for an allergological evaluation. He had a history of a severe anaphylactic reaction grade III, according to H.L. Mueller, with rapid onset of paresthesias, dyspnoea, nausea and vomiting, low blood pressure, and somnolence but no urticaria after a bee sting. Notably, he reported a similar reaction that had occurred more than a decade ago after a wasp sting. A month after the recent event, total immunoglobulin (Ig) E was normal, skin tests revealed no significant sensitisation to bee venom and an elevation of specific IgG against bee venom and wasp venom was documented. A venom immunotherapy with bee venom in an ultra-rush procedure was commenced. Basal serum tryptase was largely increased, with a value of 194 µg/l (normal range: <11.4 µg/l), and repeatedly measured with basal serum tryptase-values >125 µg/l without signs of mastocytosis in the skin. Other aetiologies associated with an elevated basal serum tryptase, such as renal failure, increased body mass, chronic inflammatory diseases or chronic infections, were excluded.

Diagnostic workup to further explore the elevated basal serum tryptase, including molecular genetic testing and bone marrow investigation, revealed a 5% infiltration of the bone marrow with neoplastic, spindle-shaped, CD25- and CD2-positive mast cells. The activating D816V point mutation in *KIT* was detected by digital droplet polymerase chain reaction (PCR). There was a normal bone density on the DXA scan, no evidence of hepato-/splenomegaly on ultrasound, and no other B- or C-findings. According to the 2017 WHO Classification, the diagnosis of indolent systemic mastocytosis was made based on the presence of four minor diagnostic criteria. Venom immunotherapy was continued with the recommendation of a life-long implementation, and an H1-blocker therapy was started. The patient was given an emergency kit with an H1-blocker, steroids and a self-injectable adrenalin injector and trained in its use.

Interestingly, the daughter of this patient also suffered from venom allergy, albeit to wasp venom. In combination with

an elevated basal serum tryptase of 31.6 µg/l, a diagnostic workup was performed in the absence of mastocytosis in the skin. Bone marrow examination revealed normal haematopoiesis with no evidence of an increase in mast cells, and no D816V point mutation in *KIT* was detected by digital droplet PCR. Therefore, systemic mastocytosis was ruled out.

Since the cause of the elevated basal serum tryptase was unclear, a quantitative digital droplet PCR for genotyping of the *TPSAB1*/*TPSB2* gene locus was performed. This analysis revealed a hereditary alpha-tryptasemia (HAT) with documentation of a total of three copies of sequences encoding alpha and beta tryptase each, compatible with the diagnosis of hereditary alpha-tryptasemia with a triplication of the alpha tryptase encoding *TPSAB1* gene (one copy of the beta tryptase encoding sequence on each *TPSB2* allele, one copy of the beta tryptase encoding sequence on one *TPSAB1* allele and three copies of the alpha tryptase encoding sequence on the other *TPSAB1* allele). These additional germline copies of the *TPSAB1* gene encoding the alpha isoform lead to the increased constitutive release of tryptase and, thus, to elevated basal serum tryptase levels.

Therefore, the father's case was again reviewed, and molecular genetic testing revealed the presence of four copies of alpha tryptase and two copies of beta tryptase, confirming the additional diagnosis of hereditary alpha-tryptasemia. Therefore, the definitive diagnosis in this case was systemic mastocytosis and hereditary alpha-tryptasemia. The subtype of systemic mastocytosis had been initially diagnosed as indolent systemic mastocytosis based on the basal serum tryptase level of ≥125 µg/l. When correcting the initial basal serum tryptase of 194 µg/l to account for the presence of an alpha tryptase gene triplication (i.e. division of basal serum tryptase by 1 plus the extra copy numbers of the alpha tryptase gene, in this case, 194 µg/l divided by 3 for two extra copies), the hereditary alpha-tryptasemia-corrected basal serum tryptase was 65 µg/l. Therefore, bone marrow mastocytosis was diagnosed according to the 2022 WHO Classification [1, 2]. Despite ongoing venom immunotherapy and usage of an H1-blocker, there was another anaphylactic reaction after a bee sting, and the dose of venom immunotherapy was subsequently doubled.

Serum tryptase – genetic background and clinical symptoms

About 99% of serum tryptases derive from mast cells, and about 1% originate from basophils [3]. Elevation of BST (≥11.4 µg/l) is a typical finding in patients with hereditary alpha-tryptasemia, where basal serum tryptase is usually ≥8 µg/l. However, this is not specific to that condition. In many other conditions, basal serum tryptase can be elevated, such as in systemic mastocytosis, chronic kidney disease, chronic spontaneous urticaria, and myeloid malignancies, such as chronic myelomonocytic leukaemia, chronic eosinophilic leukaemia, acute myeloid leukaemia or myelodysplastic neoplasms [4–10]. Therefore, in patients with an elevated basal serum tryptase, hereditary alpha-tryptasemia, systemic mastocytosis, renal failure and myeloid malignancies must be considered in the differential diagnosis, occurring either as a separate entity or in combination.

Hereditary alpha-tryptasemia is an autosomal dominant genetic trait found in 4% to 6% of the general population. Its prevalence is higher in patients with idiopathic anaphylaxis. There are four tryptase genes on chromosome 16p13.3. *TPSB2* encodes beta tryptase isoforms, *TPSAB1* encodes alpha tryptase or beta tryptase isoforms, *TPSG1* encodes gamma tryptase, and *TPSD1* encodes delta tryptase [11]. The fifth tryptase isoform, epsilon tryptase, is encoded by the serine protease 22 (*PRSS22*) gene [11]. Only alpha- and beta-tryptases are secreted in relevant amounts and are measured as serum tryptase [11]. Alpha- and beta-tryptase are produced as protryptase monomeric precursors, which can be either constitutively secreted or further processed with the formation of mature tryptase tetramers [12]. The role of mature tryptases is poorly understood; it has been reported that they are involved in tissue repair, vascular permeability, chemotaxis of neutrophils and eosinophils, and thrombolysis [13–16]. The ELISA-based immunoassays used to analyse serum tryptase levels can detect the protryptase monomeric precursors and mature tryptase forms [17].

Tryptases encoded by *TPSB2* (beta) and *TPSAB1* (alpha or beta) are inherited as a haplotype from the parents. Each parent passes on one allele from the *TPSB2* gene and one allele from the *TPSAB1* gene to their offspring. In hereditary alpha-tryptasemia, there is an excess of alpha tryptase encoding *TPSAB1* copy numbers on one allele (figure 1). Furthermore, an overactive promoter has been identified in hereditary alpha-tryptasemia [18], leading to increased alpha tryptase synthesis and secretion and, thus, increased basal serum tryptase. In hereditary alpha-tryptasemia, one additional *TPSAB1* copy increases basal serum tryptase by approximately 9.5 µg/l [19].

Furthermore, a gene-dose effect between the *TPSAB1* copy number and the severity of symptoms is frequently recorded, meaning that the more copies of the alpha tryptase encoding gene are present, the higher the basal serum tryptase level and the more symptoms may occur in affected patients [20]. However, isolated studies found no correlation between the frequency of clinical manifestations and the copy number [21].

The risk of anaphylaxis in hereditary alpha-tryptasemia is clearly increased, but symptoms in patients with hereditary alpha-tryptasemia are variably expressed. These symptoms can manifest at any age, but patients can also be completely asymptomatic. There is little evidence of the correlation between hereditary alpha-tryptasemia and clinical symptoms. In one study, one-third of healthy adults with hereditary alpha-tryptasemia had severe symptoms, one-third had mild to moderate symptoms, and one-third displayed no difference from healthy volunteers [20].

The reason for the phenotypic heterogeneity is unclear, but coinheritance of other genetic variants might play a role. In addition to allergic conditions, nonallergic diseases are also associated with hereditary alpha-tryptasemia. Females with hereditary alpha-tryptasemia are more often symptomatic, and although this is an inherited condition, the onset of symptoms is usually after puberty [22].

There is a variety of potential clinical symptoms in patients with hereditary alpha-tryptasemia. Most of these symptoms are consistent with mast cell mediator release through activation and degranulation [23]. Most commonly, there

is urticaria, flushing and/or pruritus, gastroesophageal reflux disease, irritable bowel syndrome-like symptoms and/or diarrhoea, allergic rhinitis and/or asthma, arthralgias, fibromyalgia and/or headaches as well as neuropsychiatric manifestations [20].

Anaphylaxis is significantly modified by hereditary alpha-tryptasemia, increasing both in incidence and severity [13]. Triggers of anaphylaxis include insect stings, food, drugs, radiocontrast media and specific immunotherapy; in idiopathic anaphylaxis, no specific trigger can be identified [24]. Tryptase genotyping for hereditary alpha-tryptasemia and *KIT* D816V for systemic mastocytosis should be considered clinically when evaluating individuals with a history (or are at risk) of severe anaphylaxis [13].

Hereditary alpha-tryptasemia is observed at an increased prevalence in systemic mastocytosis but is also more frequent in non-clonal mast cell disorders. In systemic mastocytosis, there is an increase in mast cell mediator symptoms if patients also have hereditary alpha-tryptasemia [25]. In those patients, hereditary alpha-tryptasemia leads to a doubling of the prevalence of anaphylaxis [13]. Modification of clinical symptoms in patients with systemic mastocytosis in that context is clearly present, although it remains unclear whether hereditary alpha-tryptasemia can independently cause mast cell activation. A recent study confirmed the association between hereditary alpha-tryptasemia and anaphylaxis in systemic mastocytosis but found no increased risk of developing anaphylaxis during the course of the disease in patients with systemic mastocytosis in whom anaphylaxis has not been part of the presenting symptoms [26]. Patients with both hereditary alpha-tryptasemia and systemic mastocytosis have higher serum tryptase levels independent of the mast cell burden and a significantly lower *KIT* D816V variant allele frequency [25, 26].

In contrast, most patients with hereditary alpha-tryptasemia have no clonal mast cell disease [27]. It is important to realise that a diagnosis of hereditary alpha-tryptasemia does not rule out a clonal mast cell disease such as systemic mastocytosis. Clinical warning signs, such as severe anaphylaxis, especially due to Hymenoptera stings (e.g. bees, bumblebees, wasps, hornets), typical skin lesions or signs of end-organ involvement, should prompt a further diagnostic workup.

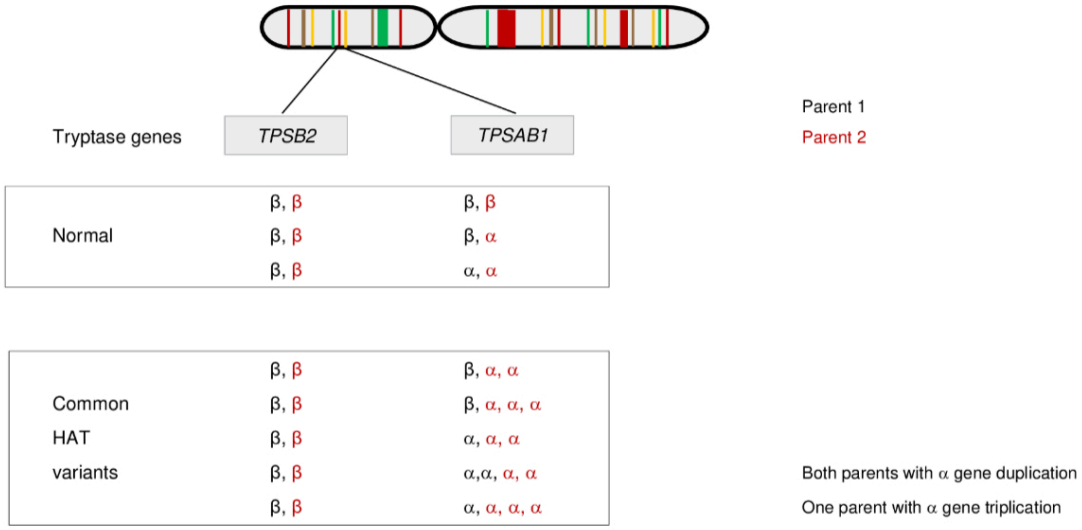
Hereditary alpha-tryptasemia – diagnostic workup

In patients with anaphylactic reactions or symptoms of mast cell mediator release, the first diagnostic step is the measurement of basal serum tryptase, which can be done inside or outside a hospital. In addition to a complete blood count to look for monocytosis or eosinophilia, clinical examination is essential, especially to evaluate for typical skin lesions and hepato-/splenomegaly.

The normal value for basal serum tryptase in asymptomatic controls, including hereditary alpha-tryptasemia-positive individuals, is ≤15 µg/l and a basal serum tryptase level >20 µg/l is a minor criterion for the diagnosis of systemic mastocytosis [1, 2, 28]. The presence of hereditary alpha-tryptasemia is unlikely if the basal serum tryptase is <8 µg/l and can be almost excluded if the basal serum tryptase is <6.5 µg/l [8].

In contrast, the presence of systemic mastocytosis cannot be reliably excluded solely based on a normal basal serum tryptase. In symptomatic patients with basal serum tryptase ≥8 µg/l, both hereditary alpha-tryptasemia and systemic mastocytosis should be considered as differential diagnoses. The diagnostic workup for hereditary alpha-tryptasemia is straightforward as it is diagnosed by genotyping *TPSAB1*/*TPSB2* by droplet digital PCR (e.g. from a sample of peripheral blood) in specialised laboratories.

Figure 1: Patterns of inheritance in alpha-tryptasemia (HAT) on chromosome 16p13.3 with different parenteral haplotypes. Alpha-tryptasemia is present when there is an excess of alpha tryptase encoding *TPSAB1* copy numbers on one allele. An increased copy number can be inherited by one or by both parents. Common alpha-tryptasemia variants include alpha tryptase duplications or triplications. Adapted from Luskin KT, White AA, Lyons JJ. The genetic basis and clinical impact of hereditary alpha-tryptasemia. J Allergy Clin Immunol Pract. 2021;9(6):2235–42. https://doi.org/10.1016/j.jaip.2021.03.005, with permission from Elsevier.



The diagnostic workup for systemic mastocytosis is more complex, but highly sensitive PCR-based techniques reliably detect the *KIT* D816V mutation in the peripheral blood in most cases [29, 30]. Thus, hereditary alpha-tryptasemia genotyping and *KIT* D816V testing from peripheral blood with a highly sensitive assay should be performed together with an evaluation of clinical red flags such as mastocytosis in the skin as reasonable steps for further workup [6].

In patients with neither the *KIT* D816V mutation in the peripheral blood nor mastocytosis in the skin or other red flags for systemic mastocytosis, one can generally avoid invasive and expensive further workup for systemic mastocytosis with a bone marrow examination if basal serum tryptase is only slightly elevated or its elevation can be attributed to another cause, especially in the presence of hereditary alpha-tryptasemia. In this scenario, even in the absence of hereditary alpha-tryptasemia, a basal serum tryptase of <15 µg/l is not an indication for bone marrow examination, and even a basal serum tryptase <20 µg/l may be acceptable [29, 31].

However, in patients with anaphylaxis with bone marrow mastocytosis, the basal serum tryptase can well be <15 µg/l. Therefore, it is important to consider the severity of symptoms when deciding on further workup with a bone marrow examination [32].

In individuals with hereditary alpha-tryptasemia and neither the *KIT* D816V mutation in the peripheral blood nor mastocytosis in the skin, even higher levels of basal serum tryptase are considered normal for the given genotype and are generally also not an indication for bone marrow examination to evaluate for systemic mastocytosis. One approach is to correct basal serum tryptase for the hereditary alpha-tryptasemia genotype, as suggested by the WHO Classification for the diagnostic minor criterion of 20 µg/l by division of basal serum tryptase by 1 plus the extra copy numbers of the alpha tryptase gene [1, 2]. Another approach is the usage of genotype-specific reference intervals for basal serum tryptase in individuals with hereditary alpha-tryptasemia – these are available via an online calculator tool (https://bst-calculater.niaid.nih.gov/) [18]. For most patients, both approaches lead to similar results [8]. For all other patients, a full workup for clonal mast cell disease is advisable.

Again, as there are patients with bone marrow mastocytosis without the *KIT* D816V mutation, one should consider the severity of symptoms in the decision regarding the workup for clonal mast cell disease.

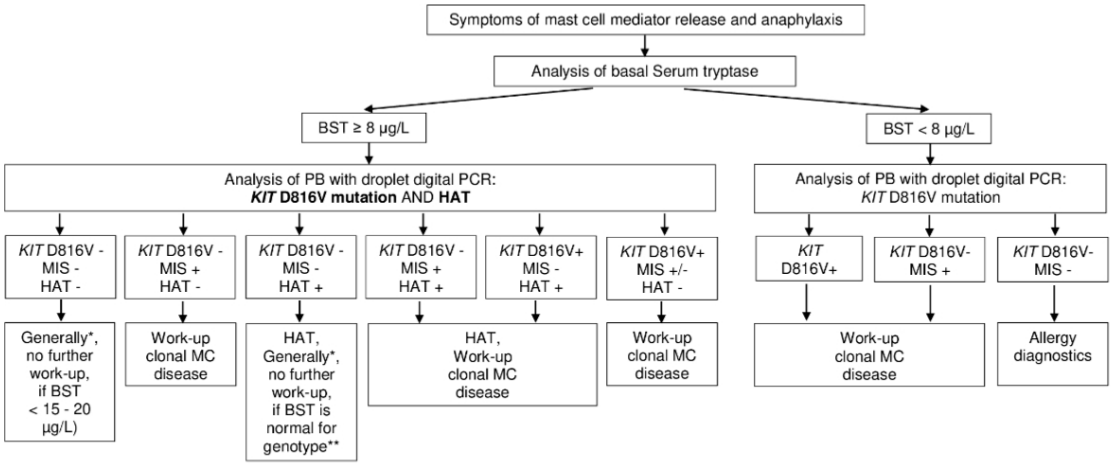
The proposed algorithm for the diagnostic workup of patients with symptoms of mast cell mediator release and anaphylaxis, considering clinical symptoms, basal serum tryptase, *KIT* D816V mutational status, genotyping for hereditary alpha-tryptasemia and presence or absence of mastocytosis in the skin is depicted in figure 2.

Such a diagnostic approach will ensure completeness of the diagnosis and avoidance of missing patients with the combination of hereditary alpha-tryptasemia and systemic mastocytosis and, therefore, a higher risk of anaphylaxis compared to the occurrence of one disease entity alone.

Hereditary alpha-tryptasemia – treatment options and open questions

There is still an ongoing discussion about whether hereditary alpha-tryptasemia represents a disease itself or is instead a risk or aggravating factor for other diseases. Asymptomatic individuals with hereditary alpha-tryptasemia should currently not be considered patients, and thus, no therapy is indicated [33]. Symptoms can become manifest at any age, usually after puberty. Symptoms can begin or get aggravated after an infection. In addition, non-steroidal antirheumatic drugs, contrast medium or emotional stress can trigger symptoms.

Figure 2: Diagnostic algorithm in parents with symptoms of mast cell mediator release and anaphylaxis – hereditary alpha-tryptasemia (HAT), systematic mastocytosis, combination of hereditary alpha-tryptasemia and systematic mastocytosis. The first step in the diagnostic workup of patients with symptoms of mast cell mediator release and anaphylaxis is the measurement of the basal serum tryptase level. The second step is the screening for the *KIT* D816V activating point mutation and for hereditary alpha tryptasemia with droplet digital polymerase chain reaction (PCR) from peripheral blood (PB). * Individual decision, as there are patients with bone marrow mastocytosis with negative results of *KIT* D816V mutation – consider also severity of symptoms and rare conditions (VIPoma, and others). ** Online calculator tool (https://bst-calculater.niaid.nih.gov/) for genotype specific reference intervals or basal serum tryptase (BST) correction by division by 1 plus the extra copy numbers of the alpha tryptase gene. MC: mast cells; MIS: mastocytosis in the skin; +: positive; –: negative.



Presently, there is no therapy targeting the genetic origin. Treatment of hereditary alpha-tryptasemia is, therefore, non-specific but symptom-based. Avoidance of known triggers is always the first step. The therapeutic approach has to be directed against the individual symptoms and consists of H1- and H2-blockers, leukotriene antagonists and cromoglicic acid for mast cell stabilisation. If severe anaphylactic reactions occur, an emergency kit with an H1-blocker, steroids and a self-injectable adrenalin injector should be provided. In cases of Hymenoptera venom anaphylaxis, venom immunotherapy should be implemented. It remains an open question how long venom immunotherapy should be performed in patients with hereditary alpha-tryptasemia without a clonal mast cell disease.

In patients with gastrointestinal, cardiac or neurological symptoms, the appropriate specialists should be consulted, and an interprofessional approach should be taken. In patients with urticaria, pruritus, nonallergic asthma or abdominal pain, treatment with the monoclonal anti-IgE-antibody omalizumab – although not approved for those indications in Switzerland – can achieve good therapeutic results [34]. This approach is supported by a retrospective study showing improvements in urticaria and anaphylaxis in patients treated with omalizumab [35]. Whether a specific drug or intervention is more suitable for a given symptom than others also remains an open question. Studies using antitryptase antibodies are underway, but no clinical data are yet available.

Conclusion

Hereditary alpha-tryptasemia is a major cause of elevated serum tryptase levels and a relevant risk factor for severe anaphylactic reactions.

The prevalence of hereditary alpha-tryptasemia is increased in patients with systemic mastocytosis, and these patients are at high risk of severe mast cell mediator symptoms and anaphylaxis. Therefore, it is crucial in the diagnostic workup to screen for both hereditary alpha-tryptasemia and systemic mastocytosis in patients with anaphylactic reactions or symptoms of mast cell mediator release. With such a screening approach, one can avoid further diagnostic workup, including bone marrow examination, in some patients with hereditary alpha-tryptasemia, and one can identify patients at high risk of anaphylactic reactions due to the occurrence of both hereditary alpha-tryptasemia and systemic mastocytosis. This is highly clinically relevant regarding the patient's information, the avoidance of triggers of mast cell mediator release if possible, and the creation of an individual, symptom-based treatment plan.

As hereditary alpha-tryptasemia is a hereditary condition, first-degree relatives with anaphylactic reactions or symptoms of mast cell mediator release should be tested for hereditary alpha-tryptasemia after measurement of basal serum tryptase.

Informed consent

Written informed consent was obtained from the patient for the publication of this article.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. *OF*, *AR* and *GM* disclose no potential conflict of interest related to the content of this manuscript. *WRS* received consulting fees and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Blueprint-Medicines, BMS-Celgene, Incyte, Jazz, Novartis, Otsuka, Pfizer, Servier, StemLine and Thermo Fisher. *GH* received payment or honoraria for lectures, presentations or educational events from Blueprint-Medicines, Cogent Biosciences, Incyte, Jazz Pharmaceuticals and Novartis; participation on a Data Safety Monitoring Board or Advisory Board for Blueprint, Cogent Biosciences and Jazz Pharmaceuticals; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid in Austrian Society of Clinical Chemistry and Laboratory Medicine; other financial or non-financial interests through employment by MLL Munich Leukaemia Laboratory.

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