

SHOULD MULTIPLE ENDOCRINE NEOPLASIA BE AN INSURANCE PROBLEM OR NOT?

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ABSTRACT

We survey the relevant literature on Multiple Endocrine Neoplasia Type 2 (MEN2), an inherited form of cancers of the endocrine system that is one of the seven disorders listed as being potentially significant for insurance by the Association of British Insurers (ABI). Unlike some other disorders on the ABI's list, genetic screening of members of at-risk families is cheap and becoming widely available, and early surgical intervention is both tolerable and effective. The advent of genetic testing ought therefore to be wholly beneficial, and this should neutralise the risk MEN2 presents to life and critical illness insurers, even to the extent of reducing or removing the risk that was presented by a family history of MEN2 before genetic screening was possible. We suggest that the priority for the insurance industry is to ensure that underwriting practices do not deter persons at risk of MEN2 from undergoing screening.

KEYWORDS

Critical Illness Insurance; Life Insurance; Multiple Endocrine Neoplasia; RET Gene

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1. INTRODUCTION

1.1 *The Genetics and Insurance Debate*

The genetics and insurance debate has mostly concentrated on single-gene disorders, since these have the most serious implications. An early indication of this was the list of eight (later seven) single-gene disorders identified as being of potential significance for insurance by the Association of British Insurers (the ABI, ABI (1997)). Their common features included:

- (a) autosomal dominant inheritance;
- (b) the onset of symptoms delayed until adult ages;
- (c) a high probability that mutation carriers will develop the disorder; and
- (d) the availability of DNA-based tests for mutations in the causative genes.

In the United Kingdom, the Genetics and Insurance Committee (GAIC) was set up in 1999, by the Department of Health, to consider applications from insurers to be allowed to use specific genetic test results for underwriting. The subsequent history of GAIC has been convoluted; see Daykin *et al.* (2003), from which we extract two important facts:

- (a) For reasons relating to the advice that the ABI had given to its members concerning the use of tests not yet approved by GAIC, the ABI submitted applications to GAIC only in respect of a subset of the tests on its list, by the end of 2000.
- (b) GAIC was reconstituted in 2002 and the whole process of considering the ABI's applications was, effectively, started all over again in early 2003.

Several of the disorders on the ABI's list have now been the subject of actuarial models, including familial breast and ovarian cancer (Lemaire *et al.*, 2000; Subramanian *et al.*, 2000; Macdonald, Waters & Wekwete, 2003a, 2003b), Huntington's disease (Smith, 1998; Gutiérrez & Macdonald, 2002a, 2002b), Adult Polycystic Kidney Disease (Gutiérrez & Macdonald, 2003) and Early-Onset Alzheimer's Disease (Gui & Macdonald, 2002a, 2002b; Gui, 2003). In all cases, the conclusions were that high extra premiums were indicated for critical illness (CI) insurance (and sometimes for life insurance) in respect of mutation carriers, moderated considerably if family history was the only known risk factor, but that adverse selection was unlikely to be a problem because of the rarity of these diseases.

Another of the disorders listed by the ABI as potentially significant is Multiple Endocrine Neoplasia Type 2 (MEN2). In this paper we survey the epidemiological literature on MEN2, with results that are completely at odds with any of the actuarial investigations of other single-gene disorders. We conclude that the clinical significance and insurance significance, even of a highly penetrant single-gene disorder, can be completely different. This is an important message in the context of the genetics and insurance debate, since it is often assumed (for example, by the ABI originally, and by most of the media almost always) that significance for insurance follows automatically from clinical significance.

1.2 A Brief Description of Multiple Endocrine Neoplasia

MEN is characterised by the occurrence of tumours in two or more endocrine glands — organs that secrete one or more hormones into the bloodstream, helping to control the metabolism. It has several subtypes, of which the major forms are MEN Type 1 (MEN1, also known as Werner's syndrome) and MEN Type 2 (MEN2, Sipple's syndrome). MEN2 is the type that was listed by the ABI as being of significance for insurance. MEN2 itself comes in three forms, called MEN2A, MEN2B and familial medullary thyroid carcinoma (FMTC) (Thakker, 1998).

- (a) MEN2A is an inherited disease characterised by medullary thyroid carcinoma (MTC), pheochromocytoma — small vascular tumour of the adrenal gland which can cause increased blood pressure and heart rate, palpitations and headaches — and parathyroid adenoma — a benign tumour of the parathyroid gland which may undergo malignant change. MEN2A accounts for 90% of inherited MTC.
- (b) The much rarer and earlier onset MEN2B is characterised by MTC, pheochromocytoma, and widespread tumours affecting the mucous membrane of the gastrointestinal tract. Patients have a characteristic facial appearance and marfanoid habitus — abnormal elongation of the long bones resulting in excessive tallness, abnormally long and slender toes and fingers.
- (c) FMTC is not associated with any endocrinopathy, and MTC occurs without the other abnormalities. FMTC represents the least aggressive form of MTC.

Table 1: Characteristics of medullary thyroid carcinoma. Source: Lewinski *et al.* (2000).

	Sporadic	In FMTC	In MEN2A	In MEN2B
% of MTC	75%	7%	15%	3%
Mean age (yrs)	44–50	41–43	21–38	12–23
Sex (M:F)	1:1.3	1:1	1:1	1:1
Proliferation	varies	slow	slow	invasive

MTC occurs in about 95% of affected persons, and phaeochromocytoma in about 50%; we consider the prognoses of these symptoms in Sections 2.1 and 2.2 respectively.

MEN2 syndromes are inherited as rare autosomal dominant disorders, and have been identified to date in 500–1,000 kindreds worldwide (Brandi *et al.*, 2001). Germline mutations in the RET (REarranged during Transfection) proto-oncogene on chromosome 10 have been identified in patients with MEN2 (Learoyd, Delbridge & Robinson, 2000; Thakker, 1998). Genetic testing is important for two reasons (Wallin *et al.*, 2001):

- (a) The syndromes also occur sporadically, so clinical screening and genetic testing of patients is essential to determine whether the syndrome is inherited. If it is, unaffected relatives can undergo genetic testing and be monitored more closely. If MEN2 is discovered early, the tumour can be removed surgically and this is often curative.
- (b) The symptoms often go undiagnosed due to their mild nature. If genetic testing detects those carrying the RET mutations, and necessary monitoring and treatment follow before irreversible damage occurs, mortality will be normalised.

As far as insurance is concerned, this means that presymptomatic genetic testing should normalise the mortality risk before the ages of economic activity are even reached.

In Section 2 we review the main sources of morbidity associated with the various MEN2 syndromes, including the outcomes of treatment, and in Section 3 we describe the mutations in the RET gene associated with MEN2. Sections 4 and 5 discuss the possibilities for screening and the insurance implications, respectively. Our conclusions are in Section 6.

2. MORBIDITY AND MORTALITY ASSOCIATED WITH MEN2

2.1 Medullary Thyroid Carcinoma

MTC, also known as C-cell hyperplasia, is the third most common thyroid cancer, after papillary and follicular thyroid cancers, accounting for approximately 4–5% of cases (Moley, 1995; Randolph, 2000). It is the main cause of morbidity from MEN2. Overproduction of a hormone called calcitonin marks the onset of MTC.

Table 1 indicates the typical course of MTC in its sporadic form (about 75% of cases) and in its three inherited forms. It is most severe in MEN2B (the rarest form) and least so in FMTC. Diagnosis of MTC is established by physical examination, elevated serum calcitonin levels and family history.

Table 2: Diagnosis and cure rates of MEN2. Source: Goretzki *et al.* (1998).

Diagnostic test	Number of patients	Age (years)		Postoperative calcitonin normal
		Mean	Median	
Genetic	11	13	12	11 (100%)
Biochemical	32	24	25	19 (59%)
Index	20	45	40	1 (5%)

Though MTC is significantly less common than the other thyroid cancers, it has the worse prognosis. It is highly malignant, not curable unless diagnosed at an early stage, and tends to spread to large numbers of lymph nodes in the very early stage. It requires total thyroidectomy (complete removal of the thyroid gland) and possibly removal of the lymph nodes of the front and sides of the neck. Survival probabilities are highest for FMTC and lowest in MEN2B; for all types of MTC, the 5-year survival rate is between 78% and 91%, and the 10-year rate between 61% and 75% (Randolph, 2000). Heshmati & Hofbauer (1997) found an overall 10-year survival rate of about 65%, and The Endocrine Web Inc. has quoted an overall 10 year survival rate of 90% when all the disease is confined to the thyroid gland, 70% with spread to cervical lymph nodes, and 20% when spread to distant sites is present. Survival of 10 years or more with metastatic disease is not common (Randolph, 2000). Age at onset, stage of disease and completeness of initial surgery affect the prognosis of patients with MTC significantly.

Table 2 shows that MEN2 patients diagnosed by biochemical or genetic screening have tumours at an earlier developmental stage, and have a higher chance of surgical cure (defined as normal calcitonin levels after surgery).

From an insurance point of view, the above suggests that MTC is sufficiently severe that an asymptomatic person in an affected family would be regarded as high risk. This assumes that, in the absence of a genetic test, prophylactic surgery on all at-risk persons would not be carried out, but would be deferred until symptoms are detected by biochemical tests, or symptoms have become clinically overt at the later stages of the disease. Therefore, the development of a presymptomatic genetic test will reduce the morbidity and mortality of the siblings and first cousins of the probands, some of whom (though asymptomatic) might have started developing tumours. They will be rated according to the current underwriting practice for MEN2 (Section 5). However, persons at-risk in the subsequent generations will be able to have their risks normalised with presymptomatic genetic screening at very young ages. Non-carriers will be cleared of their risks for MEN2 while carriers will have their risks effectively removed following prophylactic surgery. Asymptomatic carriers diagnosed genetically will have their developing or already existing malignant disease completely cured (Goretzki *et al.*, 1998).

2.2 Pheochromocytoma

Pheochromocytomas are small vascular tumours located mostly in the adrenal medulla. About 85% of pheochromocytomas are sporadic. In MEN2 they are rarely malignant, but they cause the uncontrolled and irregular secretion of hormones including adrenaline

and noradrenalin, leading to hypertension, and a wide variety of symptoms such as increased heart rate, palpitations, sweating and headache. Surgical removal of the tumour is curative in more than 90% of all cases (Sheps *et al.*, 1990; van Heerden *et al.*, 1982; Gifford, Manger & Bravo, 1994).

Phaeochromocytoma develops in about 50% of MEN2A patients (appearing about 10 years after the diagnosis of MTC), and in 40–50% of MEN2B patients (Ball, 1996; Lewinski *et al.*, 2000). The lifetime penetrance varies widely, from 10% to 90% among kindreds (Ball, 1996).

Historically, serious complications arising from undetected cases of phaeochromocytoma were common, but because of improved management, phaeochromocytoma in both MEN2A and MEN2B has not been a major cause of death (Brandi *et al.*, 2001). Genetic screening with periodic biochemical testing, and modern imaging and surgical techniques have effectively minimised the morbidity and mortality. Phaeochromocytoma discovered by genetic screening is unlikely to have significant implications for insurance because symptoms will be accompanied by the more severe, and more highly penetrant, MTC. Insurance claims, if made, will be for the associated MTC (Section 2.1).

2.3 Hyperparathyroidism

Hyperparathyroidism (HPT) is the excess secretion of parathyroid hormone and it occurs in approximately 0.02–0.1% of the population (Gard, 1998). The symptoms usually present at ages 30–60. HPT also occurs in 20–30% of MEN2A patients (Brandi *et al.*, 2001) in which tumours arise within several endocrine glands simultaneously.

The predominant symptoms of HPT are those caused by excessive levels of calcium in the blood, and if untreated, these will lead to muscular weaknesses and cardiac arrhythmias. There may be mental confusion culminating in coma and death, renal stones and bone rarefaction. The usual treatment is surgical removal of the parathyroid glands with follow-up drug treatment (Ball, 1996). Delbridge *et al.* (1998) reports a 99% cure rate for surgery though recurrences still present a significant challenge.

As with phaeochromocytoma, genetic screening for HPT in MEN2A is unlikely to have significant implications for insurance on its own, due to its low penetrance, mild nature and the availability of effective treatment. Again, insurance claims, if made, will be for the accompanying MTC which is much more severe.

3. THE RET PROTO-ONCOGENE

3.1 The RET Gene

The RET proto-oncogene encodes a cell-surface glycoprotein related to the family of receptor tyrosine kinases (cell-surface molecules that interpret signals for cell growth and differentiation) (Brandi *et al.*, 2001). It is located on chromosome 10q11.2, and contains 21 exons.

Mutations in the RET gene result in the unregulated activation of oncogenic tyrosine kinases and confer a gain of function at the cellular level. Unlike susceptibility genes implicated in other familial cancers, in which mutations confer a loss of function, mutations in the RET gene are dominant. Germline RET mutations are responsible for two very different disorders, the MEN2 syndromes and Hirschsprung disease (HSCR). Table

Table 3: RET proto-oncogene mutations. Source: Human Gene Mutation Database.

Mutation Type	Number	Phenotype(s)
Nucleotide substitution (Missense/ nonsense)	99	MEN2A/2B, FMTC, HSCR
Nucleotide substitution (Splicing)	14	HSCR
Nucleotide substitution (Regulatory)	1	HSCR
Small deletions	7	HSCR
Small insertions	5	MEN2A, FMTC, HSCR
Small insertions/deletions	2	MEN2A/2B
Gross deletions	1	HSCR
Complex rearrangements	1	HSCR
TOTAL	130	

Table 4: Summary of RET proto-oncogene mutations associated with MEN2. Source: Randolph (2000).

Subtype	Cases with mutations	Exon	Codons
MEN2A	97%	10	609, 611, 618, 620
		11	630, 634
		13	768, 790
MEN2B	95%	15	883
		16	918, 922
FMTC	86%	10	609, 611, 618, 620
		11	630, 634
		13	768, 790, 791
		14	804
		15	891

3 lists the current known number of mutations of the RET proto-oncogene classified by type, provided by the Human Gene Mutation Database (HGMD). MEN2 syndromes are associated with germline mutations in exons 10, 11, and 16.

3.2 RET Mutations

Approximately 97% of MEN2A patients, 95% of MEN2B patients and 86% of FMTC patients have germline mutations in the RET codons listed in Table 4.

Mutations causing MEN2A and FMTC are mainly confined to codons for cystine residues in exons 10 and 11 of the gene. Individuals in MEN2A families carrying the defective gene have a very high chance of developing MTC; the penetrance being age-related (Lips *et al.*, 1994). Rare mutations occurring in exons 13 and 14 have also led to FMTC.

A missense mutation (a 'T' to 'C' transversion in codon 918) resulting in the conversion of methionine to threonine, is associated with 95% of MEN2B cases (Kahn, Cote, &

Gagel, 1996; Randolph, 2000; Siegelman *et al.*, 1997; Toogood *et al.*, 1995). The mutations in codons 883 and 922 (Table 4) account for only a handful of MEN2B cases.

3.3 Prevalence and Age-Related Penetrance

The prevalence of MEN2 has been estimated to be one in 20,000–30,000 (Learoyd, Delbridge & Robinson, 2000; Wiesner & Snow-Bailey, 2003). The incidence of MTC in the UK is estimated at 20–25 new individual cases per year (among 55 million residents) (Ponder, 1997). MEN2A and FMTC are often associated with family history whereas approximately 50% of MEN2B cases are *de novo*.

Detailed, age-related penetrance estimates (such as have been used to parameterise actuarial models of other disorders) are not available. Over their lifetime, more than 95% of individuals with inherited RET mutations that are associated with MEN2 will develop MTC if the thyroid gland is not removed before the disease is diagnosed by clinical symptoms (Ball, 1996). Penetrance of MEN2 syndromes is age-related. Approximately 70% of MEN2A mutation carriers present with MTC by age 70 years (Randolph, 2000), with mean age at diagnosis about 37 years (Koch *et al.*, 2001). However, as shown in Table 1, the average age of onset differs among the three inherited syndromes. MEN2B has 100% penetrance and a variable expression.

Using standard screening tests to detect the earliest manifestation of the syndrome, Easton *et al.* (1989) reported high penetrance for RET mutations predisposing to MEN2A (93% by age 31). However, based on clinical history, an estimated 41% of carriers were not presenting with the disease by age 70.

3.4 Genotype-Phenotype Correlation

Different RET mutations are highly correlated with different clinical features of MEN2. In a study to establish the relationship between specific mutations and disease features, the International RET Mutation Consortium (Eng *et al.*, 1996) studied 477 MEN2 families from 18 tertiary referral centres worldwide. Mutations at codons 768 and 804 were seen only with FMTC, those at codon 918 only with MEN2B, and there was an association between mutations in codon 634 and the presence of pheochromocytoma and HPT. The consortium suggested that genotype-phenotype correlations existed that, if better understood, could prove useful in clinical management.

The mutated RET codon and the features within the family are important in planning thyroid management. A consensus statement was reached during the international MEN97 Workshop (Brandi *et al.*, 2001), where the risk for MTC was stratified according to the mutated RET codon, as shown in Table 5.

The correlation between genotype and phenotype in MEN2 highlights the ability of genetic testing to reveal great heterogeneity in one syndrome. Underwriting may become more complex if syndromes previously thought homogeneous but variable become heterogeneous with much reduced sample sizes. More underwriting classes, each with a smaller pool size, may be harder to administer. In line with the model pioneered in the UK by GAIC, actuarial justification may be required to justify any detailed underwriting. As this paper shows, that would be hard to establish on the basis of the existing literature.

Table 5: Stratified levels for MTC risks according to the mutated codon on the RET proto-oncogene. Level 3 is the most severe. Adapted from Brandi *et al.* (2001).

Mutated codons	Syndrome(s)	Level	Recommended action(s)
883, 918, 922	MEN2B	3	Thyroidectomy within first 6 months of life
611, 618, 620, 634	MEN2A, MEN2B, FMTC	2	Thyroidectomy before age 5 years
609, 768, 790, 791, 804, 891	MEN2A, FMTC	1	Thyroidectomy between age 5 and 10 years. Periodic biochemical testing for MTC if thyroidectomy not performed

4. GENETIC AND BIOCHEMICAL SCREENING

Genetic screening for germline RET mutations in members of MEN2 families is cost-effective and now widely performed (Delbridge *et al.*, 1998; Brandi *et al.*, 2001). A rapid, inexpensive, nonradioactive screening technique was presented by Siegelman *et al.* (1997). It can detect RET mutations with a sensitivity of about 90%. Once a RET mutation is identified in a member of a family, screening of at-risk relatives should be carried out so that beneficial total thyroidectomy can be offered to mutation carriers. A worldwide survey conducted by the International Association of Endocrine Surgeons of its members showed that molecular genetic screening for endocrine disease is available in 67% of institutions.

Of those who present with clinical signs and symptoms, almost half die of the disease and others may suffer significant morbidity. By contrast, early diagnosis by screening of family members allows for effective treatment with thyroidectomy. Testing of first-degree relatives of patients with MTC should be started by the age of 3 to 5 years. In families with the MEN2B syndrome, screening should be started during the first year after birth and include a search for the characteristic phenotype (see Table 5).

5. INSURANCE IMPLICATIONS

Rating of MEN cases depends on successful surgery to remove the tumours and effective follow-up to detect the presence of developing malignancies (Brackenridge & Elder, 1998). Carriers of RET mutations and those at risk of carrying mutations are only considered for insurance if they are subjected to yearly biochemical tests for microscopic MTC, or in the case of at-risk persons, if they are found not to be carriers by genetic screening.

We assume that the availability of genetic tests for RET mutations in a clinical setting, together with the very high success rate of surgery following genetic testing at an early enough age (Table 2) will mean that once a family has been identified as carrying a RET mutation causing MEN2, all at-risk persons will be screened, and as a result their risk will be reduced to the minimum possible. As a result, at least to a first approximation,

at-risk persons are unlikely to purchase unusually large amounts of insurance (life or CI), and that which they do purchase should not bring significantly greater risk into the pool.

One slightly circular, but vitally important, reason for making this assumption is that, were we to assume otherwise and hence load premiums for the risk that people opt not to be tested, we would create the very reason why they might opt not to be tested. This is exactly the concern that insurance considerations may deter people from having tests that are entirely beneficial — possibly the most serious of all the concerns surrounding genetics and insurance — and it is, we believe, incumbent on the industry to avoid creating the circumstances where it can happen, when it is genuinely avoidable. When effective interventions exist, any clear signal from the insurance industry (that a test either will or will not be regarded as relevant) might become self-fulfilling.

Therefore, the only remaining risk that might trouble insurers is siblings or first cousins of a person who is the first family member diagnosed with MEN2, because they may have passed the ages at which either biochemical or genetic screening can normalise the risk of MTC. This problem ought to be small, because MEN2 is very rare, and although *de novo* mutations associated with MEN2B are found relatively frequently, cases in which screening and surgery are unsuccessful are likely to be resolved at an early age.

6. CONCLUSIONS

We draw four main conclusions from this study:

- (a) The significance of genetic testing for insurance does not follow merely from the features of late onset, high penetrance, dominant inheritance and severe outcomes, but also from the availability of effective treatments. Despite its appearance on the ABI's list of potentially significant disorders, MEN2 provides a model for early prevention and cure of cancer, based on genetic screening and early intervention. This is a wholly positive development made possible by the development of genetic testing. It would be disastrous for the insurance industry, as well as for individuals, if inappropriate or excessively cautious practices deterred members of affected families from taking beneficial action. Further research into Familial Adenomatous Polyposis, also on the ABI's list, may lead to a similar conclusion.
- (b) The mutated codon of the RET gene correlates with the MEN2 variant and the aggressiveness of MTC. Although the existence of effective interventions ought to prevent this from becoming a problem for insurance, it shows that the classification of genetic disorders into single-gene/multifactorial may be too coarse for insurance purposes, as for clinical purposes. A more detailed stratification may be necessary as we learn more of the etiology and epidemiology of these genetic disorders. Because of small numbers, however, the statistical or actuarial significance of these differences may be hard to establish. This may be an important consideration for the future work of GAIC in the UK, especially since many other conditions have even more heterogeneous genetic causes.
- (c) In some conditions, such as Huntington's disease, family histories and genetic tests reveal groups with higher risks. The potential for adverse selection can be a genuine concern to the insurer because there is no effective treatment. In other conditions, such as familial breast cancer, treatments do exist but are drastic. In contrast,

cheap genetic tests and tolerable treatment will normalise or greatly reduce the risk of MEN2. Although the assumption that this process will be 100% effective may be somewhat idealistic, we suggest that presymptomatic, as opposed to diagnostic, genetic testing for MEN2 mutations in the RET gene should normally provide no additional information of practical significance.

- (d) We suggest that a moratorium on the use of genetic information, even if it extends to family medical history (as in Sweden and certain other countries) should not present a serious risk of adverse selection. The same conclusion has been reached in respect of other disorders entirely because of their rarity, and MEN2 is also rare, but in this case the positive outcome of genetic testing is a more important reason. In order for an asymptomatic at-risk person, who is aware of the risk, to obtain insurance cover much below its true cost, they would have to avoid treatment precisely in order to keep that true insurance cost high. Given good clinical genetics services, including counselling, such bizarre behaviour should not happen. In that case, the main risk of adverse selection may be posed by poorly worded CI insurance contracts that cover the diagnosis rather than the prognosis of a genetic disorder like MEN2.

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