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Impact of the introduction of a guideline on the targeted detection of hereditary haemochromatosis

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ABSTRACT

Background: In 1998 a clinical guideline for the targeted, accurate and early detection and treatment of HFE-related hereditary haemochromatosis (HH), which comprises a test for the causative HFE-gene mutations, was introduced in our outpatient department.

Methods: The impact of this guideline was evaluated retrospectively. Data were acquired from medical records of patients with discharge diagnosis codes suggestive of HH (n=878 patients), obtained from a period before (n=422) and after guideline introduction (n=456).

Results: Combined measurements of serum transferrin saturation and serum ferritin rose from 12.2% (n=53) to 29.5% (n=138, p<0.001), leaving 70% of the patients eligible for HH not tested for iron parameters. The HFE-gene mutation detection test was correctly used in 11 (40.7%) of 27 tested patients and improperly interpreted in six (22.2%) of these 27 patients. Five new HH patients were diagnosed before and 13 after introduction. Seven of these 13 patients appeared to be incorrectly diagnosed, due to misinterpretation of laboratory results. Diagnostic costs of case detection for each accurately diagnosed patient were € 2380 before and € 2600 after introduction of the guideline.

Conclusion: Evaluation of the introduction of a practical guideline for targeted HH detection reveals a low compliance with the guideline, resulting in both a small percentage of patients tested for HH and overdiagnosis of HH. Therefore, the introduction of the guideline should be combined with a more appropriate implementation strategy which includes education on its most critical points, i.e. the indication and interpretation of the iron parameters and the HFE genotype.

KEYWORDS

Genetic testing, guideline adherence, haemochromatosis, practice guideline, serum iron measurements

INTRODUCTION

The medical and scientific interest in HFE-related hereditary haemochromatosis (HH), iron overload disease, quickly expanded after the discovery of the causative C282Y and H63D mutations in the haemochromatosis (HFE) gene in 1996.¹ The C282Y mutation is now the most common autosomal recessive mutation in people of northern European descent, with an estimated prevalence of the genetic susceptibility for HH by homozygous C282Y mutation of one in 200 to 250 persons.²³ Symptoms that can be attributed to iron overload are fatigue, arthralgia and cardiac rhythm disorders.⁴⁻⁶ Furthermore, diabetes mellitus, elevated liver enzymes, liver cirrhosis, hepatocellular carcinoma and cardiac failure can be considered as signs of HH,⁵⁻⁷ the last three being the most common cause of death in untreated HH patients.⁸⁻¹⁰

The first step in the diagnosis of HH consists of the recognition that these symptoms and signs in combination with persistent elevated serum transferrin saturations and elevated serum ferritin concentrations may be attributed to HH, especially when these laboratory values remain unexplained.⁴⁻⁵⁻⁹⁻¹⁰ The diagnosis of HH is confirmed by the presence of homozygosity for the C282Y mutation, by compound heterozygosity for the C282Y and H63D mutation in the HFE gene and by iron overload shown in a liver biopsy, on exclusion of secondary causes of iron overload.
HH patients have a normal life expectancy.11,12 Therefore, the development of irreversible symptoms and damage, the local situation.8,11,16-20 The guideline was introduced expert opinion were translated into a guideline suitable for clinical chemistry. International evidence-based studies and rheumatology, clinical genetics, gastroenterology and departments of general internal medicine, haematology, group. This group consisted of physicians from the hospital by a multidisciplinary haemochromatosis study in a patient presented with signs or symptoms as described and contained recommendations to screen for HH when the multifaceted guideline was introduced in 1998 (figure 1). The guideline was developed in our university hospital in 1998 by a multidisciplinary haemochromatosis study group.

In the present study we aimed to evaluate retrospectively i) physicians’ compliance with the diagnostic procedures, ii) the number of detected HH patients, iii) the correctness of the HH diagnoses, and iv) costs per detected patient, during a two-year period before and after introduction of the clinical guideline.

METHOIDS

The multidisciplinary guideline was introduced in 1998 and contained recommendations to screen for HH when a patient presented with signs or symptoms as described in figure 1. The guideline was developed in our university hospital by a multidisciplinary haemochromatosis study group. This group consisted of physicians from the departments of general internal medicine, haematology, rheumatology, clinical genetics, gastroenterology and clinical chemistry. International evidence-based studies and expert opinion were translated into a guideline suitable for the local situation.5,10-20 The guideline was introduced and explained during sessions held in the outpatient department of internal medicine of our university medical hospital. After its introduction, the guideline was available on the intranet of our hospital server.

According to the guideline, HH was diagnosed in symptomatic patients when the serum transferrin saturation was above 50% on at least two different occasions (one of which after overnight fasting), in combination with a serum ferritin concentration at least twice the upper limit of the normal value of 280 μg/l. For the diagnosis of HH it was recommended to exclude other factors that are known to influence the iron parameters, such as blood transfusions, iron supplementation, haemolytic anaemia, (alcoholic) hepatitis, non-HH-related liver disease and acute or chronic infections. Thus, a correctly diagnosed HH patient was defined as a patient with an elevation of both serum iron parameters in the absence of concomitant factors that influence iron parameters. After detection of the biochemical iron overload, the guideline recommended testing for the C282Y and H63D mutation in the HFE gene to determine whether the patient had an HFE-related form of HH (figure 1). Genetic testing was also recommended for first-degree relatives of a symptomatic HFE-related HH proband. Liver biopsy was advised when a persistently elevated of both iron parameters was combined with a serum alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) concentration more than twice the normal value, to either exclude concomitant liver pathology or to obtain a prognosis for the condition of the iron overloaded liver. When either HFE genotype (C282Y homozygosity and C282Y/H63D compound heterozygosity) or liver biopsy confirmed the diagnosis of HH, family screening and treatment was recommended (figure 1). The latter consisted of phlebotomy therapy in two phases. The first phase of weekly phlebotomies was meant to withdraw iron from the overloaded tissues, the second phase, of two to eight phlebotomies a year, to maintain a low body iron level. For first-degree relatives who appeared to be C282Y homozygous or C282Y/H63D compound heterozygous and had not yet developed iron overload, a phlebotomy schedule consisting of two blood donations a year, similar to that used for regular blood donors, was recommended (figure 1).

We retrospectively compared the diagnostic procedures for patients with features suggestive of HH who visited the outpatient department of internal medicine between a period before (January 1995 to December 1996) and after (May 2000 to April 2002) introduction of the guideline. The choice of the latter period allowed sufficient time for uptake of the novel procedures from the 1998 guideline, whereas the first period was chosen before the discovery of the HFE-gene mutation.

Patients

Patients were selected for evaluation by using discharge diagnosis codes (classification system ICD-9-CM-codes).21 Some patients received more than one diagnosis code. The discharge codes included were ‘unexplained chronic fatigue for more than six months’, ‘elevated liver enzymes or liver cirrhosis without explanation’, ‘unexplained arthralgia’, ‘diabetes mellitus’, ‘hereditary haemochromatosis’ or ‘iron metabolism disorders’ and ‘porphyria cutanea tarda’.
Inclusion of diabetes mellitus patients was restricted to patients with concomitant elevation of liver enzymes (more than twice the upper limit of the reference value). Excluded were diabetes mellitus type 1 patients under the age of 35, patients suffering from chronic viral hepatitis, chronic alcohol abuse at the time of the study, cholestatic pathology and HH patients diagnosed with iron overload HH elsewhere. By means of an inventory form the following data were extracted from the medical records: serum transferrin saturation, serum ferritin concentration, HFE-mutation analysis, liver biopsy, HH diagnosis and the presence of co-factors that might result in falsely elevated iron parameters (such as blood transfusions, iron supplementation, haemolytic anaemia, (alcoholic) hepatitis, acute or chronic infections, hepatic injury and end-stage liver disease).

Compliance and statistics
Compliance of the physicians with the guideline was calculated by (number of guideline items followed)/items followed + items not followed) x 100%. These items consisted of serum transferrin saturation, serum ferritin concentration, HFE-gene testing and liver biopsy. For the period before guideline introduction the same items, except the HFE-gene testing, were scored. Differences in diagnosis codes, gender, age and compliance scored before and after guideline introduction were tested for significance using a \( \chi^2 \) test.

Costs
The impact of the guideline introduction on resource utilisation was assessed, taking into account direct medical costs only. The costs for diagnosing HH were approximated from laboratory costs (serum transferrin saturation, serum ferritin and HFE-mutation detection) and the costs for ultrasound-guided liver biopsy, with one-day hospital stay. For unit cost prices, national rates were used as proxies of actual resource utilisation, except for hospitalisation, for which a standard cost price was used. \(^{22}\) Volumes of tests used were derived from chart review. Costs per case of correctly diagnosed HH patients were calculated and expressed in Euros.

**RESULTS**

**Patient selection and characteristics**
During the two observation periods, a total of 9096 individual patients visited the outpatient department of internal medicine, providing us with a total of 456 patients from the period after guideline introduction (table 1). In addition, 16 patients could not be
included as their medical records were missing; four from the period before and 12 from the period after guideline introduction (table 1).

Of the patients, 352 (40%) were male; 177 (41.9%) in the group before and 175 (38.4%) after guideline introduction (table 2). Overall, 561 (63.8%) of the patients were 50 years of age or older (table 2).

Diagnostic accuracy

Serum iron parameters

In the period before guideline introduction, serum transferrin saturation was measured in 29.7% (n=129) of all diagnosis codes. After introduction of the guideline, this percentage rose to 36.8% (n=172, p<0.05) (table 3). The serum ferritin measurements were performed in 17.3% (n=75) of the patients before and in 71.8% (n=336, p<0.001) after introduction. This significant rise in serum ferritin measurements was observed for patients from all diagnosis codes, except for those with ‘liver cirrhosis of unknown origin’. There was a pronounced rise in serum ferritin measurements for the diagnosis codes of ‘chronic fatigue of unknown origin’ (from 10.9% (n=32) before to 74.7% (n=245, p<0.001) after), ‘diabetes mellitus with elevated liver enzymes’ (from 18.0% (n=11) before to 44.9%...
After (n=22, p<0.01) and ‘elevated liver enzymes of unknown origin’ (from 29.6% (n=8) before to 73.1% (n=38, p<0.01) after). The hallmark test for the diagnosis of HH, i.e. the combination of serum transferrin saturation and serum ferritin measurement, also increased with guideline introduction from 12.2% (n=53) in the period before to 29.5% (n=138, p<0.001) in the period after guideline introduction. This rise in combined measurement of serum transferrin saturation and serum ferritin concentration was significant for all diagnosis codes, except for the small groups of patients diagnosed with ‘arthralgia of unknown origin’ and ‘liver cirrhosis of unknown origin’. For all the discharge codes the absolute number of serum transferrin saturation measurements was comparable with the absolute number of serum ferritin measurements after guideline introduction. Only the ‘chronic fatigue of unknown origin’ defined group showed a striking difference between the two measurements: 87 serum transferrin saturation measurements vs 245 serum ferritin measurements in the period after guideline introduction.

HFE-mutation analysis

HFE-gene mutation analyses were performed in 27 patients after protocol introduction (table 4). According to the guideline, HFE testing was recommended for only 11 (40.7%) of these 27 patients (numbers 1-11); nine of them had a combination of elevated serum transferrin saturation and elevated serum ferritin concentration and two of them were screened within the framework of family screening. In six of these 11 patients the clinical diagnosis HH could be confirmed on follow-up, since both iron parameters remained elevated and no other explanation to account for these elevated levels was found (table 4). One of them had a non-HFE-related form of HH, confirmed by the amount of iron withdrawn by phlebotomy to obtain normal serum iron parameters (number 6). In three of these 11 patients the HH diagnosis could not be confirmed (numbers 7-9): one patient’s liver biopsy contained no iron, one patient’s serum transferrin saturation returned to normal levels when measured on a second occasion and one patient had normal transferrin saturation levels, which alternated with high transferrin saturation levels upon blood transfusion. The physicians were correct not to diagnose HH in these three patients. The two patients who were HFE-gene tested in the context of family screening (numbers 10 and 11) were falsely diagnosed as iron overloaded and treated as HH patients. The guideline recommended follow-up of these patients and to phlebotomise them only twice a year. The remaining 16 (of the 27) HFE-tested patients should not have been tested following the guideline, since only one of the two serum iron parameters was elevated. Moreover, five of these 16 patients (numbers 12-16) were incorrectly diagnosed with HH by the physicians, for some of them most likely based on their HFE-gene genotype only.

Three patients were not tested for HFE-gene mutations in the period after guideline introduction despite their combination of elevated serum iron parameters. In two of these three patients serum iron parameters appeared to be temporarily influenced by blood transfusions. The remaining patient underwent a liver biopsy to exclude liver pathology. This liver biopsy revealed no iron.

Liver biopsy

Liver biopsies were taken for 60 diagnosis codes, representing 53 patients, 26 (49.1%) before and 27 (50.9%) after guideline introduction. In 49 of these 53 patients, the decision to perform a liver biopsy was based on a suspicion of concomitant liver disease. In four of these 53 patients, liver biopsy was performed in the absence of elevated liver enzymes or (probable) liver disease. Three of these four patients underwent liver biopsy before guideline introduction and the availability of the HFE-gene test. All three patients had elevated serum transferrin saturations (>50%) and serum ferritin levels (>280 μg/l). The presence of an increased amount of iron in their liver biopsy (diagnosed by an independent pathologist)

| Table 3 Diagnostic test use for serum iron parameters before and after guideline introduction |
|-----------------------------------------------|-----------------|
| Serum iron parameters                         | Before implementation | After implementation |
|                                              | Before implementation | After implementation |
|                                              | n          | %         | n          | %         | p<0.001* |
| Serum transferrin saturation                  | 129        | 29.7      | 172        | 36.8      | p<0.05*  |
| Serum ferritin concentration                  | 75         | 17.3      | 336        | 71.8      | p<0.001* |
| Combination of serum TS and serum ferritin concentration | 53         | 12.2      | 138        | 29.5      | p<0.001* |

Diagnostic test use is expressed as the percentage of the total number of diagnosis codes included in that period. Data are obtained from the medical records. Both the serum transferrin saturation and the serum ferritin concentration were scored no more than once per diagnosis code.

*Significance of difference in increase in serum iron parameter(s) between the periods before and after implementation of the guideline. TS = transferrin concentration.
confirmed the diagnosis HH. The remaining fourth patient underwent his biopsy after guideline introduction in the presence of an elevated serum transferrin saturation and in the absence of an increased serum ferritin level. The liver biopsy revealed no increased amount of iron and HH was correctly excluded.

**Number of detected patients**

The introduction of the guideline led to an increase in diagnoses of HH, from five patients (1.2%) before to 13 patients (2.9%) after introduction of the guideline (table 4). This increase, however, was not statistically significant.

Phlebotomy treatment was started for all 18 patients. The physicians’ diagnoses of iron overload appeared to be incorrect for seven of the 13 patients, as at least one of the serum iron parameters was not elevated (patients 10-16, table 4). Three of these patients were at risk of developing iron overload based on their C282Y homozygosity, but had not yet developed iron overload as their ferritin levels were normal (patients 10-12). All three were females and aged 41, 45 and 55 years, respectively. There was no over-diagnosis of HH before guideline introduction. In total, we found one case of a missed HH diagnosis (patient 33, table 4). In this patient, included in the group

Table 4 Characteristics of patients in whom HFE-gene analysis was performed or who were diagnosed with hereditary haemochromatosis according to the physicians or the guideline

<table>
<thead>
<tr>
<th>Patient</th>
<th>Evaluation period</th>
<th>Serum iron parameters</th>
<th>HFE gene mutations</th>
<th>Liver biopsy</th>
<th>HH diagnosis</th>
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<tr>
<td></td>
<td></td>
<td>Transferrin saturation ≥50%</td>
<td>Ferritin ≥280 μg/l</td>
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<td>H63D</td>
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<tr>
<td>1</td>
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<td>6</td>
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<td>-</td>
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<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>After</td>
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<td>+</td>
<td>Heterozygous</td>
<td>Negative</td>
</tr>
<tr>
<td>8</td>
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<td>+</td>
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<td>10-11</td>
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<td>-</td>
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<td>-</td>
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<tr>
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<td>After</td>
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<td>+</td>
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<td>Homozygous</td>
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<td>+</td>
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<tr>
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<td>n.a</td>
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</table>

Hereditary haemochromatosis (HH) diagnoses according to the physician: diagnoses of iron overload based on clinical grounds and treatment started for HH. HH diagnoses according to the guideline: HH diagnoses that should have been given according to the guideline. Before = period before guideline implementation; after = period after guideline implementation. A = Transferrin saturation <50% or serum ferritin <280 μg/l; = transferrin saturation ≥50% or serum ferritin ≥280 μg/l. ; = No HH diagnosed; + HH diagnosed. Non-HFE related HH. Serum transferrin saturation that normalised when measured on a second occasion. Patient was a first-degree relative of an HFE-gene-related HH patient. HH diagnoses confirmed with either liver biopsy or number of phlebotomies. n.d. = not determined; n.a. = not available; Perls = Perls’ staining, Prussian blue reaction used to detect iron in a liver biopsy.
before guideline introduction, the diagnosis of HH was only made postmortem, on autopsy. During life, the diagnosis of liver cirrhosis of unknown origin had been made. No iron parameters had been measured. For nine patients with a combination of an elevated serum transferrin saturation and serum ferritin, HH was not diagnosed. Three of these patients were included in the period before and six patients were included in the period after guideline introduction. One patient from the first period was diagnosed with porphyria cutanea tarda and transferred to another hospital before further diagnosis and treatment could take place. For all the remaining eight patients the diagnosis of HH was correctly excluded either based on clinical evidence (blood transfusions recently given or spontaneous normalization of iron parameters), or by a liver biopsy containing no increased amount of iron.

Costs
The total cost associated with the detection of new HH patients before introduction of the guidelines amounted to € 11,900. After the introduction, these costs rose to € 15,600. When these costs were ascribed to patients correctly diagnosed with iron overload proven HH, this resulted in € 2380 per correctly diagnosed patient before and € 2600 per correctly diagnosed patient after introduction of the guideline.

DISCUSSION
The introduction of the guideline for targeted HFE-related HH detection in the outpatient department of general internal medicine of our university hospital in 1998 led to an increased number of patients with symptoms consistent with HH, who were tested for serum iron parameters (serum transferrin saturation and ferritin). The number of HH diagnoses rose when compared with a period before guideline introduction. This rise, however, was not statistically significant. A shortcoming of the introduction of the guideline was the increase in the number of patients falsely diagnosed with HH.

The increase in both serum transferrin saturation and serum ferritin measurements in the period after introduction of the guideline was likely to result from the guideline introduction. This increase might have been positively influenced by more recently (after 1998) introduced guidelines in the department of internal medicine, i.e. on ‘arthralgia’ and on ‘liver cirrhosis’, which incorporated the recommendations of the HH guideline of 1998. It should, however, be noted that despite these increased numbers of iron parameters measured after guideline introduction, still approximately 70% of the patients with symptoms and signs consistent with HH were not tested for these parameters.

There was a remarkable difference in the magnitude of the raise in serum transferrin saturation and in serum ferritin measurements in the diagnosis code group ‘chronic fatigue of unknown origin’ after guideline introduction. This could be explained by the implementation of a guideline on ‘chronic fatigue’ in the outpatient department in 1999, which recommended only the measurement of serum ferritin, not combined with serum transferrin saturation, to detect HH among patients with symptoms suggestive of chronic fatigue. Guideline compliance was also evaluated by the use of liver biopsies in the diagnosis of HH. According to the guideline, liver biopsies should be used to exclude additional liver pathology or to obtain a prognosis for the condition of the iron overloaded liver. Before the discovery of the HFE gene, liver biopsy was the gold standard for the confirmation of the diagnosis of hereditary iron overload. The compliance for the use of liver biopsies after the introduction of the guideline was good. Only one patient underwent a liver biopsy without elevation of both serum iron parameters or a possible liver disease.

The current study did not provide solid information on compliance with family screening for HH. However, the few notations made on this subject in the medical files suggested that physicians advised the proband to inform his or her family of the necessity of clinical, biochemical and/or genetic screening for HH.

Medical costs due to diagnostic procedures for each accurately diagnosed patient were similar before and after guideline introduction. However, these costs do not include costs due to incorrect diagnoses, i.e. patients in whom HH was missed or patients who were incorrectly diagnosed as having HH, nor do they include costs for treatment.

Compliance with the therapeutic aspects of the guideline was not thoroughly evaluated in the present study. However, it appeared that three homozygous C282Y patients of the 13 subjects diagnosed with HH were phlebotomised despite the absence of iron overload. For non-iron overloaded homozygous C282Y relatives of HH patients as well as for C282Y/H63D compound heterozygous relatives, the guideline recommended performing two blood donations twice a year as prevention. However, treatment of these non-iron overloaded patients is controversial and various treatment protocols have been proposed. Shortly after the discovery of the HFE gene, therapeutic protocols for these patients, such as the protocol described here, were based on the assumption of a high penetrance of the HFE-gene mutation and advised: i) performing phlebotomies several times a year to prevent iron accumulation, in order to maintain the serum ferritin level around 50 µg/l and ii) twice yearly blood donation, with control of the iron parameters once every three years.
be very low.9,29-32 But also, the fact that the diagnostic homozygosity for the evidence has accumulated that this penetrance of the ten to twenty years.24

A drawback of the guideline introduction was the incorrect diagnosis of iron overload for several patients after guideline introduction (n=7). This was mainly due to erroneous use and interpretation of the HFE genotype (n=6). It appeared that HFE testing was more often used than strictly indicated and that once the HFE gene was genotyped, it dominated the results of the serum iron parameters and the liver biopsy. This dominant use and overestimation of the value of the HFE genotype in the diagnostic process of HH might be attributed to misinterpretation of the huge amount of international literature since 1996 which suggested the clinical relevance of the C282Y mutation due to the high clinical penetrance.3,25-28 Only recently, evidence has accumulated that this penetrance of the homozygosity for the HFE-gene C282Y mutation might be very low.9,29-35 But also, the fact that the diagnostic strategy of the present guideline lacks solid scientific evidence on its most crucial points (similar to the strategies throughout literature)4,10,11,33,34 and is mainly based on professional expertise, might have decreased compliance.

While awaiting the calculation of the cost-effectivity of both population and cascade screening, most HH patients in the Netherlands are still detected by case detection, i.e. early detection of patients with HH who seek medical attention for symptoms suggestive of HH. According to a recent report by Cadet et al., this strategy of targeted HH detection has been proven to be cost-effective.35 Also the present study shows the potential cost-effectivity of targeted case detection in comparison with population screening as approximately one in 80 patients (1:84 (5 in 422) patients before, to 1:76 (6 in 457) patients after guideline introduction) have biochemical proven iron overload in comparison with one in 280 to one in 400 patients in the general population of northern European origin.36,37 A disadvantage of this targeted approach, however, is the potential diagnostic delay in the course of the disease.

There were some limitations inherent to the study. First of all it was a retrospective study. This implicated that we had to interpret the thoughts of the physicians on the differential diagnosis of their patients’ symptoms by looking at the diagnostic investigations performed on each patient. For example, we cannot be sure that every serum ferritin or serum transferrin saturation was performed in the light of HH diagnostics. Moreover, elevated iron levels might have been missed and with this also potential patients with HH, with a risk for organ damage and early death.24,26 It is not possible to give solid numbers for those patients not recognised as having HH in the current study. As 87.8% (n=381) of the diagnosis codes eligible for HH before and 70.5% (n=330) of these diagnosis codes after guideline introduction were not evaluated for serum iron parameters, there could have been a fair number of missed HH diagnoses. However, for all the patients who were tested for both their serum iron parameters, we conclude that no eligible HH patients were incorrectly judged as being healthy. This also implicates that when HH was not diagnosed, despite the elevation of both serum iron parameters, this was done on correct clinical grounds, taking into account concomitant treatment or diseases, as the guideline recommended. The second limitation was the lack of control group. Therefore, we cannot exclude that the rise in diagnostic procedures is explained by the increase in the number of physicians who adhered to a more ‘defensive’ kind of medicine by adding test and/or the general trend in time for an increased use of iron parameters (i.e. ferritin) in the last decade.

We conclude that due to a relatively low compliance to the guidelines: i) approximately 70% of the patients with symptoms and signs consistent for HH were not tested for serum iron parameters and consequently patients with HH might have been missed and on the other hand ii) indication and interpretation of the genetic and iron parameters were misunderstood with as a result overdiagnosis of HH. The reasons why physicians do not follow clinical practice guidelines have been described by several groups.38-40 One of them, Cabana et al., clearly reviewed and summarised the literature on this subject in 1999. This resulted in the recognition of a variety of barriers to guideline adherence, which include: i) knowledge (awareness, familiarity), ii) attitude (agreement, self-efficacy, outcome expectancy, ability to overcome the inertia of previous practice) and iii) external barriers to performing recommendations. We believe that in general these barriers all attributed partly to the less optimal compliance of the ‘haemochromatosis’ guideline. We expect the most critical points of misuse and interpretation of iron parameters and genetic tests, observed in the present study, can be removed by a more professional evidence-based development and dissemination of the guideline that is combined by an appropriate education strategy on its most decisive aspects. In fact this approach has been adopted by a multidisciplinary team of medical professionals in the Netherlands, which recently started to develop an evidence-based guideline under the auspices of the Medical Scientific Board of the Dutch Institute for Healthcare CBO, in close cooperation with the Order of Medical Specialists. These guidelines will be evidence based and formulated following strict regulations (www.cbo.nl). Attention will also be paid to applicability in daily routine and the implementation strategy. Also, this team may learn from the shortcomings from the present study. It is expected that implementation
of this guideline into medical practice throughout the Netherlands in around early 2007 will increase compliance with the guideline, also on the decisive points.

We summarise that the introduction of a guideline for a targeted approach to HH screening increased the number of diagnostic procedures appropriate for HH investigation. The number of detected HH patients increased non-significantly, at comparable costs per case detected, with a drawback of falsely positive HH diagnoses. The HH overdiagnoses reflected the difficulties in indication and interpretation of both serum iron parameters and HFE genotypes. Therefore, the implementation strategy of the guideline should be improved to increase awareness and guarantee compliance with the indication and interpretation of both the iron and genetic parameters.

NOTE

Annual Meeting of the Netherlands Association of Internal Medicine, April 2004, Maastricht, the Netherlands, abstract 37.

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