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Hereditary haemorrhagic telangiectasia: pathophysiology, diagnosis and treatment.

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Abstract

Hereditary haemorrhagic telangiectasia, inherited as an autosomal dominant trait, affects approximately 1 in 5,000 people. The abnormal vascular structures in HHT result from mutations in genes (most commonly *endoglin* or *ACVRL1*) whose protein products influence TGF-ß superfamily signalling in vascular endothelial cells. The cellular mechanisms underlying the generation of HHT telangiectasia and arteriovenous malformations are being unravelled, with recent data focussing on a defective response to angiogenic stimuli in particular settings. For affected individuals, there is often substantial morbidity due to sustained and repeated haemorrhages from telangiectasia in the nose and gut. Particular haematological clinical challenges include the management of severe iron deficiency anaemia; handling the intricate balance of antiplatelet or anticoagulants for HHT patients in whom there are often compelling clinical reasons to use such agents; and evaluation of apparently attractive experimental therapies promoted in high profile publications when guidelines and reviews are quickly superseded. There is also a need for sound screening programmes for silent arteriovenous malformations. These occur commonly in the pulmonary, cerebral, and hepatic circulations, may haemorrhage, but predominantly result in more complex pathophysiology due to consequences of defective endothelium, or shunts that bypass specific capillary beds. This review will focus on the new evidence and concepts in this complex and fascinating condition, placing these in context for both clinicians and scientists, with a particular emphasis on haematological settings.

1. Overview of HHT

HHT, also known as Osler Weber Rendu syndrome [1-3], is one of the most common disorders to be inherited as an autosomal dominant trait. Careful epidemiological studies reveal that it affects approximately 1 in 5,000 individuals, [4,5] with regional differences, [6] and isolated communities displaying higher prevalences due to founder effects. [7 8]

HHT was first described as a familial disease characterised by severe recurrent nasal and gastrointestinal bleeding with associated anaemia, and visible dilated blood vessels (telangiectasia) on the lips and finger tips. The majority of HHT patients are also affected by larger arteriovenous malformations (AVMs) in the pulmonary, hepatic, cerebral, pancreatic, spinal and other circulations. [1,2,9] These features, presented in more detail within Table 1, are used as criteria to diagnose HHT. [2]

The spectrum of disease within the HHT umbrella has extended beyond the telangiectatic/AVM HHT pathology delineated by the Curaçao criteria. [2] More recently recognised features include pulmonary arterial hypertension [10]; juvenile polyposis [11]; pulmonary hypertension in the context of high output cardiac failure secondary to hepatic AVMs, when PH may be reversible after hepatic AVM treatment [12-16]; a prothrombotic state associated with elevated plasma levels of factor VIII [17], and potential immune dysfunction. [18]

Three of the genes mutated in HHT have been identified: *endoglin* (resulting in HHT1, OMIM #187300) [19]; *ACRVL1*/*ALK1;* (resulting in HHT2, OMIM#600376) [20], and more rarely, *SMAD4* (mutated in HHT in association with juvenile polyposis, JPHT OMIM #175050) [11]. Many hundreds of different mutations have been described in HHT families, with no common mutation identified ([21], summarised in [3]). The mutated gene has some

influence on the resultant HHT phenotype, [22-27] although more profound variation in disease expression is seen between members of the same family.

Our understanding of why the disease gene mutations lead to the vascular pathology is finally advancing, following the generation of exquisite animal models of HHT. [28-31]. Attention now focuses on aberrant vascular responses to injury-induced angiogenic stimuli, when the mutated genes in HHT appear to result in the inability of a blood vessel to mature appropriately. [28,30,31]

In man, HHT-specific pathology develops in different contexts according to the repertoire of susceptibility genes and/or environmental triggers to which each individual is exposed. Furthermore, as illustrated in Figure 1 and Table 1, the spectrum of HHT encompasses multiple organ systems and within these, numerous forms of disease. HHT therefore spans a vast range of scientific and clinical disciplines, and is an extremely challenging disorder both to understand, and to manage.

2. HHT Pathogenesis

2.1 Insights from HHT patients

2.1.a) Histopathology

As in other telangiectatic states [89], the smallest HHT cutaneous telangiectatic lesion appears to be a focal dilatation of the post capillary venule in the upper horizontal plexus. [90]. Computer reconstruction of serial 1-2mm sections suggest that the dilated post capillary venules enlarge, connect with dilated arterioles with loss of the intervening capillary bed, and form arteriovenous communications [90], associated with a lymphocytic perivascular cell infiltrate [90].

Microscopic telangiectasia are observed not only in the skin, but also in other vascular beds such as the pulmonary circulation [91-93] where they are the presumed cause of low grade intrapulmonary right-left shunting detectable by contrast echocardiography in the absence of macroscopic vascular abnormalities [47-52].

Large AVMs are thought to arise from these smaller lesions by progressive vascular remodelling [90]. For vessels to support arterial pressure, interspecies comparisons indicate that there is an optimal wall thickness/ lumen radius ratio to minimise wall stress. [94] When human veins are transplanted into arterial settings, adaptation to that ratio normally occurs, accompanied by increasing wall thickness. [95] In HHT, however, assumption of a more arterial phenotype following establishment of the AV communication is not observed. The vessels within AVMs, and their draining veins are characterised by dilatation with walls of varying degrees of thickness even over relatively short segments and disorganised adventitia. Medial thinning is seen, though also prominent are areas of focal thickening with abundant elastin tissue and a varying contribution of smooth muscle cells [55,92,96,97]. Thus, in spite of perfusion at arterial pressure, the vessels immediately beyond the arteriovenous communication retain venous type wall structures. [95,98].

2.1.b) Challenges when interpreting clinical data in HHT

Several factors cause difficulties when interpreting clinical patterns in HHT. First, patients are now investigated more thoroughly than in the past, so that older data series underestimate the frequency of HHT manifestations, illustrated by the increasing accepted prevalence of pulmonary AVMs. [1,93,99,100] Secondly, reporting of individual cases or very small series, excluding the denominator from which the selected population was drawn, tends to overestimate risks. For example, many HHT patients understood that they had a high chance

of developing an aggressive form of pulmonary hypertension. While pulmonary arterial hypertension does affect a subgroup of HHT patients, the real risk is probably closer to 1-2%, [16,101] and is genotype-dependant. [102] Thirdly, the majority of affected individuals still remain undiagnosed: In 121 (59%) of 205 consecutive individuals with pulmonary AVMs and HHT reviewed at one UK institution, the diagnosis of HHT had not been made previously. [34] Careful and unbiassed epidemiological studies are required to unmask all HHT-affected individuals, especially those with potentially lesser symptoms than in hospital-based series. Studies in France, Italy, and Denmark in particular have shed significant light on overall prevalence, severity and life expectancy issues in HHT.

2.1.c) Age-related changes in HHT

HHT is not apparent at birth, but evolves with age into a recognisable phenotypic pattern [1,103]. HHT telangiectasia develop and get worse with age [103,104] (Fig 2a): Individual cutaneous lesions may regress, but overall, as recognised by the families, they generally become more prevalent in each individual with time. Currently, cerebral AVM development is thought to be complete during childhood, [68] and for most individuals, pulmonary AVMs by the end of puberty [105]. Further enlargement of AVMs occurs during pregnancy [106-109], and in specific settings. Understanding why vascular abnormalities arise and develop demands knowledge not only of HHT disease gene mutations, but also a broad understanding of normal vascular physiology.

Since HHT telangiectases increase with age, it might be expected that haemorrhages will also get worse. Gastrointestinal bleeding does appear to increase with age, [103,110] with severe bleeding rare in younger patients. [103,110] For nosebleeds, also associated with iron deficiency

in HHT (Fig 2b, 2c), and the symptom most frequently associated with impaired quality of life in HHT, [111,112] the assumption of age-related deterioration is less clear. Classical studies [103], mirrored in our population (Fig 2a), indicate that the proportion of individuals who have experienced nosebleeds increases with age. At an individual patient level however, there is major waxing and waning [113,114]. Many individuals with childhood or teenage onset report no further bleeds in adult life, such as 14% (23) of the 140 individuals presented in Fig 2a. In this series, there was no evidence that the frequency of nose bleeds increased in older age groups (Fig 2d).

From a pathophysiological perspective, data on HHT life expectancy are also relevant. Two series have been published, a 1973-1997 prospective study of 57 HHT patients, [4] and a retrospective analysis of the affected and unaffected parents of 70 HHT patients. [115] In these series, there was no evidence for an increase in mortality in patients presenting later in life, [4] but an excess mortality in patients who had presented with HHT at a younger age, (<60 years) [4] or in young adults (in a series precluding childhood deaths). [115] These findings are in keeping with multiple other series that indicate early mortality due to AVMs, particularly cerebral AVM bleeds in childhood and young adults [68,88,116], and pregnancy related maternal deaths [55,109], although the article by Kjeldsen AD et al [4], the strongest predictor of early mortality appeared to be the severity of nasal or gastrointestinal haemorrhage. More recent life expectancy data of 300 parents of HHT patients [117], and 562 HHT- patients [118] suggest potentially better survival rates, although formal peer reviewed publication is awaited.

2.1.d) Familial patterns of disease

While the affected status of younger generations is often difficult to determine due to the late onset penetrance, all HHT families described to date illustrate autosomal dominant inheritance: Males and females are affected equally, each passing the condition on to approximately half of their children, in keeping with the development of disease in individuals heterozygous for a mutation in an HHT disease gene. Several studies investigating children with two affected parents, [119-121] or families with two distinct HHT-causing mutations [122] support *in utero* or infantile homozygous lethality.

Even allowing for age-related penetrance considerations discussed above, a characteristic finding is that there is profound variation in disease expression between different members of the same HHT family, [123] suggesting that other genetic and/or environmental influences modify the HHT phenotype. Recognition of this pattern, in contrast to more conventional monogenic diseases [124], allowed the development of a model (Fig 3) [125] that has permitted identification of non-genetic factors associated with disease manifestations. [17,34] (Livesey et al, manuscript in preparation). Identification of HHT modifier genes is also eagerly awaited . [126]

2.2) HHT disease gene mutations and TGF-β superfamily signalling

2.2.a) Genetics

Currently, five types of HHT are recognised. The majority of HHT patients will have HHT1 due to mutations in *ENG* encoding endoglin, [19] or HHT2 due to mutations in *ACVRL1* encoding activin receptor-like kinase (ALK1). [20] One to two percent of cases [127] have mutations in *SMAD4,* mutations that also cause the gastrointestinal epithelial precancerous state of juvenile polyposis. [11] There are at least two further unidentified genes that can cause

pure HHT, *HHT3* between 141.9-146.4Mb on chromosome 5q, [128,129] and *HHT4* on chromosome 7p between *D7S2252* and *D7S510.* [130]

More than 600 different mutations have been found in *ENG* and *ACVRL1* in HHT families ([21], summarised in [3]). Mutations range from single basepair changes to whole gene (and neighbouring gene) deletions. [131] In keeping with the longevity of patients bearing heterozygous disease-causing mutations, haplotype analyses of *ACVRL1* mutations suggest recurrent mutational events occurred 100 to 550 years ago. [8] While founder effects were also demonstrated, particularly for the *ACVRL1* c.1112dupG mutation proposed to originate in a single inhabitant of the Haut-Jura mountains, again the original [21] mutation is estimated to have occurred more than 300 years ago. [8] However, worldwide, neither *ENG* nor *ACVRL1* displays a common mutation with the number of reports of each mutation corresponding to first order decay kinetics [132], and mutations occur throughout the genomic sequences. [21 3] The situation may be somewhat different for *SMAD4*, when 25% of mutations appear to arise *de novo.* [127] There were previous reports that *SMAD4* mutations in HHT tended to cluster in part of the gene encoding the MH2 domain, but a recent more extensive study has shown HHT-causing mutations also occur in other parts of *SMAD4.* [127] As would be expected for a disease gene frequency of 1 in 5,000, there are occasional families in which two proven HHT mutations co-segregate. [122]

Individual series describe *ENG* or *ACVRL1* predominance. [22-27] It is not known whether these reflect genuine geographical variation, or the clinical referral practice of the relevant HHT centres, since there are differences in patterns of HHT between families with HHT1, HHT2, and JPHT (see below).

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2.2.b) Genotype phenotype correlations

All classical features of HHT can be seen in both HHT1 and HHT2, but the prevalence of specific vascular abnormalities varies according to genotype. Pulmonary AVMs are more common in HHT1 than HHT2, [22-27] though in the relatively small number of *SMAD4* patients described, the prevalence of PAVMs may be higher still. [127] HHT1 patients are also more commonly affected by cerebral AVMs, [23-26] and by microscopic intrapulmonary shunting. In one series, positive contrast echocardiography reflecting intrapulmonary shunting was found in 85% of HHT1 patients, and 35% of HHT2 patients [52] compared to 7% of a control normal population. [47] Patients with HHT2 have a higher prevalence of hepatic AVMs, [23,25-27] and of severe disease due to hepatic AVMs [27,70]. A single series suggests HHT2 patients may have more pancreatic AVMs [9], and develop dermal telangiectasia earlier than in HHT1. [104] There are no clear data to suggest that specific mutations within a particular HHT gene confer different HHT-related phenotypes.

More recently described non-Curaçao features of HHT demonstrate stronger genotype-phenotype correlations. Juvenile polyposis (JP) occurs in patients with *SMAD4* mutations, when it appears to be indistinguishable from JP caused by *BMPRIA* mutations. In man (but not in mouse [133]), pulmonary arterial hypertension occurs predominantly and possibly exclusively within HHT2 patients [102,134,135], when it may have a worse prognosis than when due to *BMPR2* mutations [102]. HHT2 patients are also at higher risk of post capillary pulmonary hypertension associated with hepatic AVMs. [12-16]

2.2.c) TGF-β superfamily signalling

The genes mutated in HHT encode proteins that mediate signalling by the transforming growth factor (TGF)-ß superfamily (Fig 4). Superfamily ligands such as TGF-ßs, bone morphogenetic proteins (BMPs) , activins, nodals, growth/differentiation factors (GDFs) and inhibins normally regulate diverse cellular functions [136] by binding to a heteromeric complex of type I and type II transmembrane serine/threonine kinase receptors. There are structural and functional differences between the receptors belonging to the TGF-β and BMP groupings. For BMP receptors, which have relatively low affinity for ligand, receptor complex formation is enhanced by membrane colocalisation, and results in graded responses over wide ligand concentration ranges. [137] The TGF-β branch of the superfamily is hypothesised to have arisen more recently due to two evolutionary modifications in the type II and type I receptor, resulting in a co-operative assembly mechanism permitting a more switch-like mechanism: The type II receptor with very high ligand affinity, co-operatively recruits and transphosphorylates the type I receptor by direct contact to the ligand-modified N-terminus of TßRI [137]. In Smad-dependent pathways, the type I receptor subsequently phosphorylates and activates receptor associated (R)-Smads, according to the receptor complex employed. R-Smads bind to Smad4 and translocate to the nucleus where they influence transcriptional activation with co-activators and co-repressors. Negative feedback loops for these pathways include inhibitory Smads (Smad6/7) which target R-Smads for degradation. Cross talk with other signal transduction pathways also occurs [138,139].

The HHT mutations suggest that endoglin, ALK-1, and Smad4 are components of a common signal transduction pathway that is perturbed in HHT pathogenesis. Endoglin is a relatively endothelial specific co-receptor for multiple receptor complexes of the TGF-ß superfamily

[140,141]. ALK-1 represents an endothelial -specific type I receptor which structurally and mechanistically belongs to the BMP branch of type I receptors [137]. ALK-1 can associate with at least two type II receptors, BMPR2, and TβRII [142]. In turn, TβRII can associate with two different TGF-ß type I receptors in endothelial cells (TßRI [also known as ALK-5], or ALK-1), activating different Smad pathways, and apparently resulting in opposing endothelial cell responses in terms of proliferation, migration, and pro or anti-angiogenic gene expression. [143-147] Different levels of TGF-β1 may activate TβRI/ALK-5 and ALK-1 differentially [143], in keeping with the alternate types of receptor complex assembly. [137]

Recent HHT concepts include the “balance hypothesis" whereby the HHT mutations modify the predominant endothelial TGF-ß type I receptor, Smad pathway, and ultimately endothelial cell response, [144-147] and models incorporating BMP9 and BMP10 which are specific ALK-1 ligands that can also bind endoglin [148-150]. The most recent models indicate a return to TGF-ß1 rather than BMP9/10 causality in HHT [31]. Which ligand-receptor complexes contribute to HHT pathogenesis however, remains the subject of intense research [151,152]. This is likely to be clarified as other HHT disease genes are identified.

2.2.d) Generation of abnormal vessels in HHT

The gene mutations indicate that aberrant endoglin, ALK-1, or Smad4 signalling is responsible for HHT. Transgenic mice confirm that the mutations cause HHT, since some mice carrying one normal and one null copy of the respective gene (i.e. *endoglin*$^{+/-}$ *or ACVRL1* $^{+/-}$ heterozygote mice) display features of HHT [151,153-155].

The context in which these gene mutations are deleterious, when functioning apparently perfectly well for most vessels, has always proved tantalising. The somewhat simplistic concept of a somatic 'second hit' [156] whereby the remaining allele was lost in a clone of cells has always seemed unlikely in view of the multiplicity of telangiectatic foci, and evidence that AVMs in HHT1 patients still express the same level of endoglin (approximately one half normal) as the normal endothelial cells in the same HHT1 patient [97,157]. Large scale studies have not been presented, but it is currently believed that in most if not all cases, HHT results from endoglin or ALK-1 haploinsufficiency, that is that the remaining wild type allele is unable to contribute sufficient protein for normal function. Nevertheless, since even within HHT affected vascular beds, the vast majority of vessels appear to develop and function normally, perturbation of a context-dependent effect of endoglin or ALK-1 due to haploinsufficiency was required. Suggestions that wound healing or angiogenesis might be the extra trigger are not new [123], but articles written as recently as 2008-9 left the reader unclear as to how this, and the intra-individual and intra-familial variation, could be explained [132].

Within the last year however, animal models have allowed a clearer dissection of the mechanisms by which *ENG* and *ACVRL1* mutations may lead to the abnormal vasculature in HHT. These models have employed classical null mice (described for *Eng* and *Acvrl1* with embryonic homozygous lethality between E10.5-11.5 [153,158-160]); heterozygous mice which developed variable but more HHT-specific features including nosebleeds, telangiectasia, dilated vessels and AVMs [151,153-155] and in some ways represent the most appropriate model for human HHT [161]; endothelial cell specific knock outs [162]; and mice bearing conditional LoxP knockout alleles that for ALK-1 result in a model in which HHT-like vascular malformations occurred in a consistent and predictable manner [151]. As in man [90], murine

AVMs display venous type wall structures,[28,153,158,159,160] and venous molecular signatures. [30,163,164]

The latest data suggest that HHT mutations may be deleterious predominantly during some forms of angiogenesis, with specific effects on the stability of newly formed vascular sprouts. During angiogenesis, brief periods of endothelial cell activation, proliferation and migration are co-ordinated with controlled detachment of the surrounding mural cells (pericytes or smooth muscle cells), proteolytic remodelling of the basement membrane and extracellular matrix, and expression of endothelial cell survival factors. Pro-angiogenic factors such as vascular endothelial growth factor (VEGF/VEGF-A) differentially regulate defined subpopulations of endothelial cells in the angiogenic sprout, independently controlling endothelial migration at specialised tip cells, and proliferation in the stalk [165]. Mural cells are then recruited to stabilise the nascent blood vessels, [166] with TGF-ß1 strongly implicated in this stabilisation process. [167]

Key current concepts for the generation of AVMs and HHT telangiectasia are:

- Development of AVMs particularly occurs following activation of quiescent endothelial cells for example by wounding [28] and/or angiogenesis. [28 31 30]
- In the setting of HHT and an angiogenesis stimulus, there is excessive proliferation of endothelial cells, [30,146,147] excessive sprouting of vessels, [30,31,146] with attendant formation of AVMs in $Eng^{+/-}$ [30], and ALK-1 deficient [28] mice.
- HHT mutations (endoglin and ALK-1) impair recruitment of mural cells to vessels, [160,164] at least in part via reduced endothelial cell secretion of TGF-ß1 [168,169] and/or reduced TGF-ß1 induced responses. [160,168] Endogenous Smad phosphorylation in

mural cells is reduced, [168] but can be restored by exogenously administered ligand [168], implying a possible shift in thresholds for receptor activation.

- Vascular bed specificity of HHT vessel formation may reflect differential basal expression levels of endoglin and ALK-1; [170] dynamic down-regulation of endoglin or ALK-1, for example in the setting of inflammation; [171,172] different requirements for angiogenesis; [28] and/or differential generation of reactive oxygen species provoking vascular injury: Endoglin associates with the eNOS/hsp 90 complex [173]: In $Eng^{+/-}$ mice, eNOS activity is uncoupled, increasing eNOS dependent generation of reactive oxygen species. [29,173]

Support for a fundamental role for aberrant angiogenesis and reactive oxygen species in HHT disease pathogenesis is accumulating in man, with case reports and small series suggesting that anti-angiogenic and anti-oxidant strategies may be of therapeutic benefit in HHT (see Sections 4 and 5 below).

2.3) Haemorrhage, haemodynamics and iron handling considerations

The abnormal HHT vessels in HHT are prone to bleeding because of their inadequate wall structures, and high perfusion pressures.[90,174] Acute haemorrhage may be fatal or life-changing if the haemorrhage is sufficiently large to lead to acute haemodynamic compromise; occurs into an enclosed space such as from cerebral AVMs; or prevents essential organ function (for example pulmonary AVM bleeding compromising gas exchange). While these events can occur in HHT, much more commonly, more modest haemorrhage occurs into the relatively open spaces of the nasal cavity/nostrils/atmosphere, or gastrointestinal tract. Such

bleeds are better tolerated acutely, and compensatory mechanisms to replace the lost blood via bone marrow release of reticulocytes and enhanced haemoglobin synthesis should occur.

Chronic haemorrhage, however, depletes the body's intracellular iron stores. Treatment of iron deficiency represents a major component of HHT management, and it is worth briefly reviewing some of the newer regulatory insights. Normally most of the daily requirement for iron is met from recycled haem-derived iron through intracellular pool sequestration/release: When iron deficient, low portal vein concentrations of transferrin-bound iron (Fig 5) downregulate hepatic synthesis of hepcidin (HAMP) reducing internalisation and degradation of ferroportin, the sole cellular iron exporter present on all cells, resulting in its increased concentration as well as increased export of iron from duodenal enterocytes, and thus increasing gut absorption and export of iron from reticuloendothelial storage compartments. Where these routes are insufficient to replace iron lost via haemorrhage, iron deficiency will result. Sequelae include not only reduced synthesis of haemoglobin (Hb) resulting in anaemia and compromised tissue oxygen delivery, but also perturbation of many iron dependent cellular pathways.

2.4) Thrombosis and HHT

Age-specific data using a recently developed and validated nose bleed scoring system [33] are awaited, but for now, it does appear that epistaxis severity does not increase with age to the same degree as the presence of mucocutaneous telangiectasia (Fig 2). In contrast, complications from thromboembolic complications of HHT show clear age-dependent increases, [17,34] as in the general population. [175,176] 6-7% of HHT patients have pathological thromboemboli. [17,177] It seems likely, therefore, that symptoms from the increasing number of telangiectases with age are partly off-set by age-related increases in prothrombotic states.

2.5) Scientific approach to treatment modalities

While sections 4 and 5 present a clinical approach to HHT treatments, Table 2 presents a more scientific approach to possible therapeutic options, based on our current understanding of the molecular and cellular basis of HHT.

2.5.1) Bevazicimub and anti-angiogenesis strategies:

Bevazicimub (Avastin, Genentech Inc., San Francisco, CA) is a recombinant full-length humanized antibody active against all isoforms of VEGF-A, isoforms that play differing and non-overlapping roles in the induction and patterning of angiogenesis [185]. Bevazicimub was introduced into HHT because of a chance observation in a patient with HHT undergoing treatment for malignancy. [178] Plasma levels of VEGF had been noted to be increased in HHT [186], and associated with increased microvascular density in HHT [187]. A subsequent brief report of a patient whose hepatic AVMs initially responded [77] has been widely cited, and led to substantial interest from patients, though caution was expressed immediately. [78] Topical approaches are being used to reduce the serious complications associated with systemic treatments, though data from intraocular therapies indicate systemic side effects may still need to be considered. [185]

5.4.2) Thalidomide – targeting the mural cells?

Thalidomide emerged as a possible anti-angiogenic therapy with a series of Phase II clinical studies in cancer [188,189]. As for Bevazicimub, a chance observation in an HHT patient undergoing treatment for cancer [190] led to case reports [191] and a small series [31] indicating a

potential role in HHT. Recent mechanistic data indicate that thalidomide exhibits differential effects on immature blood vessel networks [192,193], and dose-dependent effects on angiogenesis are proposed [31]. Thalidomide appears to target mural cell recruitment, by increasing endothelial expression of PDGF-B at the endothelial tip cell thus facilitating recruitment of pericytes that express PDGFR-b, associated with increasing pericyte proliferation [31]. In HHT-specific studies, in an Eng $^{+/-}$ mouse model, thalidomide normalised excessive vessel sprouting in the retina [31]. In addition, in this mouse model in which vessels in the ear and skin displayed inadequate coverage by α-smooth muscle actin-containing mural cells, thalidomide rescued this defect without affecting overall vessel patterning, morphology, or density [31]. The excitement engendered by these new mechanistic insights has been accompanied by appropriate reminders of thalidomide's tragic history and toxicity. [193,194]

3) Management overview

Several helpful articles have been published in recent years guiding management practice. International HHT Guidelines published on line 12 months ago [32] were based on systematic assessments of the HHT publications up to October 2006. The 33 recommendations, representing the product of a fairly strenuous review process involving multiple experts, are a very helpful starting point for the field, and are presented in a separate column within Table 1.

The 2006-9 HHT evidence base including the American Heart Association and NICE statements on antibiotic prophylaxis [63,64] and HHT-specific responses were included within a 2009 review article [3] that also described the increasing spectrum of disease recognised within the HHT

umbrella. Within the last 12 months, in addition to the highly publicised reports on Bevazicimub and thalidomide, further evidence regarding hormonal manipulation in HHT, and other new clinical data have been presented. Clinical implications are discussed further below.

4) Diagnosis

4.1) Clinical diagnosis

The mainstay of diagnosis remain the Curaçao Criteria, international consensus diagnostic criteria developed between 1997-1999 [2] (Table 1), and recently validated [72]. An individual has a diagnosis of "definite HHT" if three criteria are present; "suspected HHT" if two are present, and "unlikely HHT" if only one is present. A crucial issue for families and medical practitioners, is that no child of a patient with HHT can be informed they do not have HHT, unless they have been shown not to have the specific known causative mutation in their affected family.

The criteria were developed in order to permit a high level of clinical suspicion without leading to overdiagnosis, given that nosebleeds (and certain telangiectasia) are common in the general population. The requirement for a third criterion means it is impossible to obtain a definite diagnosis of HHT without a more specific visceral feature or a family history. In clinical practice, where an individual from an HHT family has only one further criterion but that criterion is a visceral AVM, the diagnosis of HHT is essentially confirmed, though not for research purposes. Conversely, the estimated probability of HHT-affected status for an apparently unaffected child of an HHT-affected parent ranges from 0.5 at birth, to 0.22 at 16

years and 0.05 at 40 years [103,195,196], 'Possible HHT' is preferred for the medical records of such individuals when young. [3 32]

Haematologists will note that Von Willebrand's Disease (VWD) can cause diagnostic confusion. Like HHT, VWD is inherited as an autosomal dominant trait, frequently causes nosebleeds, and can be associated with mucocutaneous and gastrointestinal telangiectasia. Where individuals have three Curaçao criteria but there is no personal or family history of visceral AVMs, and no known HHT mutation, the author has found it helpful to retain the label "Suspected HHT" while investigating VWF status in the family.

4.2) Molecular diagnosis

Molecular diagnostic testing for HHT is available, with an updated list of laboratories offering gene testing provided by the HHT Foundation International (see http://hht.org/about-hht/genetic-testing/). Mutations detected are available at [21], and have been summarised recently. [3 132] Gene testing can confirm the HHT diagnosis for the family, and confirm or refute the diagnosis in individual family members. For patients with definite clinical HHT, molecular testing is not required to 'confirm' their diagnosis, and at present, does not modify recommended management except in the rare setting of *SMAD4* mutations, often suspected from the clinical and family history (see below). Mutations are not found in approximately 15-20% of HHT families [24,197,198]: this should not affect a clinical diagnosis of HHT. Genetic testing is most helpful in the setting of a potentially unaffected family member in whom the diagnosis of HHT cannot be excluded clinically, particularly if the individual is a parent or grandparent whose status determines the at-risk status for future generations. In this setting, identification of a much older affected relative with 'less to lose' from having a positive gene test may be helpful.

An estimated 10-20% of families have genetic variants of uncertain significance, with the potential to lead to misdiagnosis [199,200]. In part, this reflects the fact that the majority of mutations are unique to particular families. Furthermore, a high proportion, particularly in the *ACVRL1/ALK-1* gene, are single base pair changes predicting an amino acid substitution which may not be pathogenic. This is likely to become an even greater problem as next generation sequencing technologies are applied to the promoter and intronic sequences of HHT genes. For potential missense mutations, predictions of the severity of amino acid substitutions using SIFT [201,202] or Polyphen [203] are generally employed, but these can provide disparate results [200]. To define a novel missense sequence variant as an HHT disease gene, one laboratory requires co-segregation studies that indicate an 8:1 likelihood ratio that the sequence variant is associated with disease in the family, in addition to amino acid substitution evidence. [200]

The recent international guidelines recommended gene testing for adults and children with possible HHT, at an 80% level of agreement. [32] In the era of ready access to commercial DNA testing, it is important to interpret this statement within the prevailing ethos regarding genetic testing. The consequences of a genetic test differ according to national regulatory frameworks. In the US, it is only since the 2008 Genetic Information Nondiscrimination Act (GINA), that limitations have been placed on the use of genetic information by health insurers and employers. In the UK, the Government and the Association of British Insurers agreed on a moratorium on the use of genetic test results in insurance, and it is unclear whether a positive DNA test for HHT would lead to additional or even prohibitive weighting when the moratorium on gene testing is withdrawn. The UK Genetic Testing Network (UKGTN) recommends an informed discussion with the at-risk individual, before allowing them to decide whether, on balance, a gene test would be in their best interests. They also stress that special consideration is needed in children, with the UK Clinical Genetics Society (in their 1994 guidelines) advising that in the absence of anticipated medical benefit, or likely onset of disease during childhood, formal genetic testing

should generally be deferred to allow the "children" to consider the issues for themselves as autonomous adults. HHT should not differ from general paediatric recommendations, so the updated Clinical Genetics Society Paediatric DNA testing recommendations will be of great interest.

4.3) Screening

4.3.1) General principles

Screening means testing people who consider themselves well in relation to the disease that the screening relates to, and where the stated or implied purpose is either to reduce the risk of future ill-health for that individual, or, where risk cannot be altered, to give information about risk that is considered valuable [83]. Screening is not the same as investigating a problem or symptom, such as breathlessness, or anaemia. In the setting of HHT, screening refers to testing a member of an HHT family (who may or may not be symptomatic for other aspects of HHT) for the presence of silent disease such as AVMs in the lungs, liver, or brain.

Due to technological advances, imaging-based screening can identify most important vascular abnormalities present in an individual. This does not necessarily mean that individual was going to have a problem from the abnormal vessel/AVM, or if they were to have a complication, that it could be prevented. The medical justification for screening regimes in asymptomatic individuals from the HHT population depend upon detailed risk-benefit evaluations which are performed to determine whether the detection and treatment of an asymptomatic vascular abnormality is likely to carry overall health benefits for the patient. These considerations are recognised to centre on the degree of danger posed by particular silent lesions, the safety/tolerability of the screening

method; the safety and efficacy of any treatments, and the overall potential advantage offered to the recipient in terms of better management. [3]

Important general screening concepts have been articulated in recent publications [82,83]. These include the four possible outcomes if an abnormality is found by screening, and treated, and the tendency of potential recipients to consider only some of the potential outcomes (Table 3) [83]. This provides an explanation as to why screening programmes are inherently more attractive to patient populations than to clinicians.

Also detailed, [83] is an explanation of the origin of the differing philosophies regarding screening in different countries. Countries in which the general population has, for decades, been screened with annual or periodic checks have a greater acceptance of screening programmes and attendant investigations by medical professions, the public, and insurance companies. [82,83] In turn, such general population screening programmes reduce the potential harm from medicalisation of specific populations unused to regular medical checks. Recommendations for intensive screening programmes derived in such a healthcare culture may be neither appropriate, nor affordable, for other healthcare systems.

4.3.2) Screening programmes in HHT

Pulmonary: Based on evidence of long term technical efficacy and improvement in oxygenation achieved by embolization, and the potential for stroke reduction, pulmonary screening has been recommended for all patients with possible or confirmed HHT [204 1 93,205 32,100]. More recent data demonstrate that PAVM embolization does reduce stroke risk [34], and highlight that the majority of PAVM patients are undiagnosed at the time of their PAVM-induced ischaemic stroke (66.7%) or cerebral abscess (64.3%) [34], emphasising the importance of

robust PAVM screening programmes in the HHT population. While new data also draw attention to very rare complications of embolization [206207], and occasional circumstances in which it may not be appropriate to embolise PAVMs [55,62], generally the balance of risks and benefits remains strongly in favour of screening and subsequent treatment. The recommendation of first line use of contrast echocardiography (Table 1 [32]) may be modified as a result of recent data [47,49]; [51] [50] [48], particularly the study of [52] showing that 85% of HHT1 patients have a positive contrast echocardiogram. [52] This clearly has important financial implications as a large proportion of these patients will have microscopic disease which is currently not amenable to treatment. Alternative strategies based on CT scans have been proposed, [34,52] and detailed considerations are provided elsewhere [66,105]

Hepatic: Screening for hepatic AVMs was recommended to assist the diagnosis of HHT when there were fewer than 3 diagnostic criteria, and genetics tests were unhelpful. [32] Recent data, however, indicate that this does not improve the diagnosis of HHT [72] but there may be new indications for Doppler studies in ALK-1/HHT2 families in whom prediction of individuals at greater risk of high output cardiac failure (based on hepatic artery diameter and presence of regenerative nodular hyperplasia) could lead to different follow up regimes. [70]

Cerebral: The recent International Guidelines recommended screening adults (77% agreement) and children (64% agreement) with possible or definite HHT by cerebral MR, followed by referral to centres with neurovascular expertise for consideration of invasive imaging and consideration of treatment. [32] These recommendations were made recognising that there was no evidence of treatment effectiveness for asymptomatic individuals; that asymptomatic AVMs discovered during screening of HHT may carry a more favorable progress than symptomatic

AVMs; and the not inconsiderable risks of diagnostic tests (0.5% risk of permanent stroke per diagnostic angiogram) [32].

Such conclusions were not reached by all authors of large data series [88,208] and remain controversial, not least because neurovascular treatment centres are acutely conscious of the risks and limitations of treatment modalities. Recent treatment data series for nidus AVM by embolization, [68] stereotactic radiotherapy [209], and microsurgery [210] confirm the frequent need for multimodality treatments as utilised in specific centres, each with its attendant risks. [211] Issues regarding communication of expectations, treatment programme duration and limitations, and life style adjustments have been recently presented from the patient's perspective, [69] and are clearly highly challenging even to individuals who have already had a haemorrhagic stroke and represent a particularly high risk group for a future bleed. [69]

Wide-scale screening programmes will raise these issues for high proportions of screened individuals, since cerebral vascular malformations may be present in up 22.8% of patients [212,213], with high flow AVMs in 3.7-11% [88,212,213]. We find that even where an asymptomatic individual is in a higher risk group (having a family history of cerebral haemorrhage) for whom our group suggest MRI scans based on the advice from the late Prof Pierre Lasjaunias, [55,208] the decision to undergo this study is not straightforward.

Children: The international guidelines recommend screening children from HHT families for CVMs (64% agreement) and PAVMs (children not considered separately to adults). [32] There are clearly tragic cases of HHT-related deaths and disability in youngsters, {Easey, 2003 #2715; Krings, 2005 #3707; Krings, 2005 #3707; Curie, 2007 #3445; Cullen, 2006 #3706} [81 34,79] and children with symptoms require investigation, and treatments guided by knowledge of HHT pathology.

For pulmonary AVMs, the guidelines [32] and subsequent recommendations [216] appear to be predominantly based on symptomatic children in series derived from a specialist paediatric centre. As previously presented, [34] based on the paucity of evidence for childhood complications from silent PAVMs in previously healthy children, our group do not see sufficient indication to conduct a formal screen before the time of peri-pubertal PAVM growth and maturation, and resolution of the ethical, familial, and radiation issues that influence paediatric discussions. [34 3]

While the 64% agreement highlights the level of controversy surrounding the recommendation for cerebral screening in childhood [32], the issue needs to be considered carefully. The reason is that a particularly high risk cerebral vascular abnormality has been identified in children from HHT families. 34 cases of AV fistulae (spinal or cerebral) were identified in one European referral centre's 15 year experience. [68] All except two cases, occurred in children aged less than 7 years old [67,208](Fig 6), suggesting the possibility that few individuals survive the presence of these lesions (Pierre Lasjaunias, personal communication 2007). In contrast, typical (nidus type) macroAVM and microAVM presented in older ages (Fig 6). Other groups have also demonstrated AVFs in childhood HHT series [157]. For AVF in children, however, interventional risks were high. In the Bicêtre series of 31 children who were usually highly symptomatic, treatment related risks included 6.5% mortality and 6.5% new permanent neurological deficit. [68] The complete occlusion rate was 38.7% of survivors [68] although symptomatic benefit resulted from partial treatment. [68]

Extrapolating these data to asymptomatic children in HHT families is extremely difficult. All parents will hope that a screening scan will not detect a vascular malformation in their child and may restrict their considerations of some of the possible outcome (Table 3, [83]). Many

however, will have to face the possibility of treatments for a child that appears currently well; treatments aimed at reducing the likelihood of complications for which there are very few data in asymptomatic children; and treatments that carry substantial mortality and morbidity, yet may not achieve the complete occlusion desired. [69] In this delicate and emotionally charged area of uncertainty, public health policy and prevailing population backgrounds can lead to substantially different interpretations of risk benefit considerations for and by the individual. For health care systems where the current evidence base would not support the introduction of screening programmes, this author proposes that an appropriate way forward would be to seek further data through research-orientated studies, pending country-specific guidance from paediatric-based groupings.

5) Treatment

5.1 AVMs

Details of the treatment of each type of AVM are beyond the scope of this text: the interested reader is referred to the references in Table 1, and recent treatment texts for general aspects of HHT [3 32] and AVMs in cerebral [68209 210 211], pulmonary [59,60,66,105], and hepatic circulations [73,74].

5.2) Management of iron deficiency anaemia

In this chronic condition, it is essential to reserve treatments carrying higher risk, for patients with the most severe disease. Maximal attention to local therapy and iron replacement manoeuvres discussed below are required, potentially with stratification according to ongoing transfusion requirements [217], before proceeding to consideration of second line, or experimental therapies (Table 4)..

5.2.1.Epistaxis and gastrointestinal bleeding:

Conventional management of iron deficiency anaemia leads to referral to gastroenterologists for endoscopic therapy, and this is also encouraged with HHT [110], noting the limitations of endoscopic treatments [218], and recommendations for a limited number of therapy sessions. [32] Before referring to a gastroenterologist, however, a careful history of nose bleeds is warranted: A recent study of 915 HHT-affected individuals indicated that a severity score based on presence of anaemia and need for transfusion in addition to four other independent factors (nose bleed frequency; duration; gushing or pouring quality; or the need for medical attention) was a significant predictor of invasiveness of therapy required for nosebleeds [33]. These data, together with the new evidence that nosebleed frequency correlates with iron and transfusional need (Fig 2), highlight the need to obtain good ENT-based reviews of anaemic patients, for specialist ENT treatments as outlined in Table 1.

5.2.2 Anaemia:

It is unusual to be able to abolish nasal and gastrointestinal bleeding in HHT. Prevention and management of anaemia becomes paramount in at least a third of HHT patients. Dietary advice for iron containing foods, and identification of oral iron preparations that suit the individual are important steps to reduce the need or frequency of blood transfusions or iron infusions required by severely affected individuals. Unfortunately, it remains commonplace to find patients receiving intravenous iron or transfusions with minimal or no attention to oral iron intake. Dietary iron sheets are available on line, [219 220] and patients should seek to meet more than the recommended dietary allowance of iron. Where high dose iron tablets are not tolerated due to gastrointestinal side effects, lower dose regimes using small volume syrups or 'prophylactic dose' iron are preferable to no added oral intake.

5.2.3 Hormonal manipulation:

To date, the only randomised placebo-controlled trials to demonstrate benefit in prevention of HHT haemorrhage have involved hormonal manipulation in the form of oestrogen-progesterone [46], and tamoxifen [46] (Table 4). The high dose oestrogen-progesterone regime is poorly tolerated particularly in men, and there are increasing concerns about thrombotic side effect profiles. More recently, a double-blind, placebo-controlled trial of the anti-oestrogen tamoxifen [46] demonstrated a significant reduction in the frequency of epistaxis in the treated group, accompanied in many cases by either a rise in haemoglobin or reduction in transfusion requirements. There are good long term safety data for the use of tamoxifen in prevention of breast cancer, though there is concern regarding endometrial hyperplasia, a problem that may be reduced by the raloxifene, a selective estrogen receptor modulator for which there are also new data regarding beneficial effects in HHT [45].

5.3.4 Antifibrinolytics and prothrombotic agents

Therapeutic manipulation of coagulation and fibrinolytic pathways is often employed to try to limit blood loss in HHT [41,42,181,182]. These therapies have not yet been supported by data from randomized controlled trials. Recognition that venous thromboses occur in HHT, associated in many cases with coincidental inheritance of prothrombotic genetic variants such as FV Leiden, has raised concern regarding thrombophilic risk with these agents. [17] It was therefore suggested that routine measurement of FVIII, FV Leiden, and other thrombophilic markers in HHT patient assessments may assist individualised risk-benefit considerations before prothrombogenic systemic treatments are given. [3,17]

5.3.5 Antioxidants

There are recent uncontrolled short term data demonstrating efficacy from oral N acetyl cysteine in a large series of 43 HHT patients [40] (Table 4). This specific drug is not currently licensed in many countries but in general, antioxidants have favourable side effect profiles during long term use.

5.3.6) Angiogenesis based- treatments

The eagerness to treat, and recognition that in rare diseases, a handful or even single cases of data merit high impact journal publication (Table 4), naturally encourages the exuberant use of agents whose potential roles compared to the best available existing treatments, and safety profiles are yet to be determined in HHT. Side effect profiles, and better understanding of the full implications of such treatments [78], are likely to be crucial in determining whether the use of any efficacious agents becomes more widespread within the HHT patient population.

For the currently available drugs, systemic treatment can result in serious adverse events: Frequent and unpredictable side effects for antiangiogenic strategies include thrombosis, haemorrhage, decreased wound healing, and organ perforation. [223] The most commonly reported Bevacizumab-related toxicities were bleeding/haemorrhage, hypertension, proteinuria, and venous or arterial thromboembolic events [224]. In addition, the British National Formulary emphasises the risks of gastrointestinal perforation and fistulas, and that treatment should be withheld before elective surgery and avoided for at least 28 days after major surgery or until the wound is fully healed [184]. Experience within HHT is too limited (Table 3) to address whether the resistance to VEGF-targeted therapy emerging in cancer settings will also occur during long term use in HHT [185]. For thalidomide, as for Bevazicimub, there are safety concerns in long term modulation of the angiogenic process so critical for normal wound healing, menses, and enterocyte and neural viability. Thromboprophylaxis is recommended for at least the first 5 months of treatment, especially in patients with additional thrombotic risk factors [184] and pregnancy must be avoided [184].

The identification of these agents' activities as targets in HHT is anticipated to lead to further and safer therapeutic options. For now, however, use of these agents should be restricted to their evaluation in carefully selected, consenting patients in randomised control trials currently recruiting within experienced HHT centres.

5.4) Non haemorrhagic settings in HHT

5.4.1) Deep venous thromboses- prophylaxis and treatment

In contrast to advice given to patients in earlier years, it is now well recognized that there are settings in which anticoagulants (and/or antiplatelet agents) are required [32] in order to prevent major ischaemic or thromboembolic sequelae. Prophylactic dose anticoagulation for example is required during high risk periods for venous thromboemboli (VTE)[17], particularly for HHT patients hospitalized with pulmonary AVM-induced brain abscess [17]. Where VTEs occur, treatment dose heparin and warfarin can be given. In our experience, anticoagulation is tolerated surprisingly well by many patients, though patients should understand that their nosebleeds are likely to get worse, and there may be concerns (none proven to date) about haemorrhage from internal organs. In our group's experience, long term prophylaxis or primary prevention strategies are more difficult to justify in the setting of HHT. [225]

5.4.2) The HHT patient with a stroke:

HHT-affected families should be aware that in the event of stroke-like features, their doctors may need to be alerted to their three potential stroke types (haemorrhagic, ischaemic and infective) , and that neurological symptoms in HHT, including stroke, are more likely to be due to

paradoxical embolization through pulmonary AVMs than to complications of cerebral vascular malformations. [34,87,88]

Modification of local stroke management protocols [226] may be required, including consideration of early MR imaging to assist the diagnosis of brain abscess. In the case of ischaemic stroke, while in our experience anti-platelets are tolerated surprisingly well by many patients, the likely presence of AVMs would be considered an absolute contraindication to thrombolysis were HHT to be recognised [227].

5.4.3) The pregnant HHT patient

Based on small series and case reports, many women were being advised pregnancy was too dangerous to contemplate, and vasectomies or terminations advised. A recent study of 484 pregnancies in 199 women with HHT and PAVMs demonstrated that that the majority were able to have a normal pregnancy [55]. That said, a small proportion of women did experience life-threatening complications including PAVM bleed; stroke; myocardial infarction and pulmonary embolus. In this series, 1.0% (95% confidence intervals 0.13, 1.9%) of pregnancies resulted in maternal and fetal death, with all deaths occurring in women previously considered well [55].

Importantly, in women experiencing a life-threatening event, prior awareness of HHT or PAVM diagnosis was associated with improved survival [55]. General recommendations for the management of women with HHT therefore include management as " high risk pregnancies"; maternal education to consider haemoptysis of any degree or sudden severe dyspnoea as a medical emergency prompting urgent hospitalization; and specific obstetric, and obstetric anaesthetic issues discussed in detail elsewhere [55].

5.4.4 Dental treatments

For patients with PAVMs and HHT, antibiotic prophylaxis prior to dental and surgical procedures was recommended, based on the endocarditis paradigm [228] [32]. The evidence for an association between oral microorganisms and brain abscess was strengthened further [34], but in the interim, the American Heart Association [63] and British NICE guidelines [64] were published indicating that antibiotic prophylaxis is no longer required for most patients with structural heart disease at risk of infective endocarditis, and leading to confusion for dentists and medical practitioners of HHT/PAVM patients. A subsequent article explored why PAVM/HHT patients do not fall into the groups considered by AHA/NICE, and provided recommendations to reduce the risk of dental bacteremias including the use of antibiotic prophylaxis prior to dental procedures [65].

5.4.5 Air flights

While there are theoretical concerns regarding in-flight exacerbation of hypoxaemia, and risk of venous thromboembolism, there are very limited published data in HHT. The author's experience is that individuals with significant PAVM-induced hypoxaemia have flown without seeking medical advice, and suffered no ill-effects. There are reports of ischaemic stroke [34] and deep venous thrombosis [17] occurring immediately after transatlantic flights. However two cases of in-flight PAVM haemorrhage (one haemoptysis, one haemothorax) have also been reported recently [229]. Further data on flight toleration in a large series of HHT patients will be available shortly (Mason and Shovlin, m/s in preparation) and should assist in providing an evidence base for recommendations.

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6) Perspective

For families with HHT, the recent advances in scientific and medical understanding of their condition are encouraging after the decades of limited advances. There are genuine hopes for improved and targeted treatment modalities, and emerging evidence that existing strategies are already offering affected individuals a better medical outlook than their grandparents.

Yet there are others for whom the deluge of new and frightening information holds concerns. As one attendee of the 2009 UK HHT Family Meeting confided, “It is not hard to foresee a time when the label of HHT is worse than the condition itself”. As clinicians and scientists seek to improve health outcomes in HHT, the voices of the HHT family members are the most important to be heard.

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TABLE 1

Curaçao Criteria	%	Diagnosis†	Potential Complications	Management recommendations in 2009 guidelines [32]	Data published post g/line development $
1) NOSEBLEEDS (EPISTAXIS)	90	Evident	Anaemia; massive acute haemorrhage	***Acute:*** First aid; packing (self + variety of commercial devices). ***Recurrent:*** Humidification, topical lubricants. 2nd: Laser therapy; 3rd : Surgery (esp. septal dermatoplasty; Youngs) by dedicated expert ENT surgeon (No role for arterial ligation/ embolisation)	**New validated severity scoring system** ([33]; see text). **High proportion without medical or ENT review** [33,34]. **New data**: **Surgery and embolization** [35-39], **medical treatments** [37,40-45]
2) TELANGIECTASIA Lips; oral cavity fingers; nose	80	Evident	Usually cosmetic, may haemorrhage		Tamoxifen RCT [46]
3) VISCERAL LESIONS, *such as* ***a) Gastrointestinal telangiectasia*** *(with or without bleeding)*	15-30	Endoscopy *(upper /lower)*	***Haemorrhage*** (chronic) ***Anaemia***	**Annual Hb or haematocrit screen over 35 ys. Oral or iv iron** first line for mild anaemia. **Consider systemic hormonal or antifibrinolytic** therapy in selected patients to limit GI blood loss . **One or two** endocopic treatments, but avoid multiple attempts.	**Thrombogenic** concerns in HHT published [17], also relevant to stated concern of thrombogenic risks of eythropoeitin [32] **See also new data from epistaxes medical treatments above.**
b) Pulmonary AVMs	50	CXR/CT Echo	***Most asymptopmatic*** ***R-L shunt:*** Hypoxaemia +/- dyspnoea; Stroke/ TIA* Brain abscess Migraine. Decompression illness; ***Haemorrhage*** Haemoptysis Haemothorax *rare except specific circumstances*	**Screen asymptomatic adults and children. Transthoracic contrast echocardiography as intital screening test. Embolization** for all adults with PAVMs, and symptomatic children, based on feeding artery generally 3mm or greater, though targeting of smaller PAVMs may be appropriate. To be performed in HHT center of excellence, particularly for higher risk states of pregnancy and mild-moderate pulmonary hypertension . **Surgery** only in management of life threatening bleeding. **Antibiotic prophylaxis** as per AHA recoemmendations for prevention of bacterial endocarditis **. IV air** through iv access, and **Scuba diving** to be avoided. (Life long since 90% of CEs remained positive post Rx ; also for HHT if PAVMs not excluded). **Long term follow up:** Post embolisation CT at 6-12 months then 3 yearly; small untreated, or CE positive, 1-5 yearly.	**New data on echo grading and predictive values** [47-51], and frequency of positive results [52]. **New natural history** data re stroke/brain abscess (risks independent of PAVMs size imply need to treat all PAVMs feasible [34]; migraines [53,54]; pregnancy rupture [55]. **New efficacy data** for embolization: prevention of stroke [56]; reduction in migraines [57]. **New recanalisation data** [57,58]. Technical improvements in embolisation treatment devices (Amplatzer devices [59,60]). **Further data on post embolization systemic arterial supply** without haemoptysis [61] ; **Embolization with pre-existing pulmonary hypertension** [16,62]). **Dental issues** AHA [63] and NICE Guidance [64], but reconsidered and Abs still recommended [65]. SCUBA diving: alternative to complete cessation discussed [66].

c) Cerebral vascular malformations ¶ AV fistulae (AVF) Macro (nidus type) AVM Micro AVM (<1cm) Capillary telangiectasia *Other forms can occur*	10-20	*MRI Angiography*	***Haemorrhage*** *depends on type: AVF>macro>micro≥tel.* For AVM (?0.5% per annum, i.e. lower than general pop[n]. ***Headache*** ***Epilepsy*** ***High output cardiac failure (paeds)***	**Screening** of asymptomatic individuals (children from 6 months or when reviewed) recommended. **Obliteration methods:** Variety possible (embolisation; microsurgery, sterotactic radiotherapy or combination), and no dedicated evidence for HHT population. Evidence from non HHT populations indicate varying effectiveness . All cause significant procedural risks, and management in expert centres with neurovascular experience advised. **If pregnant** and asymptomatic CAVM, defer treatment until after delivery.	**New pregnancy considerations** [55]. **Better appreciation of time of development in children** [67]. New data on HHT specific mortality/morbidity of treatments in children [68]. **New patient perspective** [69]
***d)* Hepatic vascular malformations** Hepatic artery – hep. vein Hepatic artery – portal vein Portal vein – hepatic vein	30-70	*Doppler US CT +/- invasive*	Most (>90%) asymptomatic[70] ***Hepatic AVMs:*** High cardiac output +/- failure; Post capillary pulm. hyp.; Focal nodular hyperplasia [71] ***Hepato-portal VMs:*** Portal hypertension (ascites; varices; encephalopathy) ***Porto-hepatic VMs*** Biliary ischaemia, encephalopathy	**Screening to facilitate diagnosis of HHT. Avoid liver biopsy** in suspected or proven HHT. **Avoid hepatic artery embolization** **Consider referral for liver transplantation** if ischaemic biliary necrosis; intractable heart failure; or intractable portal hypertension.	Hepatic AVM screen did not add to criteria [72]. **For more** detailed recommendations see [73]. **New data** on prevalence [70], association of enlarged hepatic artery and focal nodular hyperplasia (13%) with high cardiac index [70]; **Long term liver transplant effectiveness** [74,75], but evidence of recurrence in transplant [76]. **Bevazicimub** case report [77] but cautionary comments [78]
e) Spinal AVMs	<1%	*Spinal MRI*	***Haemorrhage;*** Paraplegia (acute, subacute or progressive) ***SOL*** *+/-* ***steal****:* Pain, asymmetric growth ***Progressive myelopathy*** in adults		**Further descriptions and case details in** [68] (7 cases presented symptomatically aged 1 month -6 ys [67]), and case reports + literature reviews [79] (2 cases), [80, 81]. **New pregnancy considerations** [55].

4) FAMILY HISTORY

Legend: The four separate Curaçao criteria are spontaneous recurrent nosebleeds; mucocutaneous telangiectasia (multiple at characteristic sites: fingertip pulps, lips, oral mucosa, tongue); Visceral involvement such as gastrointestinal involvement; pulmonary, hepatic, cerebral or spinal AVM; and a first degree relative affected according to these criteria. $ Also see new data regarding general screening [82 83], and radiation sensitivity in children [84 85,86]. Other viscera affected include pancreatic telangiectasia (31%) and AVMs (11%) of 35 consecutive adult HHT patients screened (no relevant symptoms) by contrast enhanced multidetector CT [9]; with case reports for other viscera. * Neurological symptoms in HHT are more likely to be due to pulmonary than cerebral vascular malformations [34,87,88]

Table 2: Potential HHT Therapeutic Strategies

Potential strategy	***Comment***
A) Targeting the vessel	
1. Correction, or partial correction of the gene defect in endoglin, ALK-1 or Smad4:	Substantial difficulties for a finely tuned system with exquisite dynamic regulation at incompletely understood timepoints
2. Targeting the stimulus precipitating an abnormal vascular response a) Direct anti-angiogenesis strategies b) Indirect, identifying and reversing the triggers precipitating angiogenesis c) Indirect, reducing the triggers precipitating vascular damage, such as oxidant stress, or aberrant immune responses.	a) Bevazicimub: (anti-VEGF monoclonal Ab.) [178] [77] b) Trauma? Inflammation? Note chronic infection in non-HHT settings precipitates exuberant formation of aberrant bronchial vessels [105] c) N-acetyl cysteine (NAC) [40] and interferon [179,180]
3. Allow defective signalling and stimulus, but promote a corrective response to the TGF-β deficient state in mural cells	Mechanism proposed for thalidomide [31]. Note at higher doses, thalidomide acts as an inhibitor of angiogenesis.
4. Obliteration or removal of vessels once formed	a) Laser therapy for telangiectasia; b) Embolization of pulmonary/ cerebral AVMs c) Surgical resection (esp. cerebral AVMs); d) Organ transplantation (esp. hepatic AVMs)
B) Targeting haemorrhage	
5. Prevention of excessive haemorrhage with prothrombotic strategies	Antifibrinolytic agents, such as local or systemic tranexamic acid [41,181] and aminocaproic acid [182].
6. Combination approaches- Hormonal treatments a) high dose oestrogen-progesterone RCT [183] b) anti-oestrogen tamoxifen: RCT [46] c) selective oestrogen receptor modulator (SERM) raloxifene [45]	Incompletely understood mechanisms. Likely to include prothrombogenic effects (noting pathological thromboemboli recognised side effect of all agents [184]) . Possibly direct modulation of endothelial cell and vascular function. [45]
7. Treat iron deficiency anaemia	See text
C) Targeting other complications in selected patients 8. Circumstance specific, e.g. a) Pregnancy [55] b) Dental treatments: post AHA/NICE [63] [64] guidance for HHT/PAVM patients [65]. 9. Pathology-specific, e.g. c) Venous thromboemboli – see text d) Antiplatelet therapy for standard indications (ischaemic stroke, ischaemic heart disease, paradoxical atrial fibrillation etc.)- see text	a) ***Pregnancy***: HHT-specific management in view of life-threatening haemorrhagic and thrombotic events, and improved survival with prior awareness of HHT or PAVM diagnosis [55]. b) ***Dental:*** PAVM/HHT patients do not fall into the groups considered by the AHA [63] or NICE [64]. Recent guidance included improving dental hygiene and the use of antibiotic prophylaxis prior to dental procedures [65].

Legend: RCT, randomised control trial. Conventional treatments within Group A focus on option 4, and within Group B on option 7, with randomised control trial evidence for option 6 (hormonal treatment). Options 2 and 3 remain experimental and are currently dependent on the use of highly toxic agents. The author is unaware of any plans to attempt option 1.

Table 3: The 4 possible outcomes of screening for the individual

	Benefit	**No benefit ***
No harm	**a**. Screening and treatment help. No side effects or harm	**b.** Screening and treatment no help. No side effects or harm
Harm	**c**. Screening and treatment help, but side effects or harm	**d.** Screening and treatment no help, but side effects or harm

Legend: Adapted from table in reference [83]. * In the setting of these discussions, the AVM was never going to cause that individual a problem. As described in [83], individuals want to be in group a), realise they might be in groups b) or c), and try to ignore the chance that they personally will be in group d). Clinicians are more likely to include the possibility of d) in their evaluations. To minimise harm, it was advised that balanced information should be provided to all potential recipients to ensure that they understand the benefits without overlooking the potential negative aspects of the screening/treatment programme. [83]

Table 4 Summary of new trials reporting benefit from new HHT treatments

Treatment	*N=*	*Comparison group*	**Comment**
A) Randomised control trials in HHT			
Tamoxifen [46]	10 vs 11	untreated controls	previous RCT evidence for hormones in GI bleeding (50 mcg of ethinylestradiol plus 1 mg norethisterone) [183] but not epistaxes [221]
B) Observational			
i) ENT procedures ¥			
Septodermatoplasty[35];	301	KTP laser alone	
Fibrin sealant nasal packing [36]	64	KTP laser alone	
Argon plasma laser [37]	43		
Embolization [38]	12		
Septectomy [39]	9		
ii) Medical agents			
N- acetyl cysteine (NAC) [40]	43	None	Prospective
Tranexamic acid [41]	14	None	Prospective
[42]	10	None	Retrospective
Thalidomide* [31]	7	None	
Avastin (bevazicimub)			
Systemic [77]	1 liver case		See follow up cautionary comments [78]
Topical [43]	10 vs 9		topical as adjunct to KTP laser
[44]	1		Topical
Raloxifen [45] 2nd generation selective estradiol receptor antagonist	19		*In vitro*, stimulated endoglin and ALK-1 promoter activity, increased protein expression and modified EC function

§ post HHT Guidelines evaluation; *¥/ observational studies where N<5 not reported. * Case reports included* [222] [191]

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FIGURE LEGENDS

Figure 1: Circulatory sites of vessels commonly affected by HHT

Schematic of systemic and pulmonary circulations indicating vascular beds commonly affected by HHT. Red arrows denote AVMs. PV denotes portal vein. The pulmonary circulation indicates pulmonary AVMs, and distinguishes sites of pulmonary arterial (PAH), and post capillary (PCPH) pulmonary hypertension. The hepatic and portal circulations indicate the 3 anatomical forms of aberrant hepatic vascular communications: 1: hepatic artery to hepatic vein (arteriovenous, associated with high output states and PCPH), 2: hepato-portal (hepatic artery to portal vein, associated with portal hypertension), and 3, porto-venous (portal vein to hepatic vein). Note that conventional hypertension, i.e. the blood pressure in systemic arteries, does not relate to either pulmonary or portal hypertension.

Figure 2: Cross section of epistaxis in an HHT population:

Maximum nosebleed severity described by HHT/PAVM patients in [34], a population without an ENT ascertainment bias. **a):** Cumulative frequency diagrams of nosebleeds and diagnostic telangiectasia. Red solid line: age of onset of nose bleeds as described by patient 'pre school'; child; teenager; and adult ages. Black dotted line: prevalence of nosebleeds at age groups: Note the lower prevalence in adults as nosebleeds regressed in 14% of affected children and teenagers. Blue telangiectatic line represents survival curve modelling based on the presence of diagnostic telangiectasia at particular ages when PAVMs were diagnosed (defined by physician). **b):** Maximum nosebleed severity indicating % of population (bars) and actual numbers per group. **c):** Maximum nosebleed severity data reported in different age quartiles. Note that in contrast to the prevalence of skin and mucosal telangiectasia in a, there is no clear increase in number of patients reporting nosebleeds in these more severe categories with age. **d):** Use of iron supplements (bars) and transfusions (triangles) stratified by nosebleed severity. Note more frequent nosebleeds associated with a higher use of iron ($p=0.002$).

Figure 3: HHT and the spectrum of genetic disease

HHT is a monogenic disease and lies at the right hand of the spectrum. Nevertheless, HHT, or a particular characteristic of HHT in an affected individual may depend upon other genes or environmental factors influencing the phenotype. Originally published as Fig 1.30 in [125].

Figure 4: TGF-β superfamily signalling

Adapted from original figure published in [128]

Figure 5: Iron homeostasis

Most of the 20mg daily requirement for iron is met from recycled haem-derived iron, and not intestinal absorption. Both processes are regulated by hepcidin (HAMP), a hormone synthesised predominantly in the liver that induces internalisation and degradation of ferroportin, the sole cellular iron exporter present on all cells. Iron not incorporated into proteins is complexed into non-toxic transport or storage protein aggregates, with transferrin ($Fe\bullet Tf$; $Fe_2\bullet Tf$) in serum, and ferritin ($Fe_{>100}\bullet$ferritin) in cells.

Figure 6 Age at presentation of the four different encountered cerebral vascular abnormalities in HHT.

Presentation ages are represented on a logarithmic scale, with black diamonds representing the mean age of presentation. [67] (Needs permission).

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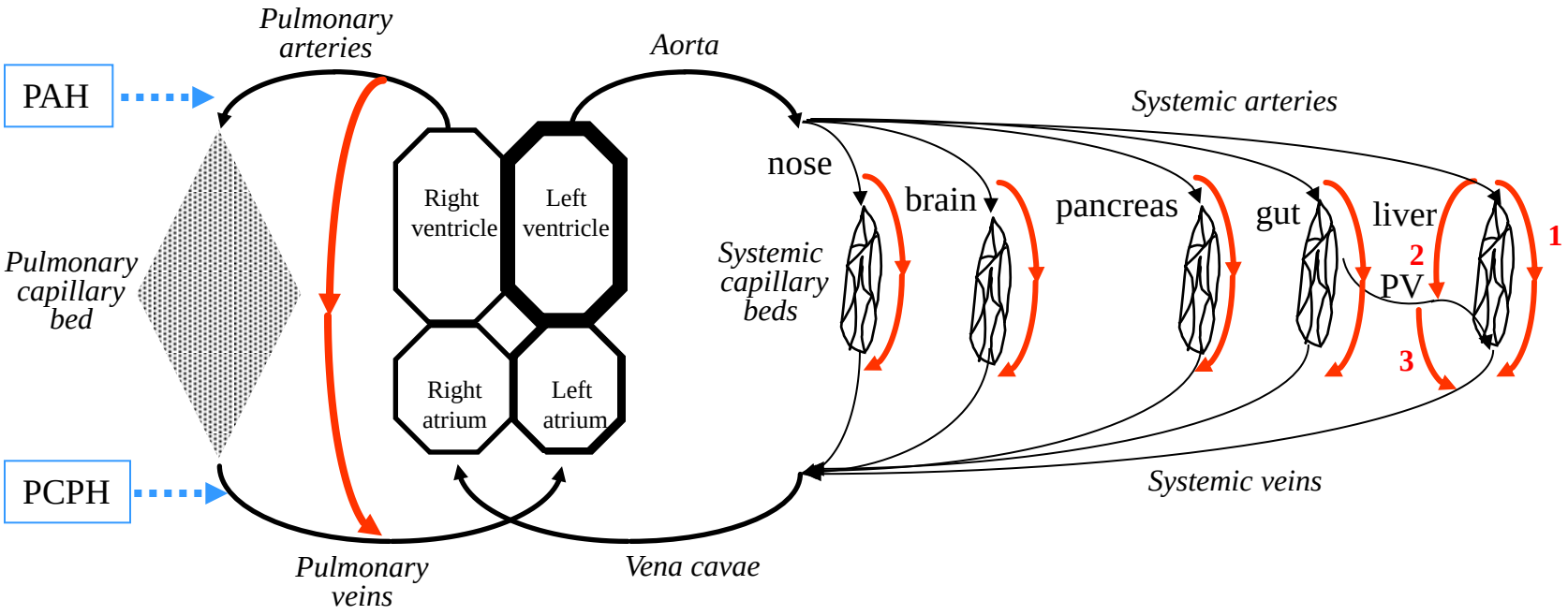
Figure 1



Shovlin CL. Blood Reviews 2010

Figure 2

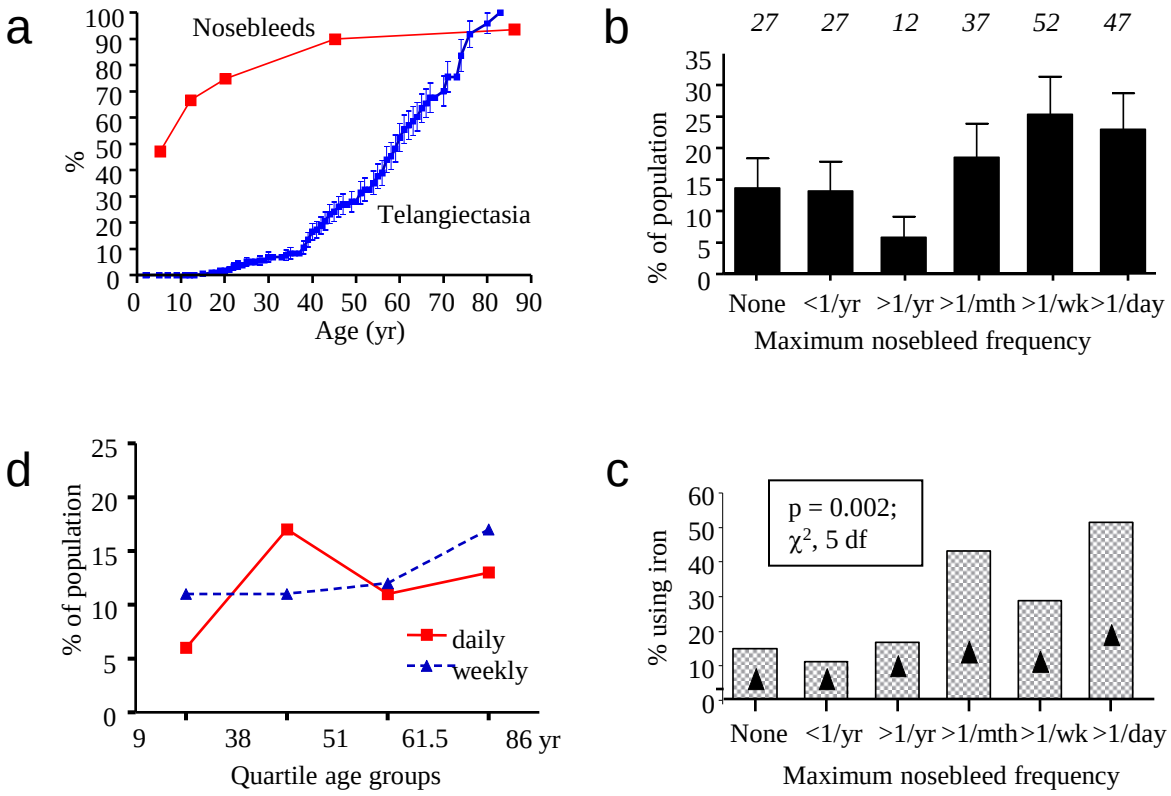


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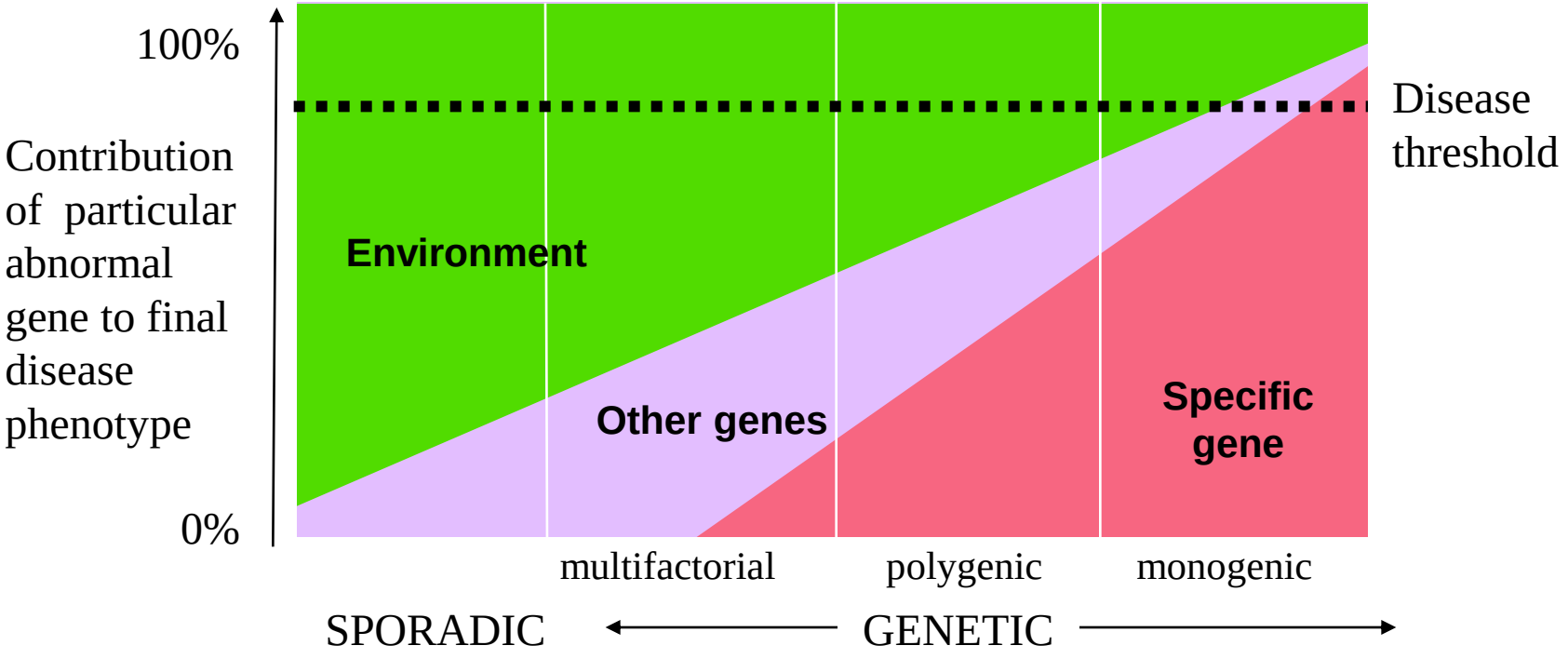
Figure 3



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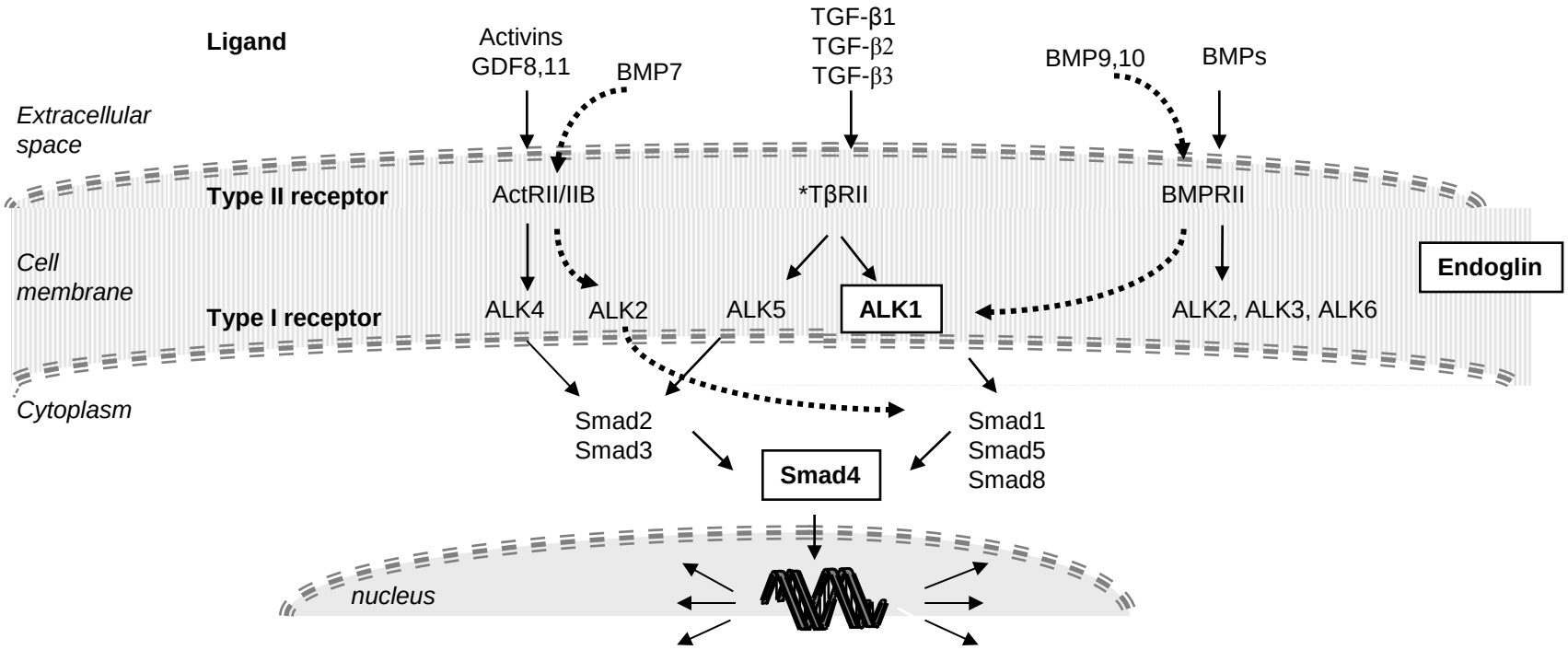

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Figure 5

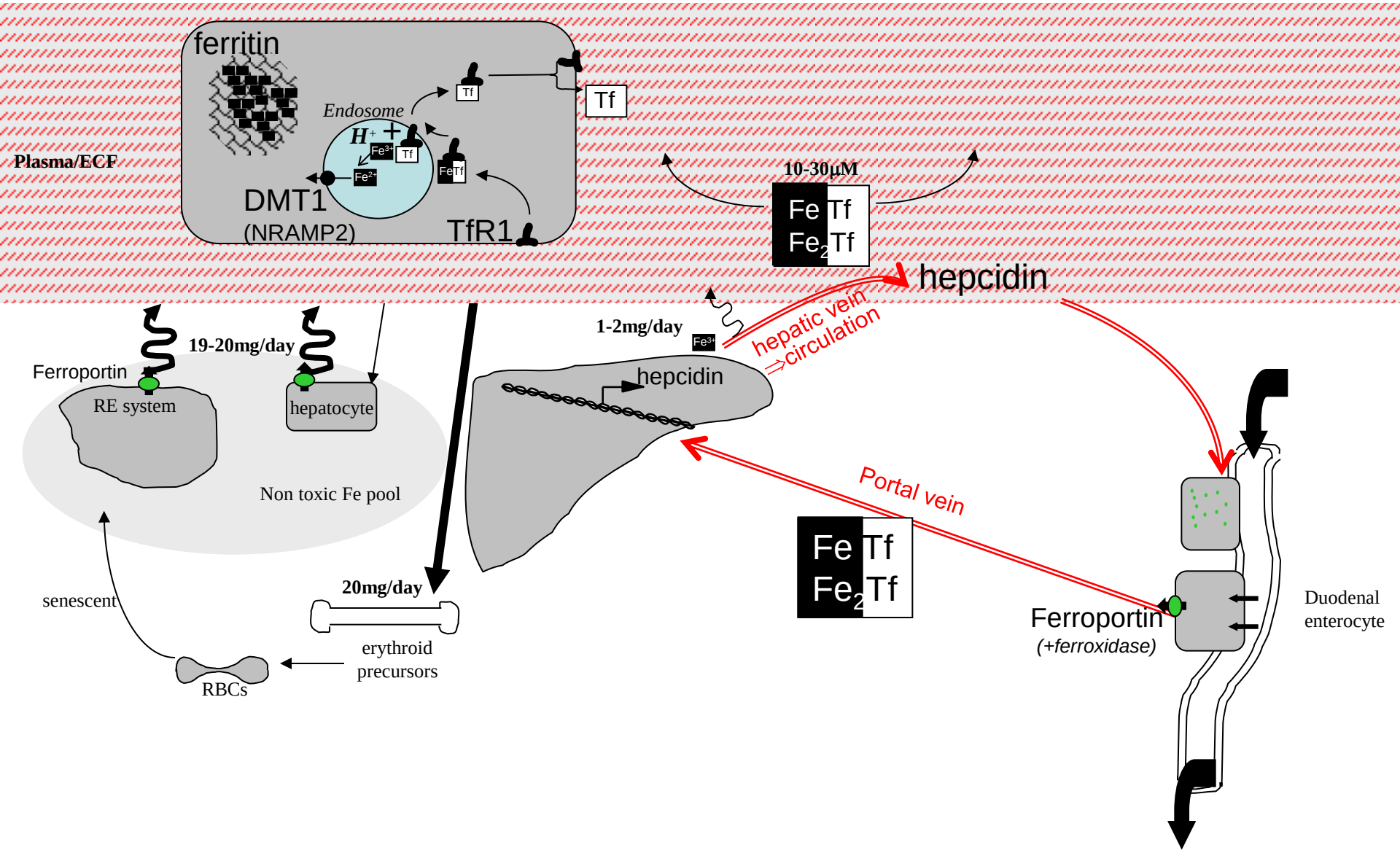

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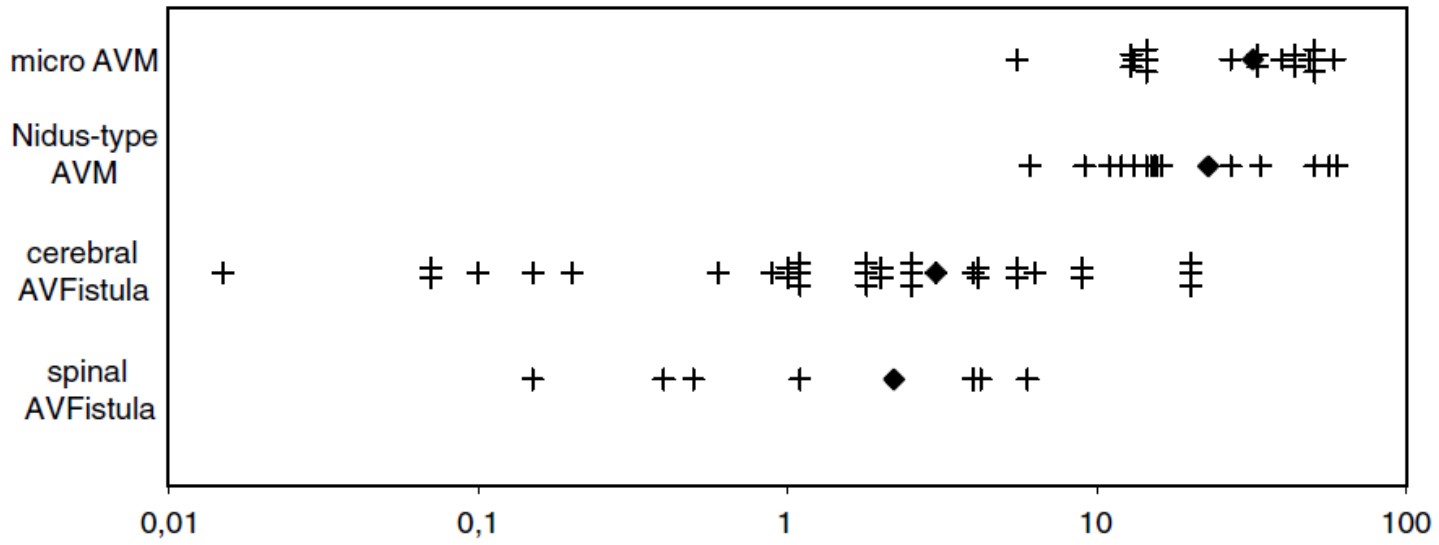
Figure 6



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