



Federaal Kenniscentrum
voor de Gezondheidszorg
Centre Fédéral d'Expertise
des Soins de Santé

HTA Molecular Diagnostics in Belgium

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Project Scope

- **In scope**
 - **CMD tests microbiology and (hemato)-oncology**
- **Out of scope**
 - **HPV (separate KCE HTA project)**
 - **Human genetic tests**
 - **(Hemato)-oncology tests at Centers for Medical Genetics (CMGs)**
 - **ARLs, blood supply, tissue typing, epidemiology**



Centres for Molecular Diagnosis

- **Royal Decree 1998: Centers for Molecular Diagnosis (CMDs)**
 - **Transient solution**
 - **Fixed RIZIV/INAMI budget of 6.5 Mio Euro**
- **2000: from 10 to 18 CMDs**
- **2005: legal basis rejected by Council of State**



Mission of the CMD's (RD 1998)

- **Inform hospitals**
- **Perform clinical 'routine' testing**
- **Specialists' training**
- **Evaluate diagnostic value (incl. kits)**
- **Propose nomenclature**
- **Implement internal and external QA**
- **Participate to international EQA**
- **QA of nomenclature tests**



Data Sources

- **Tests: questionnaires, SOPs, CMD activity reports and QA reports, RIZIV/INAMI**
- **Costs: CMD financial report and invoices**
- **Customer feedback: interviews in 6 non-CMD hospitals**
- **IVD kits: IVD industry**
- **International comparison: billing codes**



Results - Survey CMD Test Methods

- **594 method questionnaires received for 94 tests**
- **In-house methods: 79%**
 - **Not standardized across CMDs**
 - **67% of the in-house methods are not validated**
 - **SOP available for 60% of the non-validated in-house methods**
- **Reported average test turnaround time (TAT)**
 - **RT-PCR/PCR tests in microbiology: mean 1.8 - 9.4 d**
 - **RT-PCR/PCR tests in hemato-oncology: mean 6 - 12 d**
- **Test interpretation by laboratory alone in 80%**



Survey Test Characteristics - 1

- **Extrapolation of reported studies to local in-house method may not be appropriate**
- **Hemato-oncology**
 - **Diagnostic accuracy of (RT-)PCR vs cytogenetics not well-documented, eg t(8;21) and t(15;17)**
 - **Healthy individuals may test positive for (RT-)PCR eg t(14;18), t(2;5), t(8;21) and t(15;17)**
 - **Bad quality of samples often cited as reason for no test result**



Survey Test Characteristics - 2

	Micro Hem/Onc	% reported	Negative impact on patient health	Additional health care costs
No result	Micro	<10%		Yes
	Hem/Onc	5-10%		Yes
False positives	Micro	<10%	Yes	Yes
	Hem/Onc	Unknown	Yes	Yes
False negatives	Micro	May be higher		Yes
	Hem/Onc	Unknown	Yes	Yes



Feedback of CMD Customers

- **Involvement of local lab varies**
 - **CMD often selected by clinician: many CMDs offer services to a single hospital**
 - **Hemato-oncologist ships samples to CMD and CMG**
 - **Test selection/addition by receiving lab**
 - **TAT may be too long e.g. for HSV**
- **CMDs are phoned for results, written report is late, no standardised reporting, little backup expertise**
- **Clinicians lack information on molecular tests**
- **Demand for education/training exceeds supply**



CMD Quality Aspects

- **No internal QA guidelines**
- **External QA for molecular tests in nomenclature**
 - **Mission CMDs in contradiction to IPH mission**
 - **No specific molecular test EQA was organized by either party**
- **External QA for CMD tests**
 - **CMD QA rounds organised and reported**
 - **Not really “external”**
 - **Results and concepts used: excellent to poor**
- **CMD participation to international EQA: limited**
- **ISO accreditation: introduced in 3 CMDs**



International Regulations IVDs

- **EU**
 - IVD (CE label, >200 kits for CMD tests) or RUO
 - Often IVD CE self-certification by manufacturer
 - No clear rules for in-house tests
- **US**
 - FDA clearance or approval, often also used as condition for financing. Small number of kits available.
 - GMPs required for in-house test components (ASRs, no RUO)
 - Intellectual property licence fees (in-house tests)



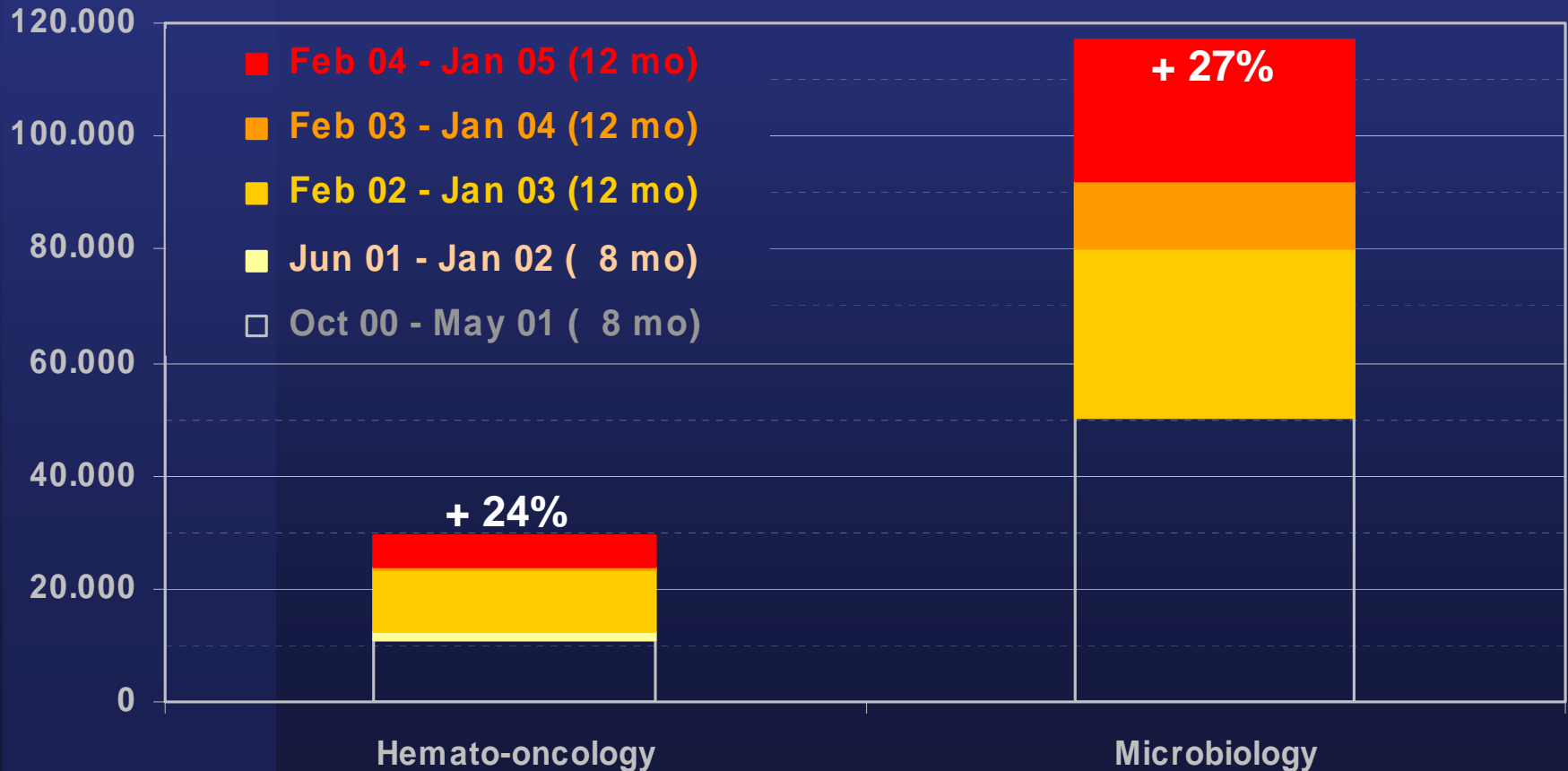
Billing systems in other countries

- **Billing codes in ambulatory care**
 - Studied for Australia (Au), France (Fr), Germany (Ge), Switzerland (Swi), The Netherlands (NI), UK, US.
- **Microbiology**
 - Specific code per micro-organism, list differs by country, also generic codes in Au, Ge, NI.
 - Fee per test differs by country, but is similar for Ge and Fr
- **Hemato-oncology**
 - Generic codes for cytogenetics and amplification based tests
 - France: no codes for PCR tests
 - Switzerland: limited list of translocations (PCR)
 - Australia: PCR only for acute leukemia and CML



Year-to-year Growth in Volume

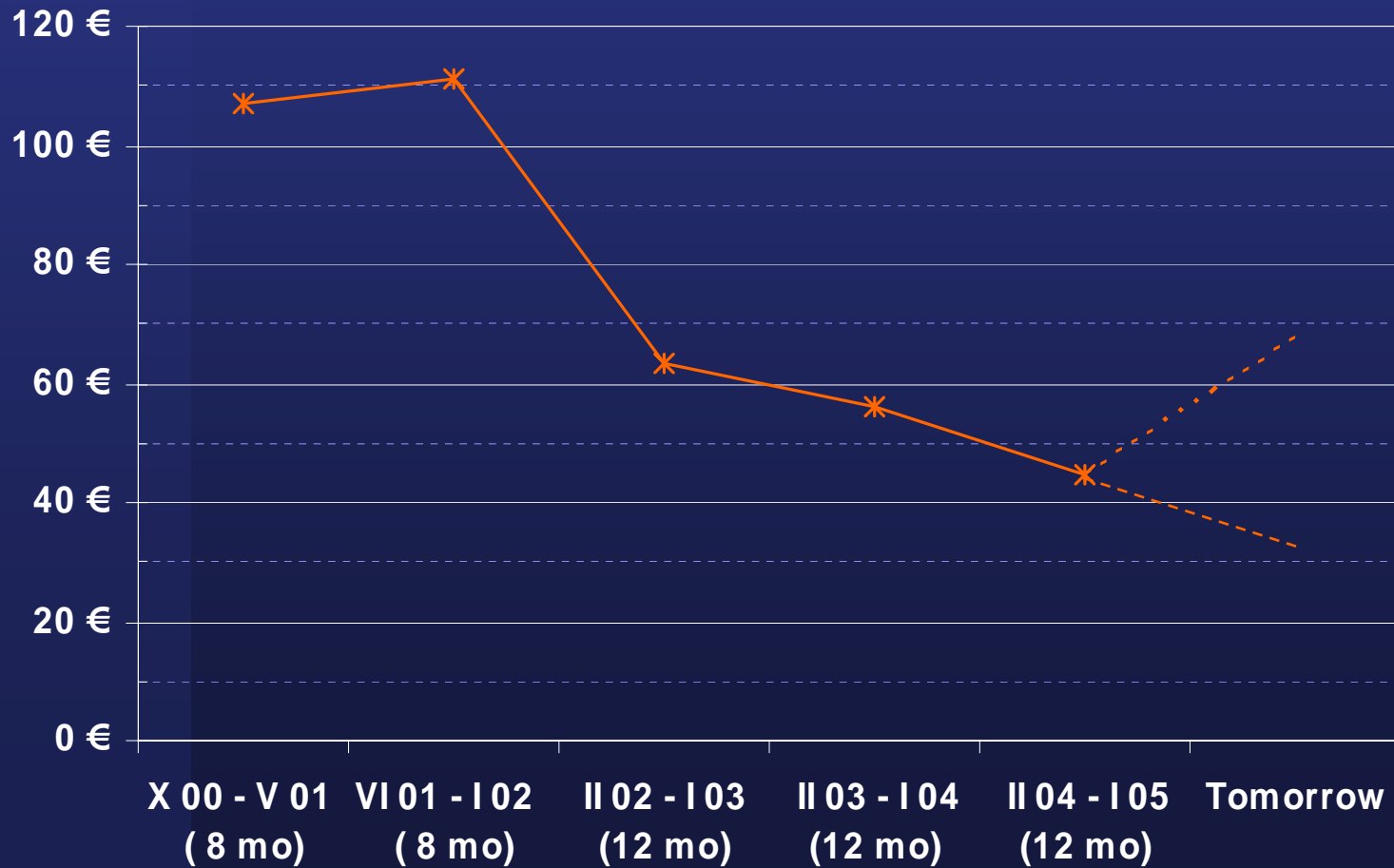
Tests per year





Mean reimbursement per test

EURO/test





Deviations and irregularities

Depreciation :

- Inadequate allocation of depreciations according to their use
- Y-to-Y variation in the acquisition value of the same equipment
- No mention of the acquisition date
- Extra financial costs charged
- Equipment not in the CMD (but invoiced) or used for other purposes (Agilent)

Small equipment :

- Inadequate allocation of equipments according to their use
- Expenses sliced or not allowed (office, computer, printers,...)
- Expenses nested elsewhere (usually within the reagents)
- Discrepancy with regards to the accounted value

Maintenance contracts & repairs:

- Inadequate allocation of the contracts according to their use
- Discrepancy with regards to the accounted value
- Repairs nested elsewhere (usually within the reagents)

Reagents :

- No copy of the invoice for the reagents bought (mandatory)
- Invoices out of the time period considered, Belgian VAT charged twice
- Cost of MTB, CT, NG, HCV qual, inherited diseases diagnostics
- Computers, books, translations, transportation costs of employees, catering
- Training, membership, financial agreement with a non-CMD lab,
- No mention of the VAT paid on goods bought outside Belgium according to hospital books



The Polymerase Chain Reaction

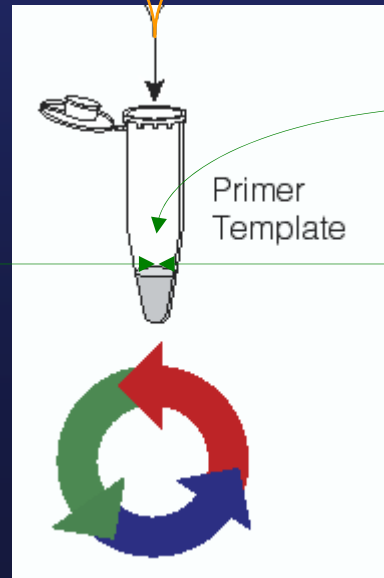
PCR Master Mix

includes

Taq DNA Polymerase
1.25 U

Template
 10^4 copies

Final
volume
50 μ l



Forward & reverse
primers 15-30 bases long
20 pMol each
Probe
5 pMol



Activity of CMDs in 2003

Total nr. of tests	In-house tests*	Nr. based on <i>Taq invoices</i> **	Ratio **/*
5 172	4 089	10 320	2.5
8 808	7 156	23 300	3.3
4 459	2 326	8 000	3.4
8 378	5 739	21 400	3.7
7 062	5 894	22 000	3.7
1 682	1 605	7 200	4.5
19 373	13 754	65 800	4.8
6 801	4 682	25 300	5.4
7 341	4 596	28 000	6.1
5 022	3 856	27 412	7.1
5 533	2 062	15 600	7.6
3 317	1 811	14 450	8.0
5 865	3 226	26 856	8.3
4 004	4 004	36 450	9.1
5 218	3 231	33 200	10.3
8 219	3 853	57 000	14.8
106 254	71 884	422 288	5.9
2 571	301	3 900	13.0
5 619	3 760	75 100	20.0



Personnel at work for PCRs in the 16 CMDs

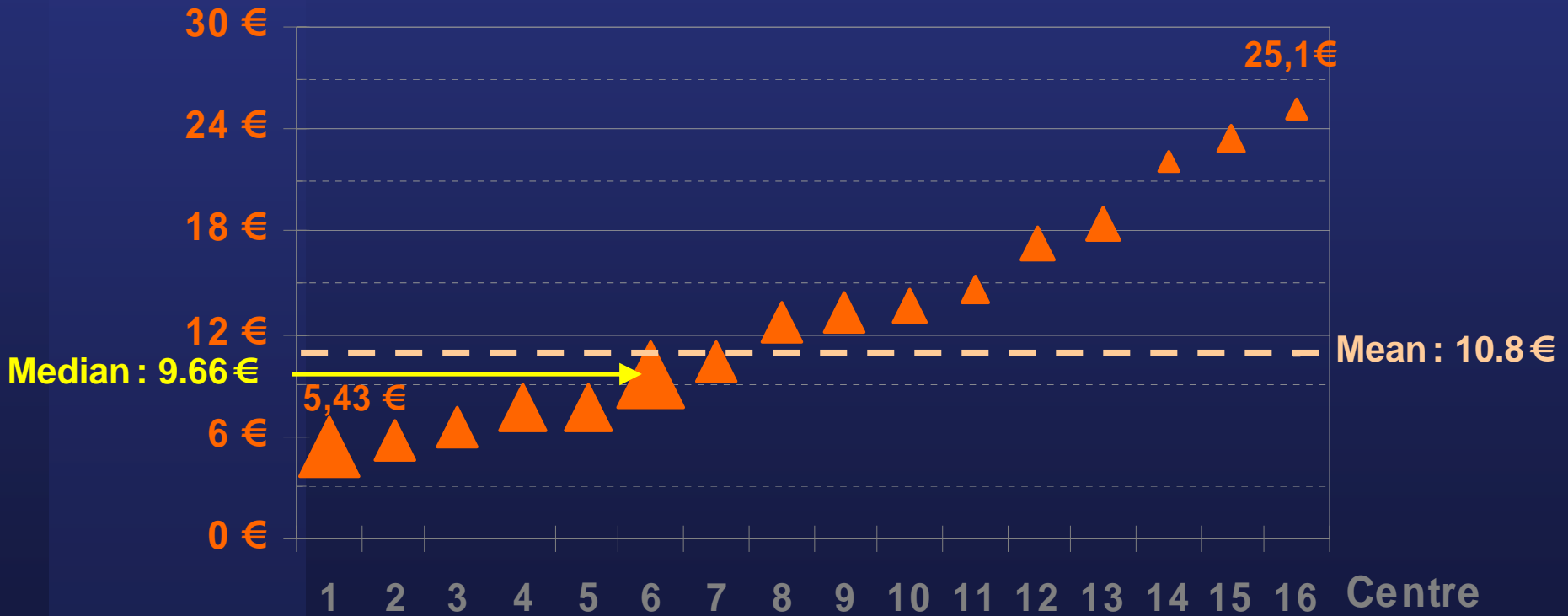
Personnel	Wage at start	Today
28.21 full time scientists (42 315 hrs)	49 579 €	54 379 €
68.10 full time technologists (102 150 hrs)	37 184 €	40 784 €
7.62 full time secretaries (11 430 hrs)	29 747 €	32 627 €

Assumptions: 200 workdays per year, 7.5 hours per workday



Personnel Cost per single PCR

Cost per test





Consumables cost of a HBV qualitative PCR

Purification - Extraction

250 QIAamp DNA blood Mini Kit (QI 51 106)	2.7632 €
1 L Ethanol 99-100% PA UCB 1115 (4 111 152)	0.0407 €

Amplification

800 tests HotStarTaq PCR Master Mix 1000 U (QI 203 445)	0.8663 €(x2)
Forward primer 0.20 µMol (4 353 424)	0.0003 €(x2)
Reverse primer 0.20 µMol (4 353 424)	0.0003 €(x2)
25 ml Nuclease-Free Water (P1193)	0.0278 €(x2)

Electrophoresis

500 gr Pronarose D-1 LEO (S103a)	0.1983 €(x2)
4 l Tris-Borate-EDTA Buffer 10x Concentrate (T4415)	0.1713 €(x2)
250 µl (50 lanes) 100 bp dna ladder (G2101)	0.1190 €(x2)

Consumables

1000 thin wall pcr tubes 200 µl with cap (179 401)	0.0643 €(x2)
960 filtertips 1-100 µl (ART2065E)	0.0832 €(x3)
960 filtertips 1-200 µl (MBP2069)	0.0742 €
800 filtertips 100-1000 µl (MBP2079E)	0.0890 €
100 safeskin purple nitril gloves M (SSK52 002M)	0.0330 €

Total

6.1447 €



Consumables for an in-house RT-PCR (HCV Qual.)

Purification - extraction

250 QIAamp Viral RNA Mini Kit (QI 52 906)	3.7485 €
1 L Ethanol 99-100% PA UCB 1115 (4 111 152)	0.0517 €

Reverse transcription

MLV-RT 40,000 U (28 025 013)	0.1128 €(x2)
DnTP 40 µMoles (U1240)	0.1239 €(x2)
10,000 units rRNasin Ribonuclease Inhibitor (N2 515)	0.4641 €(x2)
Reverse primer 0.20 µMol (4 353 424)	0.0001 €(x2)
1 ml M-MLV RI Buffer (18 057 018)	0.0607 €(x2)

Amplification

Probe TAQ-FT 0.20 µMol (4 353 426)	0.0001 €(x2)
Forward primer 0.20 µMol (4 353 424)	0.0001 €(x2)
Reverse primer 0.20 µMol (4 353 424)	0.0001 €(x2)
25 ml Nuclease-Free Water (P1193)	0.0139 €(x2)
2,000 tests TaqMan Universal PCR Master Mix (4 305 719)	1.9396 €(x2)

Consumables

960 ABI PRISM 96-Well Optical Reaction Plate (4 306 737)	0.0700 €(x2)
2400 ABI PRISM Optical Caps (4 323 032)	0.0431 €(x2)
960 filtertips 1-100 µl (ART2065E)	0.0832 €(x3)
960 filtertips 1-200 µl (MBP2069)	0.0742 €
800 filtertips 100-1000 µl (MBP2079E)	0.0890 €
100 safeskin purple nitril gloves M (SSK52 002M)	0.0330 €

Total

9.8192 €



Full cost of an in-house test (in duplicate)

	DNA	RNA
Consumables cost	6.14 €	9.82 €
Depreciation cost	2.98 €	2.98 €
Subtotal	9.12 €	12.80 €
Labour*, mean :	21.60 €	21.60 €
TOTAL	30.72 €	34.40 €

* Mean 21.60, range: 10.86 – 50.22 €



Cost of kits

HBV quantitative CA HBV Monitor (1 118 331) Roche, 9 centres: 58.11 €

HCV qualitative CA HCV AMP 2^d gen (1 111 132) Roche, 9 centres: 20.34 €

HCV quantitative CA HCV Monitor (1 118 404) Roche, 10 centres: 85.10 €

HCV genotyping LINEPRB HCV GENO Bayer , 11 centres: 70.72 €

HPV Hybrid Capture II (5196-1230) Digene, 14 centres: 14.28 €

HER-2/neu HER-2/neu (F-ISH-CPT200) Ventana, 8 centres: 87.31 €

Cost of controls included (8 per 100 samples)

Depreciation of COBAS (3.00 €) not included nor personnel costs



CMD Study – Conclusions

- Easy access to 94 molecular tests
- Increasing test volumes, fixed overall budget
- PCR test (in duplo) costs 33 Euro on average

But ...

- Little activity to evaluate diagnostic efficacy
- Guaranties for quality not sufficient
- Communication and service can be improved
- Aims were achieved only partially



Proposed Framework - Efficacy

- **Levels of diagnostic efficacy**
 - **Level 1: technical efficacy**
 - **Level 2: diagnostic efficacy**
 - **Level 3: diagnostic gain**
 - **Level 4: effect on management**
 - **Level 5: effect on patient outcome**
 - **Level 6: cost-effectiveness**
- **Level 3-4 (clinical utility) needed to include test in routine**



Proposed Framework - Effectiveness

- **Effectiveness in daily routine**
 - **Availability kits**
 - **Local validation, QA, ISO accreditation**
 - **Local cost, budget impact**
 - **Local service (TAT, standardised report)**
 - **Effect of decentralisation on quality of patient care and cost**
 - **Risk of inappropriate prescription**



Diagnostic sensitivity of t(14;18) PCR for follicular lymphoma

Region, year published	# Patients and Sample Type	PCR Type	t(14;18) diagnostic sensitivity (PCR)	t(14;18) MBR positive	t(14;18) Mcr positive	t(14;18) other breakpoints (and remarks)
South Africa, 1999 ³⁵	64 FL (fixed, paraffin)	PCR	29 (45%)	25 (39%)	4 (6%)	
Turkey, 2000 ³⁶	67 FL (fixed, paraffin)	PCR	46 (69%)	43 (64%)	3 (4%)	
Czech Rep., 2001 ³⁷	53 FL (blood or BM)	PCR	25 (47%)	22 (42%)	2 (4%)	1 (2%) both MBR/mcr
Switzerland, 2002 ²⁶	59 FL (fixed, paraffin)	PCR and LD-PCR	PCR: 27 (46%) LD-PCR: 42 (71%)	19 (32%)	2 (3%)	icr: 6 (10%)
UK, 2003 ²⁴	28 FL (frozen)	PCR (BIOMED-2)	23 (82%)	16 (70%)	5 (21%)	5'mcr: 3 (9%)
UK, 2003 ²⁴	20 FL (fixed, paraffin, paired)	PCR (BIOMED-2)	8 (40%)	5 (25%)	3 (15%)	
Spain, 2003 ³⁸	60 FL (fixed, paraffin, blood, BM)	PCR	40 (67%)	39 (65%)	1 (2%)	DNA quality too low in another 9 patients



Diagnostic sensitivity of t(14;18) PCR for follicular lymphoma

Region, year published	# Patients and Sample Type	PCR Type	t(14;18) diagnostic sensitivity (PCR)	t(14;18) MBR positive	t(14;18) Mcr positive	t(14;18) other breakpoints (and remarks)
Malaysia, 2003 ²⁸	50 FL (fixed, paraffin)	Nested PCR	30 (60%)	25 (50%)	5 (10%)	FISH identified t(14;18) in another 4
Malaysia, 2004 ³⁹	62 FL (fixed, paraffin)	Nested PCR	42 (68%)	32 (52%)	9 (14%)	1 (2%) both MBR/mcr
Argentina, 2004 ³⁰	83 FL (fresh tissue and blood)	PCR and LD-PCR	PCR: 42 (51%) LD-PCR: 65 (78%)	28 (34%)	14 (17%)	
Brazil, 2004 ⁴⁰	48 FL (fixed, paraffin)	PCR	46 (96%)	41 (86%)	5 (10%)	
UK, 2004 ⁴¹	88 FL (mainly LN)	Real-time PCR	41 (47%)	41 (47%)	NA	NA
France, 2002 ³⁴	113 t(14;18)+ FL (LN or BM)	PCR	104 (92%)	73 (65%)	10 (9%)	3'Bcl-2: 14 (12%); 5'mcr: 7 (6%)
Europe, 2003 ³² (pre optimisat.)	124 t(14;18)+ FL	PCR	109 (88%)	83 (67%)		2 nd multiplex for mcr, 5'mcr, 3'MBR: 26 (21%)
UK, 2005 ⁴²	57 t(14;18)+ FL		33 (58%)	26 (46%)	4 (7%)	lcr: 3 (5%)



Selected Test Evaluations – t(14;18)

- **Diagnostic sensitivity of t(14;18) PCR for follicular lymphoma**
 - Overall, t(14;18) is detected in about 45 to 70% of histologically confirmed FL cases using short range PCR
 - This is lower compared with the diagnostic sensitivity reported for interphase FISH of 88% and 100%.
 - Some PCR studies only included t(14;18) positive FL samples, which of course resulted in a higher detection rate by PCR.



Selected Test Evaluations – t(14;18)

- **t(14;18) BCL2-IgH in follicular lymphoma**
 - **Detection can be of use at diagnosis**
 - **FISH is superior to PCR at diagnosis**
 - **Routine use of PCR for MRD monitoring not recommended**



HTAs and Systematic Reviews

<i>Test</i>	<i>Indication</i>	<i>Level of diagnostic efficacy</i>	<i>Reference</i>
HCV qualitative, quantitative and genotyping	Selection and management of interferon based treatment	Level 6: cost-effective	Pilot assessment
Mycobacterium tuberculosis	Smear-positive samples	Level 6: cost-effective, if testing is centralised	Dowdy, 2003
Borrelia burgdorferi	Lyme disease	Level 2: fair diagnostic sensitivity, not suitable for primary diagnosis	Dumler, 2001
PCR Herpes simplex virus	Meningo-encephalitis	Level 1: further research needed	Linde, 1997
PCR Enterovirus	Meningitis	Level 1: analytical accuracy not sufficient	Pilot assessment
PCR t(8;21) AML1-ETO en inv(16) CBFB-MYH11	Acute myeloid leukemia	Level 6: cost-effective	MSAC, 2003
PCR t(15;17) PML-RARA	Acute promyelocytic leukemia	Level 6: cost-effective	MSAC, 2003
PCR t(14;18) BCL2-IgH	Follicular lymphoma	Level 2: lower diagnostic sensitivity, but less expensive than FISH	Pilot assessment



Sources of Evidence Synthesis

- **If HTA reports or systematic reviews do not exist, are of inferior quality or are outdated, original research should be searched.**



General Recommendations

- **Emerging test (not validated, no clinical evidence)**
 - **Testing (and financing) only in the context of clinical research with study protocol**
- **Validated test with clinical evidence of utility**
 - **Introduce in clinical routine at an appropriate cost per test**
 - **EQA participation and ISO accreditation mandatory (incl. in-house tests)**
 - **Kit validation data should be made accessible**
- **Medicines evaluation should include test assessment**
- **A policy of systematic test assessments will impact on (human) resources needed**



Recommendations Hemato-oncology

- **Testing schemes to be included in hospital handbook for oncology care**
- **Laboratories should also perform the cytogenetic testing (need for stepwise testing and integrated interpretation)**
- **Different options for financing (incl. nomenclature)**
- **Full panel (per disease) of accredited tests is required**
- **Stop financing by human genetics nomenclature**



Implementation Flowchart

Validation and clinical efficacy

Availability kits, Cost
Effect of decentralisation
Risk inappropriate prescription

Yes No →

↓
Implement
↓
↓

Additional studies
(project-based financing)

ISO 15189, EQA

Microbiology large volume *or*
shipment inappropriate →

Nomenclature

Diagnostic rules

Microbiology small volume
(panel) →

Microbiology
reference centre

Transparent selection
Epidemiology link

Hemato-onco / pathology
(full panel) →

Nomenclature or
other

Oncology handbook
scheme
Cytogenetic and
molecular full service



Thank you!