THEMATIC REVIEW

Advances in risk-oriented surgery for multiple endocrine neoplasia type 2

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Abstract

Genetic association studies hinge on definite clinical case definitions of the disease of interest. This is why more penetrant mutations were overrepresented in early multiple endocrine neoplasia type 2 (MEN2) studies, whereas less penetrant mutations went underrepresented. Enrichment of genetic association studies with advanced disease may produce a flawed understanding of disease evolution, precipitating far-reaching surgical strategies like bilateral total adrenalectomy and 4-gland parathyroidectomy in MEN2. The insight into the natural course of the disease gleaned over the past 25 years caused a paradigm shift in MEN2: from the removal of target organs at the expense of greater operative morbidity to close biochemical surveillance and targeted resection of adrenal tumors and hyperplastic parathyroid glands. The lead time provided by early identification of asymptomatic MEN2 carriers under biochemical surveillance delimits a 'window of opportunity', within which (i) pre-emptive total thyroidectomy alone is adequate, circumventing morbidity attendant to central node dissection; (ii) subtotal 'tissue-sparing' adrenalectomy is sufficient, trading the risk of steroid dependency for the risk of a second pheochromocytoma in the adrenal remnant and (iii) parathyroidectomy is limited to enlarged glands, trading the risk of postoperative hypoparathyroidism for the risk of leaving behind hyperactive parathyroid glands. Future research should delineate further the mutation-specific, age-dependent penetrance of pheochromocytoma and primary hyperparathyroidism to refine the risk-oriented approach to MEN2. The sweeping changes in the management of MEN2 since the new millenium hold the hope that death and major morbidity from this uncommon disease can be eliminated in our lifetime.

Key Words

- biochemical screening
- DNA-based screening
- *RET* proto-oncogene
- gene test
- gene carrier
- multiple endocrine neoplasia type 2A

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Introduction

More than fifty years ago, the medical community witnessed the birth of a new hereditary endocrine syndrome encompassing medullary thyroid cancer (MTC) and pheochromocytoma: 'Sipple syndrome', named after the author of this seminal description (Sipple 1961).

It is now commonly referred to as multiple endocrine neoplasia type 2 or MEN2, especially when complemented by primary hyperparathyroidism. This achievement was brought about by a combination of astute clinical observation (Sipple 1961, Williams 1965) coupled with

advances in immunohistochemistry and hormonal assay technology.

Before that landmark event, individuals operated on for MTC would be misdiagnosed with papillary, follicular or undifferentiated thyroid cancer. Some individuals used to succumb to acute cardiovascular or cerebrovascular events, typically during childbirth masquerading as eclampsia or on invasive procedures, which in hindsight were ascribed to adrenergic hormonal excess from occult pheochromocytoma (Lips *et al.* 1981). ‘Sipple syndrome’, or MEN2A, came to attention in 1961 because it is a ‘noisy’ syndrome with as many patients initially identified based on the presence of hypercalcemia or pheochromocytoma as MTC, facilitating its recognition (Grubbs & Gagel 2015). Although most patients with fully penetrant MEN2 were ascertained quickly as having MEN2, patients featuring just one of the three syndromic constituents continued to be misdiagnosed with ‘sporadic’ disease.

The molecular era for MEN2 was ushered in with the discovery of *RET* (rearranged during transfection) as the susceptibility gene on chromosome 10q11.2 in 1993 (Donis-Keller *et al.* 1993, Mulligan *et al.* 1993). It became immediately apparent that DNA-based screening, revealing

an individual’s genetic predisposition to MEN2, was superior to biochemical screening for subclinical disease (Lips *et al.* 1994, Wells *et al.* 1994, Learoyd *et al.* 1997, Dralle *et al.* 1998). Because genetic association studies are critically dependent on definite clinical case definitions of the disease of interest, more penetrant *RET* mutations were overrepresented in early MEN2 studies (Fig. 1; Eng *et al.* 1996, Frank-Raue *et al.* 2010, Machens *et al.* 2013a), including the International MEN2 Consortium analysis (Eng *et al.* 1996):

- Highest risk mutations in codon 918 (classic MEN2B; American Thyroid Association/ATA HST) (Wells *et al.* 2015);
- High-risk mutations in codon 634 (classic MEN2A; ATA H) (Wells *et al.* 2015).

Initially underrepresented went moderate-risk mutations in codons 609, 611, 618, 620 and 630 (‘incomplete’ MEN2A; ATA MOD), whereas the weaker moderate-risk mutations in codons 768, 790, 804 and 891 (‘familial MTC’/FMTC; ATA MOD) were missed altogether. These weaker mutations were subsequently reported in 1995–1998 (Bolino *et al.* 1995, Eng *et al.* 1995, Hofstra *et al.* 1997, Berndt *et al.* 1998).

Figure 1

Prevalence of highest, high- and moderate-risk mutations in MEN2.

The enrichment of genetic association studies with individuals who manifest advanced disease (multifocal disease with involvement of multiple glands) is a methodological limitation ('selection bias'), which is unavoidable when the susceptibility gene is unknown. Less well appreciated are the clinical ramifications of such enrichment for hereditary conditions like MEN2 in which every thyroid C-cell, adrenal medullary cell and parathyroid chief cell has inherited the predisposition to MTC, pheochromocytoma or pseudonodular parathyroid hyperplasia (Eng *et al.* 1996, Machens *et al.* 2003). These theoretical considerations, supported by histopathological evidence of diffuse multifocal disease in multiple glands in MEN2 (Lips *et al.* 1978) and fueled by reports about clusters of fatal outcome in certain MEN2 families (Lips *et al.* 1981), resulted in fairly extensive initial surgical strategies for pre-emption, in particular bilateral total adrenalectomy (Lips *et al.* 1981) and 4-gland parathyroidectomy with or without autografting of parathyroid slivers to the sternocleidomastoid muscle or the brachioradial muscle of the nondominant forearm (Yoshida *et al.* 2009, Moley *et al.* 2015).

Twenty-five years after the advent of the genomic epoch for MEN2, it may be pertinent to take stock of the wealth of genomic and outcome data accrued. This review article endeavors to gauge mutation-specific risks of tumor development in MEN2-associated glands over time against the sequelae of organ loss vs tumor recurrence in remnant glands with a view of striking a benefit–risk balance based on most current evidence from the international literature.

Evidence acquisition

Search strategy

An electronic MEDLINE search of the international literature was conducted with a cutoff of May 31, 2017 using key words that included the terms 'medullary thyroid cancer/carcinoma', 'pheochromocytoma', 'hyperparathyroidism', 'hypercalcemia', 'multiple endocrine neoplasia type 2' or 'MEN2', 'thyroidectomy', 'adrenalectomy', 'parathyroidectomy', 'recurrence' or 'recurrent', 'steroid dependency', 'Addison's disease' or 'Addisonian crisis', 'recurrent laryngeal nerve palsy' or 'vocal cord palsy', 'hypoparathyroidism' and 'hypocalcemia'.

The terms of this literature search were identified in the title, abstract or medical subject heading.

Mere review articles were excluded from review. To avoid duplication, earlier reports from groups that updated previously published information in a subsequent, more comprehensive report were not considered. Pertinent publications were reviewed further, and data elements were extracted as appropriate in structured format.

Case definitions of MEN2 components

A diagnosis of medullary thyroid carcinoma typically required tumor extension beyond the basement membrane, demonstration of lymphatic or vascular invasion or both.

Pheochromocytoma typically was diagnosed in the presence of raised plasma-free metanephrines and normetanephrines, or 24-h urine metanephrines and normetanephrines, supported by histopathological confirmation of the biochemical diagnosis on the adrenal specimens.

A diagnosis of primary hyperparathyroidism was based on the evidence of hypercalcemia, typically in the presence of increased parathyroid hormone levels.

Results

Transformation from cellular hyperplasia to neoplasia

The *RET* proto-oncogene encodes for a transmembrane tyrosine kinase receptor expressed mainly in neuroendocrine cells from the neural crest. The constitutive activation of the mutated RET receptor protein is thought to give rise to hyperplasia of parafollicular C-cells, adrenal medullary cells and parathyroid chief cells. A second mutation in one of these neuroendocrine cells ('second hit') is thought to cause MTC (C-cell cancer), pheochromocytoma or primary hyperparathyroidism due to multiple hyperplastic nodules in a pattern best defined as pseudonodular parathyroid hyperplasia. Because acquisition of somatic mutations by these cells reflects the play of chance, the development of the different MEN2 components varies even among members of the same family, compromising predictions by which age the various MEN2 components may become clinically apparent (Machens *et al.* 2009b, Wells *et al.* 2013). As a corollary, the weaker is the transforming activity of inherited RET mutations (genotype), the less complete tends to be the penetrance of the other MEN2-associated components (phenotype).

Transformation of the thyroid gland

Progression from C-cell hyperplasia to early medullary thyroid cancer

Table 1 illustrates the age-related progression from C-cell hyperplasia to early MTC, with steep gradients among highest risk (ATA category HST), high-risk (ATA category H) and moderate-risk (ATA category MOD) RET mutations. The lead time provided by early identification of asymptomatic infants and young children as RET carriers delimits a 'window of opportunity', within which total thyroidectomy alone represents adequate therapy:

- For carriers of highest risk mutations (ATA category HST, notably M918T; classic MEN2B), surgical cure is achievable in expert hands before the age of four years but becomes exceptional thereafter (Elisei et al. 2012, Brauckhoff et al. 2014).
- For carriers of high- and moderate-risk mutations (ATA categories H and MOD; classic and atypical MEN2A), nodal spread is very rarely present before the age of 10 years (Skinner et al. 2005, Elisei et al. 2012, Wells et al. 2015).

Depending on the location of a moderate-risk mutation on the RET receptor (Fig. 1), there are further, though

clinically more subtle codon-specific differences: earlier progression to MTC when the mutation lodges in the extracellular cysteine-rich domain, especially in close proximity to the cell membrane (Machens et al. 2009a), as compared to a position in one of the intracellular tyrosine kinase domains (Rich et al. 2014).

The thyroid gland is more expendable than the adrenal or parathyroid glands, rendering pre-emptive thyroidectomy a more viable strategy than bilateral total adrenalectomy or 4-gland parathyroidectomy.

Biochemical window of opportunity: pre-emptive thyroidectomy

There is good evidence to suggest that MTC has not developed as long as basal calcitonin serum levels remain within normal limits (Machens et al. 2009c, Elisei et al. 2012). When these levels begin exceeding the upper normal limit of the calcitonin assay, usually <10 pg/mL for children aged 2 years and older (Castagna et al. 2015), the point of malignant transformation is coming closer. In the presence of basal calcitonin serum levels ≤ 30 pg/mL, node metastases have not been reported (Rohmer et al. 2011). If this biochemical 'window of opportunity' has been missed and neck nodes need to be dissected at

Table 1 Age-related penetrance of medullary thyroid cancer in children with RET mutations (literature review).

			Children with medullary thyroid cancer, <i>n</i> (%)					Biochemical cure, <i>n</i> (%)
			Age at thyroidectomy, year					
ATA 2015 category	Mutation in codon	Reference	≤3	4–6	7–12	13–18	Total	Total
HST (highest)	918	Brauckhoff <i>et al.</i> (2014)	6 of 7 (86)	2 of 2 (100)	N/A	N/A	8 of 9 (88)	9 of 9 (100)
		Elisei <i>et al.</i> (2012)	–	–	2 of 2 (100) ^a	1 of 1 (100) ^a	3 of 3 (100)	0 of 3 (0)
H (high)	634	Elisei <i>et al.</i> (2012)	–	1 of 1 (100)	3 of 3 (100)	3 of 3 (100) ^b	7 of 7 (100)	7 of 7 (100)
		Skinner <i>et al.</i> (2005)	–	6 of 9 (66)	8 of 8 (100)	1 of 1 (100)	15 of 18 (83)	16 of 18 (89)
MOD (moderate)	609–620	Skinner <i>et al.</i> (2005)	0 of 1 (0)	1 of 7 (14)	4 of 8 (50)	10 of 13 (77)	15 of 29 (52)	26 of 29 (90)
	609	Skinner <i>et al.</i> (2005)	–	–	–	1 of 3 (33)	1 of 3 (33)	3 of 3 (100)
	611	Skinner <i>et al.</i> (2005)	–	–	–	1 of 1 (100)	1 of 1 (100)	1 of 1 (100)
	618	Skinner <i>et al.</i> (2005)	–	0 of 2 (0)	2 of 4 (50)	4 of 4 (100) ^b	6 of 10 (60)	9 of 10 (90%)
	620	Skinner <i>et al.</i> (2005)	0 of 1 (0)	1 of 5 (20)	2 of 4 (50)	4 of 5 (80) ^c	7 of 15 (47)	13 of 15 (87)

ATA, American Thyroid Association; RET, rearranged during transfection.

^aNode-positive children aged 8, 12, and 14 years.

^bNode-positive child aged 11 years.

^cNode-positive child aged 10 years.

incremental operative morbidity, chances of immediate biochemical cure become slimmer: only 57–31% with 1–10 node metastases, and a mere 0–4% with >10 node metastases (Machens *et al.* 2000, Scollo *et al.* 2003).

Complications by the child's age at thyroidectomy and central node dissection

Table 2 depicts the incidence of complications, after thyroidectomy without and with central node dissection, stratified by the child's age (Kluijfhout *et al.* 2015, Machens *et al.* 2016). Addition of central node dissection seems to raise the frequency of transient and permanent hypoparathyroidism, and more subtly, the frequency of transient recurrent laryngeal nerve palsy (Machens *et al.* 2016). The latter finding may reflect space constraints in the neck of children aged 3 years and younger whose recurrent laryngeal nerves may be less resilient to traction and hyperthermia from electrocoagulation. In line with the concept of greater vulnerability of infants, children younger than 3 years of age developed more often transient and permanent hypoparathyroidism, in particular when postoperative hypoparathyroidism was more prevalent overall (Table 2). To diminish operative morbidity, it may be prudent to use optical magnification, bipolar forceps coagulation and nerve-monitoring devices and preserve parathyroid glands in situ as much as possible.

Transformation of the adrenal glands

Age-related penetrance of adrenal pheochromocytoma

Pheochromocytomas in MEN2 have more of an adrenal phenotype secondary to predominant epinephrine production from the adrenal tumor. Extraadrenal pheochromocytoma and adrenal ganglioneuroma in MEN2 are exceptional (Lora *et al.* 2005).

Table 3 summarizes the literature on the penetrance of MEN2-associated pheochromocytoma:

- Highest and high-risk mutations (ATA categories HST and H; classic MEN2B and classic MEN2A) carried comparable risks of pheochromocytoma in the order of 27–32.3% around the age of 26 and 35 years, respectively (Asari *et al.* 2006, Rodriguez *et al.* 2008, Machens *et al.* 2013a). These pheochromocytomas involved both adrenals in 50–60%, two-thirds synchronously and one-third metachronously.
- Moderate-risk mutations (ATA category MOD; atypical MEN2A) entailed much lower risks of pheochromocytoma in the order of 17% by the early

Table 2 Age-related incidence of complications after thyroidectomy in children (literature review).

Complication	Central node dissection	Reference	Children with complication after total thyroidectomy, n (%)						
			Age at thyroidectomy, year						
			≤3	<3	3–6	4–6	7–12	13–18	>6
Transient RLN palsy	Not performed	Kluijfhout <i>et al.</i> (2015)	1 of 9 (11)	0 of 25 (0)	0 of 15 (0)	0 of 39 (0)	N/A	N/A	1 of 20 (5)
	Not performed	Machens <i>et al.</i> (2016)		2 of 12 (17)		0 of 21 (0)	0 of 24 (0)	0 of 11 (0)	0 of 35 (0)
Permanent RLN palsy	Performed	Machens <i>et al.</i> (2016)					2 of 43 (5)	4 of 55 (7)	6 of 98 (6)
	Not performed	Kluijfhout <i>et al.</i> (2015)	1 of 9 (11)	0 of 25 (0)	0 of 15 (0)	0 of 39 (0)	N/A	N/A	0 of 20 (0)
Transient hypoparathyroidism	Not performed	Machens <i>et al.</i> (2016)		0 of 12 (0)		0 of 21 (0)	0 of 24 (0)	0 of 11 (0)	0 of 35 (0)
	Performed	Machens <i>et al.</i> (2016)	6 of 9 (67)	0 of 12 (0)	7 of 15 (47)	0 of 21 (0)	0 of 43 (0)	0 of 55 (0)	0 of 98 (0)
Permanent hypoparathyroidism	Not performed	Kluijfhout <i>et al.</i> (2015)					N/A	N/A	8 of 20 (40)
	Not performed	Machens <i>et al.</i> (2016)		1 of 25 (4)		3 of 39 (8)	3 of 24 (13)	4 of 11 (36)	7 of 35 (20)
	Performed	Machens <i>et al.</i> (2016)		0 of 12 (0)		3 of 21 (14)	19 of 43 (44)	22 of 55 (40)	41 of 98 (42)
Permanent hypoparathyroidism	Not performed	Kluijfhout <i>et al.</i> (2015)	2 of 9 (22)		2 of 15 (13)		N/A	N/A	5 of 20 (25)
	Not performed	Machens <i>et al.</i> (2016)		0 of 25 (0)		0 of 39 (0)	0 of 24 (0)	0 of 11 (0)	0 of 35 (0)
	Performed	Machens <i>et al.</i> (2016)		0 of 12 (0)		1 of 21 (5)	5 of 43 (12)	7 of 55 (13)	12 of 98 (12)

N/A, not available.

Table 3 Age-related penetrance of pheochromocytoma in MEN2 (literature review).

ATA 2015 category	Mutation in codon	Reference	Pheochromocytoma			
			Penetrance overall, n (%)	Age at first diagnosis, year, mean	Unilateral penetrance, n %	Bilateral penetrance, n (%)
HST (highest)	918	Machens <i>et al.</i> (2013a)	10 of 37 (27)	25.5	4 of 37 (11)	6 of 37 (16)
H (high)	634	Asari <i>et al.</i> (2006)	N/A	N/A	1	6 ^a
		Rodriguez <i>et al.</i> (2008)	52 of 161 (32.3)	36.4–38.1	26 of 161 (16.1)	26 of 161 (16.1)
		Machens <i>et al.</i> (2013a)	51 of 170 (30.0)	34.7	19 of 170 (11.2)	32 of 170 (18.8)
		Asari <i>et al.</i> (2006)	N/A	N/A	4	4 ^b
		Frank-Raue <i>et al.</i> (2011)	54 of 319 (16.9)	42 (median)	39 of 319 (12.2)	15 of 319 (4.7)
MOD (moderate)	609–620 609–630	Machens <i>et al.</i> (2013a)	19 of 112 (17.0)	40.5	15 of 112 (13.4)	4 of 112 (3.6)
		Asari <i>et al.</i> (2006)	N/A	N/A	2	0
		Machens <i>et al.</i> (2013a)	4 of 155 (2.6)	56.5	4 of 155 (2.6)	0 of 155 (0)

^aBilateral pheochromocytomas were metachronous in 2 (33%) and synchronous in 4 (67%) of all 6 children with bilateral pheochromocytoma; ^bBilateral pheochromocytomas were metachronous in 3 (75%) and synchronous in 1 (25%) of all 4 children with bilateral pheochromocytoma. ATA, American Thyroid Association.

40s for mutations in cysteine codons 609–620/630, and 2.6% by the age of 56.5 years for mutations in non-cysteine codons 768–891 ([Asari *et al.* 2006](#), [Frank-Raue *et al.* 2011](#), [Machens *et al.* 2013a](#)). Three-quarters of these pheochromocytomas were unilateral only.

In children carrying the highest and high-risk mutations (ATA categories HST and H), screening for pheochromocytoma generally is recommended to start at 8 years of age ([Rowland *et al.* 2013](#), [Wells *et al.* 2015](#)), and for moderate-risk mutations (ATA category MOD) after 15 years of age ([Machens *et al.* 2013a](#), [Wells *et al.* 2015](#)). To determine personal lifetime risks of pheochromocytoma, it is more worthwhile to evaluate mutation-specific risks by age (in 10–20 year increments), rather than referring to summary data. That level of detail is rarely available for ATA risk categories. Exceptions include moderate-risk mutations in exon 10 (ATA category MOD; mutations in cysteine codons 609–620), in which the penetrance of pheochromocytoma was 0% by age 10 years; 0.8% by age 20 years; 5.1% by age 30 years, 12.0% by age 40 years; 23.1% by age 50 years and 33.2% by age 60 years ([Frank-Raue *et al.* 2011](#)).

For such long-term observation, patient compliance with follow-up over decades is imperative.

Because adrenal mortality has been reported almost exclusively in connection with big pheochromocytomas ([Dralle *et al.* 1992](#)), there is evidence to suggest that continual

biochemical screening may spot pheochromocytoma before it gives rise to adrenergic crisis.

Subtotal vs total adrenalectomy: risk of recurrence vs steroid dependence

Owing to the infrequency of pheochromocytoma, there is a paucity of data about the mutation-specific risk of developing a second pheochromocytoma:

- Ipsilaterally after unilateral-subtotal adrenalectomy inside the adrenal remnant, and
- Contralaterally without or after contralateral-subtotal adrenalectomy

The risk of developing a second pheochromocytoma inside an adrenal remnant, by implication, should be no greater, or perhaps even lower, than the risk of developing the first pheochromocytoma in an entire adrenal gland. In keeping ([Table 4](#)), a second pheochromocytoma rarely originates from an adrenal remnant ipsilaterally (0–14%) and more often from an intact adrenal gland contralaterally (43–57%) ([Lairmore *et al.* 1993](#), [Scholten *et al.* 2011](#), [Castinetti *et al.* 2014](#)).

Before the turn of the century, bilateral total adrenalectomy used to be the gold standard approach to the adrenal glands in MEN2 because of

- Histopathological demonstration that both adrenal glands were riddled with adrenal medullary hyperplasia ([Lips *et al.* 1978](#)).

Table 4 Unilateral and contralateral adrenal recurrence after initial adrenalectomy in MEN type 2 (literature review).

Initial adrenalectomy	Reference	Adrenal recurrence after initial adrenalectomy				Steroid dependency	Follow-up, year, median (range)	
		Unilateral		Contralateral				
		Patients, n (%)	Time to event, year, median (range)	Patients, n (%)	Time to event, year, median (range)			
Unilateral	Subtotal	Scholten <i>et al.</i> (2011)	1 of 7 (14)	N/A	4 of 7 (57)	[6.3 (1.8–9.7)]	0 of 7 (0)	15.8 (1.2–31.9)
	Total	Lairmore <i>et al.</i> (1993)	0 of 23 (0)	[9.4 (0.7–28.5)]**	12 of 23 (52)	11.9 (0.4–21.2)**	0 of 23 (0)	9.4 (0.7–28.5)**
		Scholten <i>et al.</i> (2011)	0 of 30 (0)	[5.5 (0.1–38.6)]	13 of 30 (43)	[8.5 (0.5–19.9)]	0 of 30 (0)	11.5 (0.1–41.8)
Bilateral	Subtotal	Scholten <i>et al.</i> (2011)	2 of 2 (100)	7.1 (4.1–10.2)	0 of 2 (0)	7.2 (4.1–10.2)	0 of 2 (0)	14.5 (12.8–16.3)
	Total	Lairmore <i>et al.</i> (1993)	0 of 32 (0)		0 of 32 (0)		***	
		Scholten <i>et al.</i> (2011)	1 of 22 (5)	34.1	0 of 22 (0)	23.0 (0.1–34.1)	22 of 22 (100)	23.0 (0.1–35.2)
Any	Subtotal	Castinetti <i>et al.</i> (2014)	4 of 114 (4)	9.5 (6–13)		N/A		10** (1–28)
	Total	Castinetti <i>et al.</i> (2014)	11 of 438 (3)	14.2** (1–23)		N/A		13** (1–40)
Bilateral	Subtotal*	Castinetti <i>et al.</i> (2014)		N/A			35 of 82 (43)	
	Any	Castinetti <i>et al.</i> (2014)		N/A			292 of 339 (86)	

Numbers in squared brackets indicate approximations.

Scholten et al. 2011: ≥75% ATA H mutations.

Castinetti et al. (2014): 5% ATA HST mutations; 84% ATA H mutations; 11% ATA MOD mutations.

*One or both adrenals; **Mean; ***10 of 43 (23%) patients experienced at least one episode of adrenal insufficiency/Addisonian crisis (fatal in one patient).

- A perceived high probability of developing a second pheochromocytoma (Lairmore et al. 1993).
- Reports of MEN2 families affected by multiple fatal cardiovascular and cerebrovascular events attributable to adrenergic crisis from occult pheochromocytoma (Lips et al. 1981).
- Lingering concerns about malignancy because initial estimates of developing malignant pheochromocytoma exceeded current risk estimates of ≤1%, perhaps due to initial ‘publication bias’.

Only gradually appreciated were the adverse consequences of bilateral total adrenalectomy, tipping the balance away from total adrenalectomy:

- Steroid dependency in up to 100% (Scholten et al. 2011; Table 4), and
- Addisonian crisis in 23%, which was fatal under less fortunate circumstances (Lairmore et al. 1993; Table 4).
- Furthermore, pheochromocytoma turned out to be almost invariably benign in MEN2, being malignant in no more than 1% of tumors (Machens et al. 2013a).

The limited risk of recurrence for adrenal remnants (Table 4) and the availability of tissue-sparing surgical technology made subtotal adrenalectomy – attuned to the extent of the adrenal tumor – the surgical intervention of choice for pheochromocytoma (Dralle et al. 1992, Lairmore et al. 1993, Brauckhoff et al. 2003, Asari et al. 2006, Scholten et al. 2011, Machens et al. 2013a, Wells et al. 2015). Rare exceptions include technical unfeasibility of subtotal adrenalectomy when the adrenal tumor occupies most or all of the adrenal gland.

Accurately determining residual adrenal volume, in which ‘recurrent’ pheochromocytoma may develop, has come as a challenge. Three-dimensional reconstruction on computed tomography overestimates residual adrenal volume. In fact, the posterior extension of an adrenal remnant cannot be precisely measured without mobilization, which would jeopardize its blood supply (Brauckhoff et al. 2008). In the absence of more precise measurements, residual adrenal volume continues to be put in proportion to the volume of the entire adrenal gland before resection. These intraoperative estimates suggest that preservation of one-third of the adrenal gland offers adrenal stress capacity sufficient to obviate the need for corticosteroid supplementation (Brauckhoff et al. 2003). Even after bilateral subtotal adrenalectomy, loss of 70–85% of adrenal tissue can be compensated for by the adrenal remnants, although some subclinical compromise commonly remains (Wells et al. 2015).

Transformation of the parathyroid glands**Age-related penetrance of
primary hyperparathyroidism**

The risk of parathyroid disease is genetically determined and not a response to elevated calcitonin serum levels (Dralle *et al.* 1992).

Table 5 provides information on the penetrance of MEN2-associated primary hyperparathyroidism, typically caused by no more than one enlarged parathyroid gland:

- Highest risk mutations (ATA category HST; classic MEN2B) do not produce primary hyperparathyroidism.
- High-risk mutations (ATA category H; classic MEN2A) entail a risk of primary hyperparathyroidism of 9.4% by the age of 40 years using institutional data (Machens *et al.* 2013a). This risk was estimated twice as high (19.1% by age 34 years) based on the data from a national MEN2 registry going back to 1984 (Schuffenecker *et al.* 1998) or more than fourfold greater in an earlier institutional series (Asari *et al.* 2006). The penetrance of primary hyperparathyroidism was rated using these MEN2 registry data at 14% by age 30 years; 26% by age 40 years; 48% by age 60 years and 81% by age 70 years (Schuffenecker *et al.* 1998).
- Moderate-risk mutations (ATA category MOD; atypical MEN2A) infrequently go along with primary hyperparathyroidism (Asari *et al.* 2006, Frank-Raue *et al.* 2011, Machens *et al.* 2013a). Current estimates range from 1.3% by the age of 54.5 years (mutations in non-cysteine codons 768–891) to 2.7% by the age of 46 years (mutations in cysteine codons 609–620 in exon 10). The penetrance of primary hyperparathyroidism, pooling data of 27 centers from 15 countries, was

estimated at 0% by age 20 years; 0.5% by age 30 years, 1.8% by age 40 years; 3.9% by age 50 years and 3.9% by age 60 years (Frank-Raue *et al.* 2011).

For high-risk mutations (ATA category H), screening for primary hyperparathyroidism usually is advocated to begin after 10 years of age, and for moderate-risk mutations (ATA category MOD), after 15 years of age (Machens *et al.* 2013a, Wells *et al.* 2015).

**Limited vs total parathyroidectomy:
risk of recurrence vs permanent
postoperative hypoparathyroidism**

Because primary hyperparathyroidism in MEN2 almost always is mild and benign, removing only enlarged parathyroid glands is adequate most of the time (Dralle *et al.* 1992, Wells *et al.* 2015). The adequacy of parathyroidectomy is judged intraoperatively by the prompt fall of the intact parathyroid hormone levels by 50% and more. As a matter of principle, normal parathyroid glands should be preserved in situ on a vascular pedicle.

The risk of recurrent primary hyperparathyroidism, arising from the transformation of one of three or fewer remaining parathyroid gland, by implication, should be less than the initial risk of primary hyperparathyroidism for all four parathyroid glands:

- For high-risk mutations (ATA category H; classic MEN2A), the risk of recurrence should be modest ($\leq 19.1\%$).
- For moderate-risk mutations (ATA category MOD; atypical MEN2A), the risk of recurrence should be negligible ($\leq 2.7\%$).

Table 5 Age-related penetrance of primary hyperparathyroidism in MEN2 (literature review).

ATA 2015 category	Mutation in codon	Reference	Primary hyperparathyroidism	
			Penetrance, n(%)	Age at first diagnosis, year, mean
HST (highest)	918	–	–	–
H (high)	634	Asari <i>et al.</i> (2006)	3 of 7 (43)	(42.6–49.0)*
		Schuffenecker <i>et al.</i> (1998)	36 of 188 (19.1)	33.7
		Machens <i>et al.</i> (2013a)	16 of 170 (9.4)	39.7
MOD (moderate)	609–620	Asari <i>et al.</i> (2006)	0 of 8 (0)	(42.6–49.0)*
		Frank-Raue <i>et al.</i> (2011)	8 of 299 (2.7)	46 (median)
	609–620 (609–630)	Machens <i>et al.</i> (2013a)	2 of 112 (1.8)	38.5
	768	Asari <i>et al.</i> (2006)	0 of 2 (0)	(42.6–49.0)*
	–891	Machens <i>et al.</i> (2013a)	2 of 155 (1.3)	54.5

ATA, American Thyroid Association.

*Whole study population.

Although frequently used before the millennium, total parathyroidectomy with autotransplantation of parathyroid slivers to the nondominant forearm or the neck has been abandoned because of its attendant 6–9% risk of permanent hypoparathyroidism. That risk compares unfavorably with the 1–4% risk attendant to in situ preservation of the parathyroid glands (Dralle *et al.* 1998, Moley *et al.* 2015).

Discussion

The advent of sensitive calcitonin, catecholamine and parathyroid hormone assays and DNA-based screening programs changed the landscape for MEN2 (Graze *et al.* 1978, Gagel *et al.* 1988, Machens *et al.* 2013a, Machens & Dralle 2015). Biochemical (i.e., calcitonin) screening was shown to be more sensitive than anatomical screening (i.e., neck ultrasonography) for microscopic disease (i.e., MTC) in asymptomatic children at risk of MEN2A (Morris *et al.* 2013). At inception, calcitonin screening was largely cross-sectional, encompassing gene carriers at various stages of tumor development. With the increasing inclusion of asymptomatic infants and young children, the focus of screening programs shifted toward longitudinal observation of family members at risk of developing MEN2 tumors. This yielded an unprecedented opportunity to monitor individuals at risk of developing MEN2 over decades and to learn more about the molecular epidemiology of the various mutations underlying MEN2 (Machens *et al.* 2013b).

Paradigm shift from the removal of target organs to targeted surgical intervention

The important insight into the natural evolution of MEN2 gained over the past 25 years (i.e., one generation) changed the scene for the management of MEN2 in the new millennium: from removing target organs early in the course, at the expense of greater operative morbidity, to enabling better quality of life under close biochemical surveillance, with targeted ('tissue-sparing') resection of adrenal tumors and hyperplastic parathyroid glands. This progress has rendered prophylactic removal of organs for asymptomatic benign lesions rarely, if ever, acceptable in a well-organized society.

In the genomic era, the natural course of the disease is interfered with ideally as soon as the upper normal limit of the respective organ-specific assay has been exceeded (Machens *et al.* 2009c, Elisei *et al.* 2012) and a

valid adrenal and parathyroid surgical target has been identified (Machens *et al.* 2013a), respectively:

- Pre-emptive total thyroidectomy, circumventing incremental operative morbidity associated with central node dissection in the neck (Machens *et al.* 2009c, Machens *et al.* 2016);
- Subtotal adrenalectomy attuned to the adrenal tumor(s), trading a grave risk of steroid dependency and Addisonian crisis for a smaller risk of developing a second pheochromocytoma inside an adrenal remnant (Brauckhoff *et al.* 2003);
- Parathyroidectomy of enlarged glands only, trading a 6% risk of postoperative hypoparathyroidism (Moley *et al.* 2015) for a smaller risk of developing another parathyroid tumor ('recurrent' hyperparathyroidism).

This paradigm shift, consisting in weighing mutation-specific risks of tumor development against the sequelae of organ loss and the risk of developing additional tumors inside remnant organs during informed consent, falls within the realms of personalized medicine and value-based decision making. Value-based decisions always have a personal component and require clinician and patient to take personal responsibility.

Population-based effectiveness of DNA-based screening for MEN2

In countries like Germany where health care systems cover the analysis of all relevant *RET* mutations, the effectiveness of DNA-based screening for control of MTC at the population level has been impressive (Machens & Dralle 2015):

For high-risk mutations (ATA category H; 'classic' MEN2A), a decline since 1963 in the percentage of:

- Index patients among all carriers from 50 to 16%;
- MTC among non-index patients from 100 to 28%;
- Node-positive MTC from 100 to 0%;

whereas biochemical cure increased from 0 to 100%.

For moderate-risk mutations (ATA category MOD; 'incomplete' MEN2A), a fall since 1995 in the percentage of:

- Index patients among all carriers from 100% to 29–31%
- MTC among non-index patients from 48–81% to 19–60%;
- Node-positive MTC from 67 to 33% (cysteine codons 609–630) and 11 to 10% (non-cysteine codons 768–891),

whereas biochemical cure increased from 71 to 78% (cysteine codons 609–630) and 95–100% (non-cysteine codons 768–891).

Based on data from the French MEN2 registry, 5.6–9.1% of germline mutations (running in 8–13 of 143 families) occur *de novo* in the parental germline (Schuffenecker *et al.* 1997), replenishing the pool of index patients that screening programs seek to deplete. These countervailing effects may make it unfeasible to diminish the percentage of index patients below the spontaneous mutation rate of 5.6–9.1%.

Future perspectives

Twenty-five years into the molecular era, correlations between genotype (mutations in RET codons 609, 611, 618, 620, 630, 634, 768, 790, 804, 891 and 918) and phenotype (MTC, pheochromocytoma, hyperplastic parathyroid glands) are well established at the population level, allowing clinicians to practice the law of averages and/or worst-case scenarios. These mutational profiles provide for a genetic framework within which transformation from cellular hyperplasia to neoplasia unfolds at a variable pace.

Predicting this cellular transformation precisely in terms of time (age at onset) and space (affected glands) at the individual level has proved elusive. This is why screening for cellular biomarkers with sensitive calcitonin, catecholamine and parathyroid hormone assays has been gathering momentum since the millennium. These biochemical screening programs strive to open a surgical ‘window of opportunity’ by detecting:

- MTC before it has spread to neck nodes or beyond (Machens *et al.* 2009c, Elisei *et al.* 2012);
- Pheochromocytoma as long as it is small (Machens *et al.* 2013a); and
- Hyperplastic parathyroid glands ahead of chronic renal and/or arterial disease (Machens *et al.* 2013a).

Within this ‘window of opportunity’, the extent of the operation, its attendant morbidity and the resultant organ loss, with its risk of steroid and/or calcium/vitamin D dependency, can be kept low.

Because patient age confounds genotype–phenotype correlations, future research in MEN2 should be directed at delineating further the mutation-specific, age-dependent penetrance of pheochromocytoma and primary hyperparathyroidism in older adults carrying the trait. Far longer follow-up periods, encompassing several decades, will be necessary to accrue more adrenal and

parathyroid events. Larger event rates would help refine the current risk-oriented approach to MEN2 and foster wider dissemination of Bayesian inference considering the proband’s age at the time of assessment (Ponder *et al.* 1988) in addition to mutational risk.

More research is warranted into the risk of developing secondary pheochromocytoma in adrenal remnants or intact glands, taking the adrenal volume at risk into account. Furthermore, survival data will increasingly need to be fit into the benefit–risk equation (Grubbs & Gagel 2015).

The sweeping changes in the management of MEN2 since the new millennium hold the hope that death and major morbidity from this uncommon disease can be eliminated in our lifetime.

Declaration of interest

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