



1st. Quarter 2008 Presentation

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Chief Executive Officer

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DiA**G**ENiC

FOR EARLIER DISEASE DETECTION



1st Quarter Highlights

- New Patents Accepted on Alzheimer's Disease for Europe
- Patient inclusion completed in the Indian multi centre study
- MoU for distribution of breast cancer test in India
- Development of a diagnostic product for Parkinson's disease has been initiated
- Increased global recognition following scientific presentations

Agenda:

1st Quarter
2008
Presentation

- 1st Quarter Highlights
- 1st Quarter Finance
- Product Development and Clinical Studies
- Commercial Strategies
- Outlook

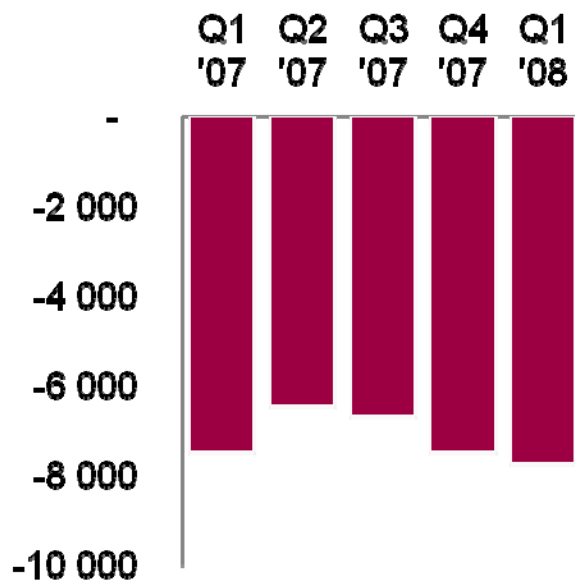
Agenda:

1st Quarter 2008 Presentation

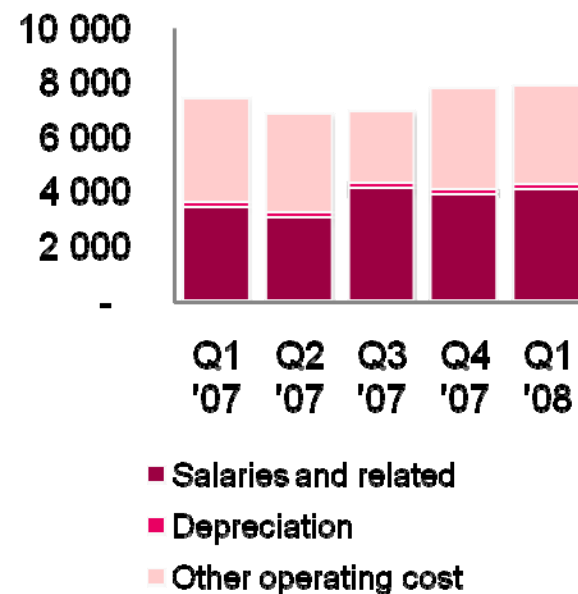
- 1st Quarter Highlights
- **1st Quarter Finance**
- Product Development and Clinical Studies
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Finance, Profit & Loss

Net Income
(thousand NOK)



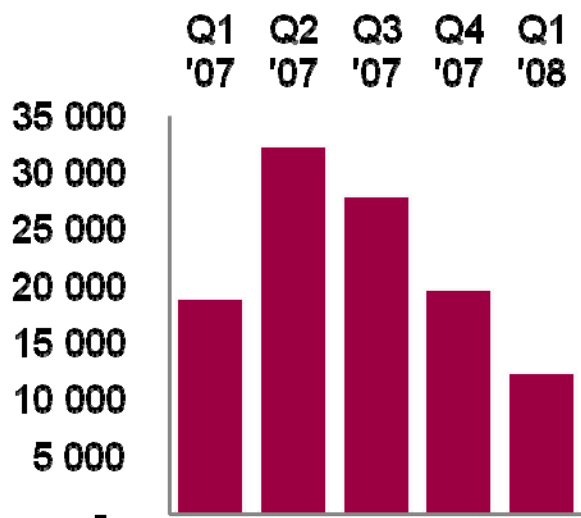
Operating Cost
(thousand NOK)



- Salaries and related
- Depreciation
- Other operating cost

Finance, Cash Position

Cash and Cash equivalents (thousand NOK)



- Cash and cash equivalents NOK 12.4m at 31 March 2008
- Board of directors have the power of attorney to raise share capital by up to 8m shares
- Kaupthing engaged as manager in the equity offering

Finance, 2008 outlook

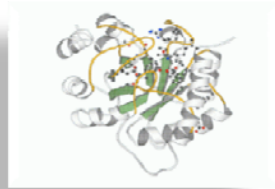
- Key milestones for Q2 '08
 - Equity offering expected to be completed
- High activity with limited increases in burn rate for Q2 '08 compared with previous quarter

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Central Theme in DiaGenic Technology



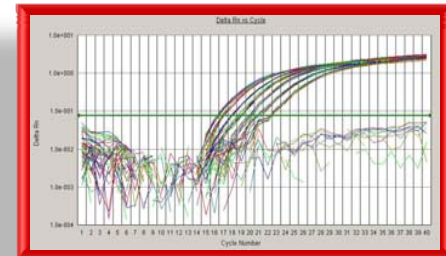
DNA



RNA



Protein



- RNA plays a central role in translating what is written in our genes to what is expressed in our bloodstream
- RNA expression is measured by qRT-PCR and forms the basis of our proprietary gene signature

DiaGenic's
Product
Development
Focus



Alzheimers
Disease



Parkinsons
Disease



Breast Cancer

DiaGenic's
Product
Development
Focus



Alzheimers
Disease



Parkinsons Disease



Breast Cancer

Summary Table of AD Clinical Studies

Study size includes both patient and control samples

Study Code	Description	Study size (patients) *	Current Status
AD0501	AB1700 Discovery Study	280	Completed
AD060M	TaqMan® Pilot Study	59	Completed
prAD106	CodeLink Gene Validation	120	Completed
AD0602	TaqMan® Gene Validation	120	Completed
AD0702	TaqMan® Prototype Optimization	104	Completed
AD0601	FUGE AD Norway	900	Ongoing
AD0701	FUGE AD Sweden	190	Ongoing
AD0703	New Platform Gene Validation	104	Ongoing
AD0706	EDAR EU study for AD biomarkers	360	Ongoing
AD0704	UCD multiethnicity Study (FDA)	TBD	Planning phase

*Study size indicates the total number of patients recruited to each study

Alzheimer's
Disease

DiaGenic
Studies

CLINICAL GRADING OF ALZHEIMER'S DISEASE AND EARLY DETECTION WITH A BLOOD BASED GENE EXPRESSION SIGNATURE



CLINICAL GRADING OF ALZHEIMER'S DISEASE AND EARLY DETECTION WITH A BLOOD BASED GENE EXPRESSION SIGNATURE

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Introduction

Alzheimer's is the most common form (around 50-60%) of all dementia types and is the seventh leading cause of death in all ages in the USA. Although it is estimated that there are over 24 million people worldwide with dementia today [3], this figure is projected to double by 2025 as a result of the rising age in populations particularly in less developed countries.

Clearly the socio-economic costs are huge with the average lifetime cost of care for an individual with Alzheimer's estimated to be \$174,000. Moreover, this does not include the additional costs to business for employees who are caregivers. Although there is currently a lack of treatment options to arrest the disease, early diagnosis and active management strategies can temporarily delay the onset of the more debilitating symptoms. Thus, early and accurate detection of AD is therefore critical to improving the quality of life of the patient and caregivers.

Current diagnosis of AD involves detailed clinical interviews, cognitive tests, imaging techniques (e.g., MRI, CT, PET, SPECT) and in some countries routine CSF biomarkers. However, despite this variety of testing approaches it is still difficult to make an accurate diagnosis at an early stage of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult.

Previous independent studies have recently indicated that a peripheral blood based test could be used for diagnostic profiling in neurological diseases [24]. Indeed, we have more recently shown that a blood based gene signature can accurately identify AD patients [7, 8] using the Applied Biosystems AB7900 platform on 36- and 48-gene format TLDA (TaqMan Low Density Array) cards [9-11]. Prediction accuracies using independent patient cohorts on different technology platforms ranged between 81-87% and exceed those recommended for AD [25]. However, it was not clear if this same signature could be used to identify differences in clinically graded AD samples. We therefore performed a validation study to determine if any of the gene signatures used in the development of the prototype could be used to differentiate AD patient samples based on the severity of disease.

Materials and Methods

Patient samples

Whole blood was collected prior to diagnosis from 251 individuals in PATgene™ Blood RNA tubes from memory clinics in Norway. These included 125 patients subsequently diagnosed with AD (based on the ICD-10 criteria for dementia syndrome), 98 age-matched healthy controls and 28 young healthy controls (see Table 1). In addition 10 MCI patients were included in the study.

Table 3. Demographic information of patient and control groups, 1995

Samples	Age [years]		MMSE score		Gender	
	Mean	SD	Mean	SD	Female	Male
Alzheimer's disease (N=125)	77.3	7.9	21.9	4.5	59%	41%
Age-matched controls (N=98)	78.0	7.0	28.8	0.9	85%	15%
Young controls (N=28)	22.3	2.7	-	-	67%	33%

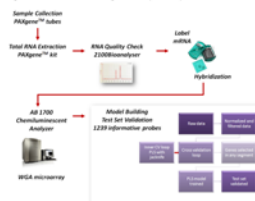
Table 2. Prediction results from the AG1700 Human whole genome array [8]

Study / Assay Format	Sensitivity	Specificity	Accuracy	ROC (AUC)
AB 1700 WGA Training set	85%	88%	87% (5%)	0.93
AB 1700 WGA Test set	84%	91%	87% (8%)	0.94

Sample preparation

An overview of the sample preparation and processing is shown in figure 1. Total RNA was extracted from blood samples using RNeasy[®] Blood RNA kit according to manufacturers instructions and quality assessed by NanoDrop spectrophotometer and Agilent 2100 Bioanalyzer. cDNA was prepared using the high-capacity cDNA archive kit from Applied Biosystems.

Figure 1. Overview of ABI 1700 whole genome survey microarray



Patient grading

In retrospectively grading the patients, the following factors were considered: MMSE score, clock drawing test score and Kendrick object learning test (KO) score. Although patients were graded according to the Clinical Dementia Rating Scale categories (CDR), the MMSE score was primarily used to determine the most appropriate AD grade.

Table 3. AD Grading Structure.

Patient Status	Grade	CDR	MMSE
Healthy controls	0	0	>28
Very Mild AD	1	0.5	26-30
Mild AD	2	1.0	23-25
Moderate AD	3	2.0	11-20
Severe AD	4	3.0	0-10

Gene sets and expression analysis

The gene expression analysis was done on the AB 1700 System, which contained an AD-specific gene signature in a custom format. The genes were selected based on the performance characteristics from previous studies using an Applied Biosystems Whole Genome Array [36]. A total of 9340 gene probes were available after data normalization. Some subsets of variables were selected previously for prototyping development. However, AD-grading was not used in the selection process (only AD/Healthy status). Subsequent testing of the following variables (probe sets) was done with respect to the assigned AD-grades: All variables; 1200-set; 384-set; and the 52-set.

AD-grade was used directly in model building. Cross-validation using ST-PLS regression on AD grades was conducted to see whether these grades (as continuous measures) were predictable from gene expression data.

ACKNOWLEDGMENTS

Initially PLS-DA classifiers for diseased/healthy prediction were used to predict health status. The predicted status was related to AD-grade for each AD-sample to see whether the most severe cases are predicted as most likely to be diseased [i.e., the largest distance from the classification border]. Statistical approaches used in the study included:

Plotting Predictions vs AD-grade, and PLS correlation-loading plots
Linear model fitting, predicting health status vs stage

ANOVA (one-way analysis for grade 1-3 with multiple testing adjustments)

Results and Discussion

The data presented show the lack of a definite trend of AD classification with AD grade from 1-4 indicating the complexity in predicting AD-grade solely from the currently available gene expression data (Figure 2). The differences between grade 1, 2 and 3 are subtle, with trained predictors tending to classify samples as grade 2, which is the dominating class in the data set.

The lack of a clear correlation with advancing AD grade is also consistent with other biomarkers [12]. CSF biomarker studies for A β 42 [13] and phosphorylated-tau [14] show stable levels throughout the course of the disease, while amyloid imaging studies with PIB-PET in mild AD patients suggests that amyloid deposition reaches an equilibrium or plateau very early in the course of AD [15]. This may reflect a more general principle in the biological progression of the disease and further emphasizes the need for early detection.

Interestingly, the MCI group identified in the current study support an increasing trend from healthy controls to AD grade 3, suggesting that the current gene expression signature could be of value in AD detection in the early stages of the disease. Continued follow-up of the MCI group may provide additional insight into the predictive value of the gene signature in identifying those patients most likely to progress to AD.

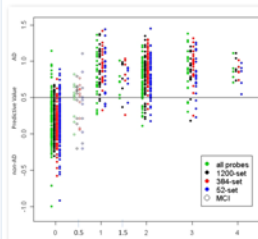


Figure 2. Prediction of AD based on the four models derived from the variable sets (all probes, 1280-set, 384-set and the 52-set). The predicted health-status for the minimum CV error model is plotted against the AD-grading. Grade 0 are healthy controls, 1 to 4 are AD grades very mild (1), mild (2), moderate (3) and severe (4). Twenty four AD patients were graded as "1" or "2" and were allocated grade 1.5 in the plot, in addition 20 MCQ patients were predicted and were allocated grade 0.5 in the plot.

Conclusions

- ❑ The gene expression signature appears to detect AD grades 1-4 with a similar level of accuracy independent of disease severity.
- ❑ A linear increasing trend from the healthy controls via the MCI group to AD grade 1 suggests some predictive value.
- ❑ Absence of a clear trend with increasing AD grade 1-4 may reflect the biological nature of the disease progression.
- ❑ Individuals within the MCI group may be associated with a tendency for

References

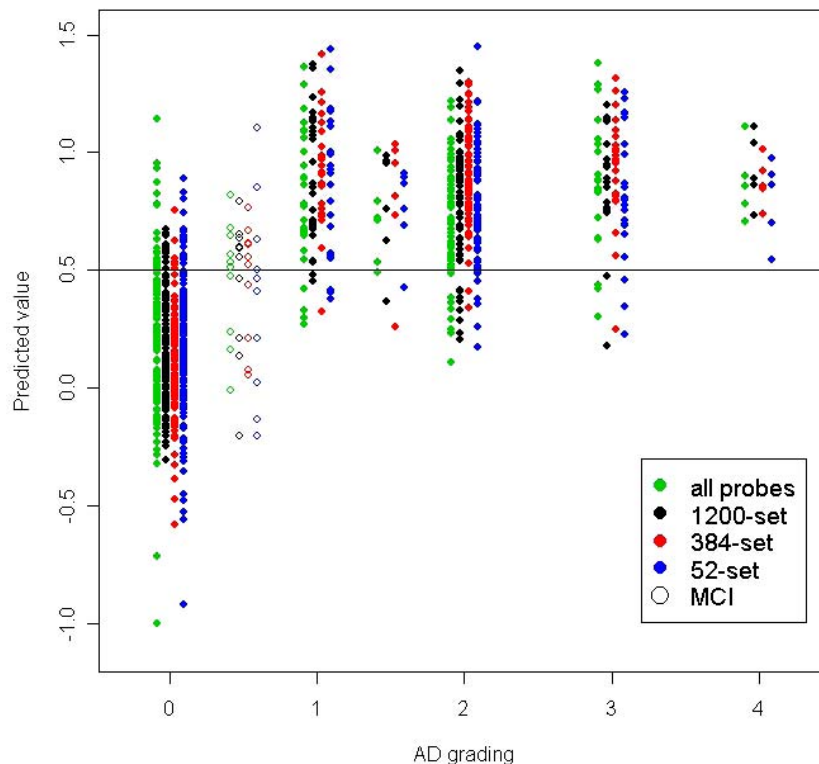
9. Linnemann AG, et al. (2007) Recurrence and early detection of Alzheimer's disease using a gene expression signature in blood. *J. Proteom. Anal.*, **8**, 1069-1076.
10. Linnemann AG, et al. (2007) Use of a gene expression signature in blood for early assessment of Alzheimer's disease. *Am. J. Geriatr.*, **55**, 101-107.
11. Linnemann AG, et al. (2007) Development of a blood-based gene expression test for the early detection of Alzheimer's disease. *P. J. Biomed. Biotechnol.*, **1**, 10-16.
12. Engelhardt J, et al. (2007) No association of CYP19A1 polymorphisms with ApoE4 genotype and length survival in definite Alzheimer's disease. *Biom. J.*, **100**, 2320-2324.
13. Anderson KE, et al. (2006) Cerebral amyloid-beta levels predict cognitive decline in Alzheimer's disease. *Arch. Neurol.*, **63**, 674-678.
14. Anderson KE, et al. (2006) Cerebrospinal fluid levels of amyloid-beta in Alzheimer's disease. *Alzheimer's Dis. Cogn. Dis.*, **20**, 289-293.
15. Engler M, et al. (2006) The use of amyloid deposition in patients with Alzheimer's disease. *Biom. J.*, **100**, 2309-2316.

All authors from Diafanis have competing interests. Authors from other institution have no competing interest.

5th
International
Pharmaco-
Economic
Conference on
Alzheimer's
Disease
(IPECAD),
Newark, USA



Predicted value vs. AD grading



- Gene expression signature show the same high accuracy independent of AD stage
- The test is useful in detecting very mild to moderate AD.
- Potentially even earlier stages of the disease.

DiaGenic's
Product
Development
Focus



Alzheimers Disease



Parkinsons
Disease



Breast Cancer



Parkinson's
disease

Project
initiated

- Development of DiaGenic's third product candidate, for the early diagnosis of Parkinson's disease has commenced with funding from the Michael J. Fox Foundation
- Based on information on informative probes from its partner in the USA (Dr Clemens Scherzer from Brigham and Women's Hospital) and from our own research, DiaGenic has assembled a gene selection.
- This selection is first being qualified on a RT-PCR based platform before being tested with Parkinson's samples collected from Harvard.

DiaGenic's
Product
Development
Focus



Alzheimers Disease



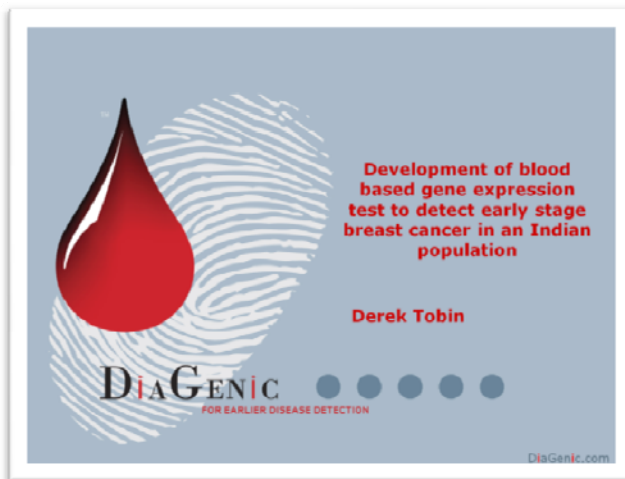
Parkinsons Disease



Breast Cancer

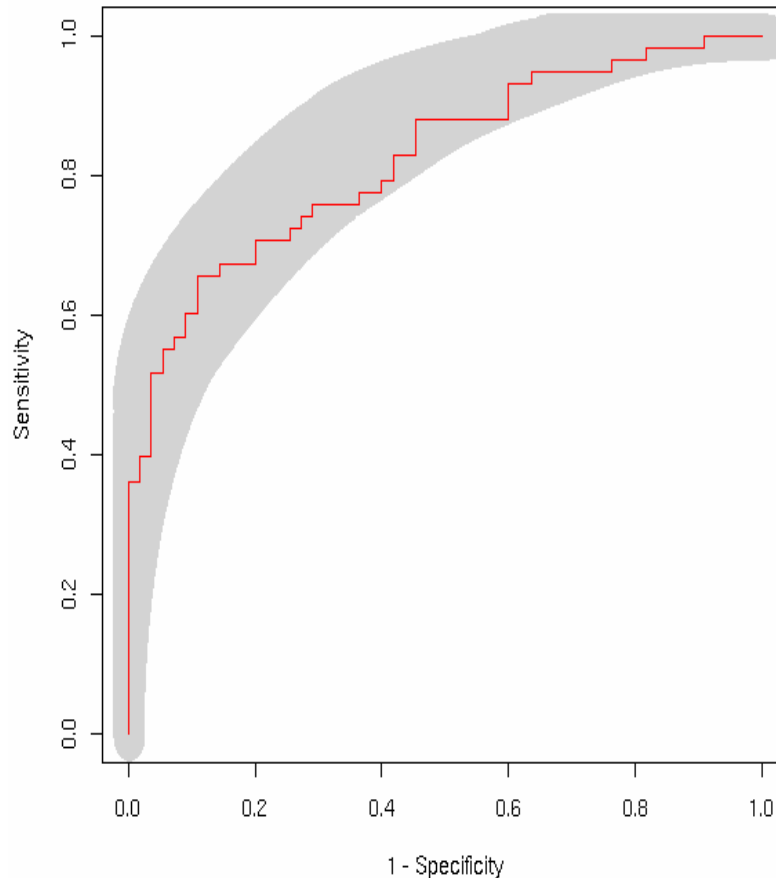
India clinical study

Congress presentations and posters



Interim
study
reported:

ROC
curve
from 113
patients



- Grey area = EU/US studies
- AUC India = 0.82
- Ethnic variability has no impact on diagnostic results
- Similar performance for pre- and post-menopausal
 - Improved sensitivity vs published data for mammography in pre-menopausal women
- Final enrolment Feb 08
- Planned launch of India kit mid 08

Targeting
launch in
India
in
2008

- **Laboratory partner:**
 - The Applied Biosystems partner and local distributor in India
 - Our current laboratory for the clinical study
 - Have during the last year demonstrated highly professional laboratory operations using our product and procedures
 - Will, through Applied Biosystem Inc, support new diagnostic assays in the Indian marketplace
- **Partner profile:**
 - Two shortlisted..



- South East Asia's & India's fastest growing Pathology Services
 - 750 collection centres
 - 321 laboratories
 - 1.100 employees
 - 5 mill patients pr year
- Extensive competencies within molecular diagnostics and experience in launching new diagnostic methods
 - A strategic and broad cooperation

*Link up for
a winning streak*

DiaGenic's Indian operations

- Analytical and Molecular diagnostic expertise
- Developer of test and owner of the IP

DiaGenic



- Molecular diagnostic expertise
- Blood collection and transport
- Test result report

**SRL
Ranbaxy**



- Analytical molecular expertise
- Blood extraction and PCR analysis

LabIndia



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Intellectual Property update


US 2002/022222A1

(19) **United States**
(12) **Patent Application Publication** (10) Pub. No.: **US 2002/0022222 A1**
(41) Pub. Date: **Feb. 21, 2002**

(54) **METHOD OF PREPARING A STANDARD DIAGNOSTIC GENE TRANSCRIPT PATTERN**

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(*) Notice: This is a publication of a continued prosecution application (CPA) filed under 37 CFR 1.53(d).

(21) Appl. No.: **09/429,003**
(22) Filed: **Oct. 28, 1999**

Related U.S. Application Data

(83) Continuation of application No. PCT/GB98/01261, filed on Apr. 30, 1998.

Foreign Application Priority Data

Apr. 30, 1997 (NO)..... NO 972086

Publication Classification

(51) Int. Cl.⁷ **C12Q 1/68; C07H 21/02; C07H 21/04; C12P 19/34**
(52) U.S. Cl. **435/6; 536/23.1; 435/91.2**

ABSTRACT

A method for preparing a gene transcript pattern probe kit characteristic of a disease or condition at a stage thereof in a prokaryotic or eukaryotic organism using mRNA which is differentially expressed in the disease or condition or stage as probes, methods of diagnosis using the method and kits for performing the same are disclosed.


US 2007/013465A1

(19) **United States**
(12) **Patent Application Publication** (10) Pub. No.: **US 2007/0134656 A1**
(41) Pub. Date: **Jun. 14, 2007**

(54) **PRODUCT AND METHOD**

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(21) Appl. No.: **10/535,414**
(22) PCT Filed: **Nov. 21, 2003**
(86) PCT No.: **PCT/GB03/05142**
§ 371(c)(1),
(2), (4) Date: **May 1, 2006**

Foreign Application Priority Data

Nov. 21, 2002 (GB)..... 0227238.3

Publication Classification

(51) Int. Cl.⁷ **C12Q 1/68 (2006.01); G06P 1/00 (2006.01); C07H 21/04 (2006.01)**
(52) U.S. Cl. **435/6; 762/20; 536/24.3**

ABSTRACT

The present invention relates to oligonucleotide probes, for use in assessing gene transcript levels in a cell, which may be used in analytical techniques, particularly diagnostic techniques and kits containing the same.

IP

Status

- **Broad IP**
 - covers blood based gene signature diagnostics in Alzheimer's disease (US6720138) and (EU03075068.1-2402) and breast cancer
- **Three patent family groups**
 - Methods for preparing standard diagnostic gene transcript pattern
 - Product and method (includes AD gene set)
 - Oligonucleotides for cancer diagnosis (includes BC gene families)

Patent Status

	Family 1 (WO 98/49342)			Family 2 (WO 2004/046382)			Family 3 (WO 2005/118851)		
Expiry year	2017			2023			2024		
Countries/ Region	G	A	P	G	A	P	G	A	P
US	Alz		BC, MS			G			C
Europe*	G, nSB	Alz							
Europe**						G			C
Norway	G, nSB		G, dD			G			C
Japan			G, dD			G			C
Canada						G			C
Hong Kong	G, nSB					G			C
China						G			C
Australia					Alz, BC				C
New Zealand						G			C
India					Alz, BC				C
South Africa				G					C
ARIPO*						G			C

Abbreviations

Alz: Alzheimer's Disease

BC: Breast cancer

C: Cancer

G: No disease limitation.

G, dD: No disease limitation. Samples collected distant to the area of the disease

G, nSB: No disease limitation. Limited to **only** non-sequence based methods.

MS: Multiple sclerosis.

G = Granted
A = Accepted by examiner
P = In-process

1

Research Use Only

H2 07

RUO

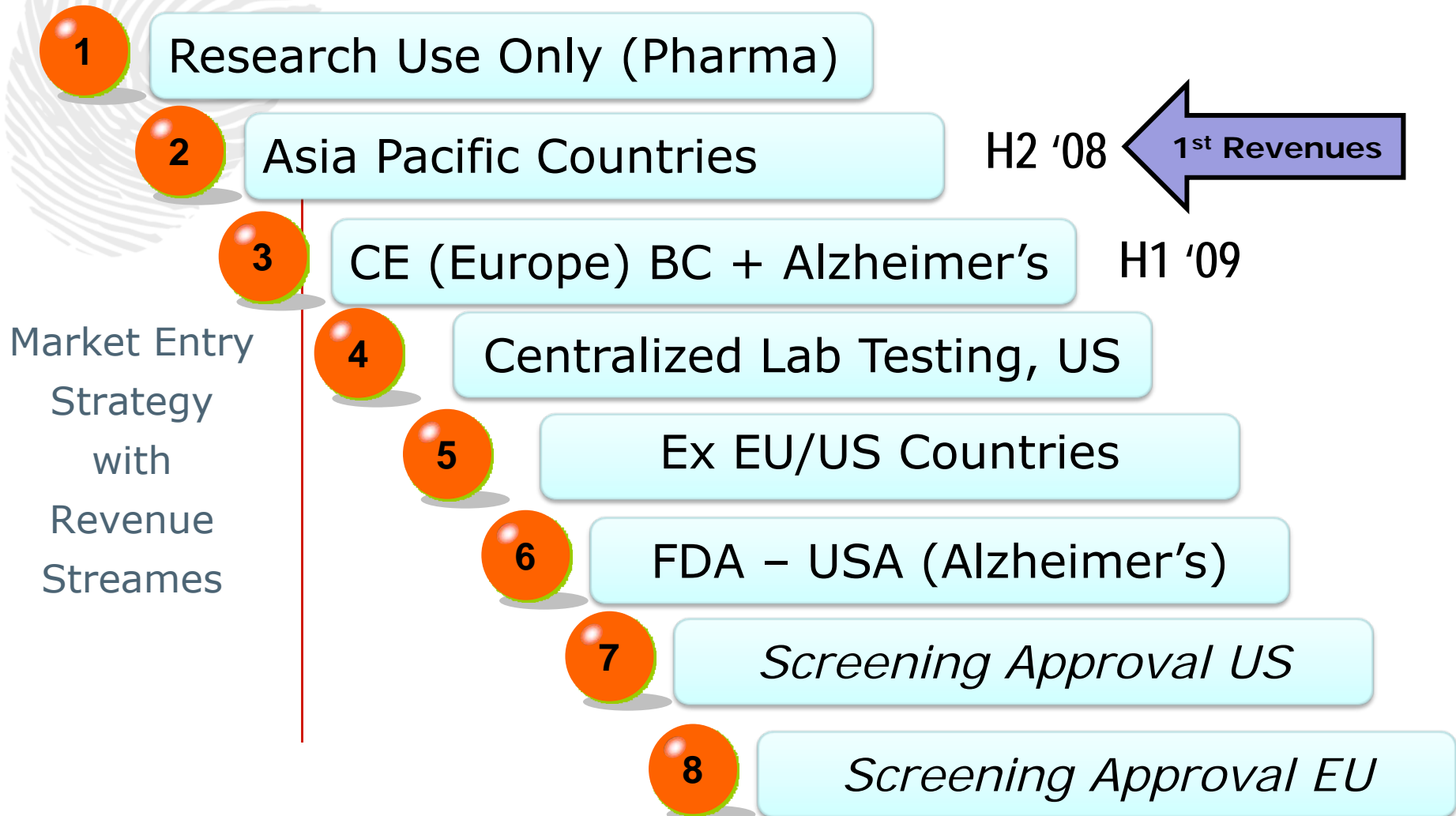
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Research
Use Only

- Documentation needed for:
 - Marketing acceptance
 - New market approaches
- Biomarker for the pharma industry in new drug development and life cycle management
 - Early disease diagnostics
 - Accurate and precise recruitment strategies
 - Include the right patients!
 - Identify responders to treatment
 - Monitor the effect of treatment
 - Identify new indications

Regulatory Compliance

- **ISO 13485:2003 Certification**
 - Certification of DiaGenic quality management system, Q3/Q4 2008
- **CE-mark of Alzheimer's Disease and Breast Cancer assays for the EU market**
 - end Q4 2008
- **Successful first meeting with the United States Food and Drug Administration (FDA).**
 - The purpose of the meeting was mainly to get feedback on DiaGenic's proposal for clinical application of the Alzheimer's test in the USA.



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- **Outlook**

Outlook

- DiaGenic will complete the study in India and prepare for the forthcoming product launch together with the selected partners during 2008.
- Communication with selected IVD, pharmaceutical and laboratory companies will continue, supported by new documentation from product development.
- Based on discussions with the FDA, intense work is in progress to prepare for clinical studies on Alzheimer's disease in the USA.
- The objective of a CE mark for marketing and diagnostic use of both DiaGenic's breast cancer and Alzheimer's tests by the end of 2008 is unchanged.



DiAGENiC

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20 Largest Share Holders

April 29th
17:00

Shares	Percent	Name
3 543 135	8.10	VERDIPAPIRFONDET NOR V/NORDEA FONDENE AS
2 910 000	6.65	SHARMA PRAVEEN
2 890 000	6.61	LØNNEBORG ERIK ANDERS
1 944 000	4.44	TREDJE AP-FONDEN
1 914 000	4.38	A/S SKARV
1 397 100	3.19	NORDEA BANK SWEDEN A
1 280 900	2.93	JPMBLSA NORDEA LUX LENDING A
1 088 570	2.49	HOLBERG NORDEN V/HOLBERG FONDSFORVA
1 003 100	2.29	LIVSFORSIKRINGSSSELSK STRATEGISK
901 000	2.06	SKAGEN VEKST
828 933	1.90	INVESTOR CORPORATE A
785 387	1.80	HOLBERG NORGE V/HOLBERG FONDSFORVA
769 300	1.76	VERDIPAPIRFONDET NOR V/NORDEA FONDENE AS
702 000	1.61	AMFIBIEN AS
646 000	1.48	ANDERSEN RUBEN
476 100	1.09	SANDEN A/S C/O JAN PETTER COLLI
420 000	0.96	HAAVIND KARL WILHELM
410 000	0.94	SEB ENSKILDA ASA EGENHANDELSKONTO
406 378	0.93	STORHAUG DAG
400 000	0.91	STENE IVAR
24 715 903	56.52	Sum

Breast cancer

- Breast cancer is the most common for of cancers among women with more 600,000 new cases and 150,000 deaths in Europe and the US alone. Early diagnosis and treatments holds the key to survival. This has lead most western countries to establish a screening program for BC. However, the current testing methods - mammography, ultrasound and MRI - all have increasingly recognized limitations. The too low accuracy of mammography especially in women below the age of 50 and in women with dense breasts results in too many missed cancers. There is a clear need for additional and better diagnostic tools, both to improve the detection rate when using conventional mammography, and to select the appropriate patients for the new and costly MRI method. DiaGenic's concept is ideal – peripheral blood is a convenient and easily accessible clinical sample



Parkinson's disease

- Parkinson's disease (PD) is a chronic, degenerative neurological disorder and belongs to a group of conditions called motor system disorders. There is no objective test, or [biomarker](#), for Parkinson's, so the rate of misdiagnosis can be relatively high, especially when the diagnosis is made by a non-specialist. Estimates regarding the number of people in the United States with Parkinson's range from 500,000 to 1,500,000 with 50,000 new cases reported annually. Since Parkinson's is more common in people 60 years old and older, it is expected that the incidence of Parkinson's will increase with the ageing of the baby boomers. Although PD is more common in older persons, some people begin to show symptoms before reach the age of 40. The diagnostic accuracy is only 47% in a community setting, 74% in standard geriatric and neurological practice. Experts in neurological movements disorders achieve 92-98% accuracy.
- The MJ Fox Foundation is funding a DiaGenic study together with Dr Clemens R Scherzer, Assistant Professor of Neurology at Brigham and Womens Hospital and Harvard Medical School to develop the first blood test for Parkinson's disease. This involves identification of, and independent validation of a unique gene expression signature for Parkinson using peripheral blood. Since blood samples have already been collected, the immediate start of the analytical and bioinformatics studies will ensure a rapid development of a prototype of the blood test preceding an approved diagnostic test

Alzheimer's disease



- Alzheimer's disease is the leading cause of dementia and a recent update estimates that more than 20 million people currently have the disease. Even more threatening is that these figures expect to triple in the next 30-40 years. Diagnosis of AD involves a large battery of assessments, including clinical interviews, cognitive function, and, sometimes, also functional imaging and measurements of neurophysiological function. However, with all these tests it is still difficult to make an accurate diagnosis, especially at an early stage of the disease. There are today more than 14 disease modifying drugs in clinical phase III and it is expected that several of them will be on the market in 2 - 4 years time. Efficacy of the new drugs will depend on early diagnosis and thus boost the diagnostic market.