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(21) International Application Number: PCT/NL98/00542 (22) International Filing Date: 18 September 1998 (18.09.98) (30) Priority Data: 97202858.3 18 September 1997 (18.09.97) EP (71) Applicant (for all designated States except US): ERASMUS UNIVERSITEIT ROTTERDAM [NL/NL]; Dr. Molewater- plein 50, NL-3015 GE Rotterdam (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): VAN DONGEN, Jacobus, Johannes, Maria [NL/NL]; Parallelweg Zuid 147, NL-2914 LE Nieuwerkerk aan den IJssel (NL). PONGERS-WILLEMSE, Martha, Jacoba [NL/NL]; C. Kouwenbergzoom 197, NL-3065 HG Rotterdam (NL). (74) Agent: SMULDERS, Th., A., H., J.; Vereenigde Octrooibu- reau, Nieuwe Parklaan 97, NL-2587 BN The Hague (NL).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims</i> <i>and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 6 May 1999 (06.05.99)
(54) Title: DETECTION OF MINIMAL RESIDUAL DISEASE IN LYMPHOID MALIGNANCIES (57) Abstract The invention relates to the field of cancer diagnosis, more specific to the monitoring of disease development during and after treatment. The invention comprises a method for determining minimal residual disease comprising amplifying nucleic acid molecules using at least one primer reactive with a common gene segment and further comprising identifying malignancy-specific nucleic acid sequences by hybridising with a fluorogenic probe specifically and selectively reactive with said malignancy-specific nucleic acid sequences.		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/NL 98/00542

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GIBSON U E M ET AL: "A NOVEL METHOD FOR REAL TIME QUANTITATIVE RT-PCR" GENOME RESEARCH, vol. 6, no. 10, October 1996, pages 995-1001, XP000642796 see the whole document	1-9
Y	GELMINI ET AL.: "QUANTITATIVE POLYMERASE CHAIN REACTION-BASED HOMOGENEOUS ASSAY WITH FLUOROGENIC PROBES TO MEASURE c-erbB-2 ONCOGENE AMPLIFICATION" CLIN. CHEMISTRY, vol. 43, no. 5, May 1997, pages 752-758, XP002070263 see the whole document	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HEID C A ET AL: "REAL TIME QUANTITATIVE PCR" GENOME RESEARCH, vol. 6, no. 10, October 1996, pages 986-994, XP000642795 see the whole document ---	1-9
Y	LEE L G ET AL: "ALLELIC DISCRIMINATION BY NICK-TRANSLATION PCR WITH FLUOROGENIC PROBES" NUCLEIC ACIDS RESEARCH, vol. 21, no. 16, 11 August 1993, pages 3761-3766, XP000470188 see the whole document ---	1-9
Y	WO 97 05278 A (DALGETY PLC ;ANDERSSON LEIF (SE); MOLLER MARIA JOHANSSON (SE); WAL) 13 February 1997 see the whole document ---	1-9
Y	WO 96 34983 A (PERKIN ELMER CORP) 7 November 1996 see the whole document ---	1-9
Y	US 5 538 848 A (LIVAK KENNETH J ET AL) 23 July 1996 see the whole document ---	1-9
Y	LANG R ET AL: "A rapid method for semiquantitative analysis of the human Vbeta -repertoire using TaqManPCR" JOURNAL OF IMMUNOLOGICAL METHODS, vol. 203, no. 2, 25 April 1997, page 181-192 XP004059583 see the whole document ---	1-9
Y	BEISHUIZEN ET AL.: "MOLECULAR BIOLOGY OF ACUTE LYMPHOBLASTIC LEUKEMIA: IMPLICATIONS FOR DETECTION OF MINIMAL RESIDUAL DISEASE" ACUTE LEUKEMIAS V, 1996, pages 460-474, XP002095128 see the whole document ---	1-9
Y	WO 92 09702 A (UNIV TEXAS) 11 June 1992 see the whole document ---	1-9
Y	WO 91 15600 A (HOPE CITY) 17 October 1991 see the whole document ---	1-9
	-/--	

INTERNATIONAL SEARCH REPORT

In ternational Application No

PCT/NL 98/00542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CALLAGHAN ET AL.: "CHARACTERISATION OF K-ras MUTATIONS BY A NON GEL-BASED PROCEDURE COMBINING ARMS PRIMER EXTENSION AND TaqMan" AM. J. OF HUM. GEN., vol. 61, no. 4 Suppl., 28 October 1997, page A62/332 XP002070264 see the whole document ----	1-9
P,X	GERARD ET AL.: "IMPROVED QUANTITATION OF MINIMAL RESIDUAL DISEASE IN MULTIPLE MYELOMA USING REAL-TIME POLYMERASE CHAIN REACTION AND PLASMID-DNA COMPLEMENTARITY DETERMINING REGION III STANDARDS" CANCER RESEARCH, vol. 58, 1 September 1998, pages 3957-3964, XP002095189 see the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/NL 98/00542

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9705278 A	13-02-1997	AU 6621296 A	26-02-1997
		CA 2227826 A	13-02-1997
		CN 1196755 A	21-10-1998
		EP 0842296 A	20-05-1998
WO 9634983 A	07-11-1996	AU 693023 B	18-06-1998
		AU 5442896 A	21-11-1996
		CA 2219891 A	07-11-1996
		EP 0826066 A	04-03-1998
		US 5691146 A	25-11-1997
US 5538848 A	23-07-1996	AU 695561 B	13-08-1998
		AU 4283696 A	06-06-1996
		CA 2201756 A	23-05-1996
		EP 0792374 A	03-09-1997
		JP 10510982 T	27-10-1998
		WO 9615270 A	23-05-1996
		US 5723591 A	03-03-1998
WO 9209702 A	11-06-1992	AU 9147991 A	25-06-1992
		US 5840492 A	24-11-1998
WO 9115600 A	17-10-1991	AU 7762091 A	30-10-1991