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Case No: HC-2015-001175
HC-2015-000047
HP-2016-000001

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
PATENTS COURT (ChD)

Royal Courts of Justice
Rolls Building
Fetter Lane, London, EC4A 1NL

Date: Tuesday 21 November 2017

Before :

THE HON MR JUSTICE HENRY CARR

- -

Between :

(1) ILLUMINA, INC **(2) VERINATA HEALTH, INC** **(3) SEQUENOM, INC** **(4) THE TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY**	**Claimants to case no HC-2015-001175**
(1) ILLUMINA, INC **(2) THE CHINESE UNIVERSITY OF HONG KONG**	**Claimants in case no HP-2015-000047**
-and-	
(1) PREMAITHA HEALTH PLC **(2) PREMAITHA LIMITED**	**Defendants in case nos HC-2015-001175 HP-2015-000047**
- and between-	
(1) ILLUMINA, INC **(2) SEQUENOM, INC**	**Claimants in case no HP-2016-000001**
-and-	
(1) TDL GENETICS LIMITED **(2) THE DOCTORS LABORATORY LIMITED** **(3) ARIOSA DIAGNOSTICS, INC**	**Defendants in case no HP-2016-000001**

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MR IAIN PURVIS QC, DR PIERS ACLAND QC and DR JAMES WHYTE (instructed by **Powell Gilbert LLP**) for the **Claimants**
MR THOMAS MITCHESON QC, MR THOMAS HINCHLIFFE QC and MS. GEORGINA MESSENGER (instructed by **Allen & Overy LLP**) for the **Defendants Premaitha Health Plc and Premaitha Limited**
DR MICHAEL TAPPIN QC and MR JOE DELANEY (instructed by **Herbert Smith Freehills LLP**) for the **Defendant Ariosa Diagnostics, Inc, and** (instructed by **Clyde & Co LLP**) for the **Defendants TDL Genetics Limited and The Doctors Laboratory Limited.**

Hearing dates: 4-7, 10-14,17,18 and 25-17 July 2017

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Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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MR JUSTICE HENRY CARR

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Mr Justice Henry Carr :

Introduction

1. These proceedings concern three Claims in respect of five biotechnology patents, all of which were heard at the same trial. The first two Claims (HC-2015-001175 and HP-2015-000047) were brought against Premaitha Health Plc and Premaitha Limited (collectively "Premaitha"). The third Claim (HP-2016-000001) was brought against TDL Genetics Limited, The Doctors Laboratory Limited and Ariosa Diagnostics Inc. (collectively "TDL/Ariosa"). The legal teams were outstanding in their presentation of what was, in effect, three inter-related trials.

2. All of the patents in suit ("the Patents") concern non-invasive prenatal diagnosis ("NIPD") i.e. genetic testing on a foetus (also spelt "fetus") that requires only sampling of the mother's blood, or other non-invasively collected analyte. NIPD is to be contrasted with methods such as amniocentesis and chorionic villus sampling ("CVS") that involve invasive sampling of cells from the amniotic fluid and placenta respectively.

3. The importance of this area of research will be apparent to all those who have faced the difficult decision of whether to test for genetic disorders, such as Down's syndrome, during pregnancy. Invasive sampling carries with it a risk to the foetus. A genetic test which can be performed without any such risk, merely by taking a blood sample, is of great public benefit.

4. The Patents comprise three principal patents and two divisionals, namely:

   i) EP (UK) 0,994,963 ("Lo 1") which claims a priority date of 4 March 1997 and concerns a method of detecting the presence of a paternally inherited nucleic acid sequence of foetal origin, which is not possessed by the pregnant female, in a maternal serum or plasma sample.

   ii) EP (UK) 1,981,995 ("Quake 1") which claims a priority date of 2 February 2006 and concerns a method of detecting foetal aneuploidy in a mixture of maternal and foetal genetic material in a sample of maternal tissue by digital analysis methods. EP (UK) 2,385,143 ("Quake 2") is a divisional of Quake 1 and claims the same priority date.

   iii) EP (UK) 2,183,693 ("Lo 2") which claims a priority date of 23 July 2007 and concerns a method of detecting foetal aneuploidy in a mixture of maternal and foetal genetic material in a sample of maternal tissue by random DNA sequencing. EP (UK) 2,514,842 ("Lo 3") is a divisional of Lo 2 and claims the same priority date.

5. Premaitha has developed a non-invasive prenatal test called "IONA". TDL/Ariosa has developed a non-invasive prenatal test called "Harmony". IONA is claimed by Illumina to infringe all of the Patents, whereas Harmony is claimed to infringe only Lo 1. Premaitha and TDL/Ariosa ("the Defendants") claim that the patents under which they are sued are invalid. Dr Tappin QC, on behalf of TDL/Ariosa, took the lead in relation to Lo 1 and Mr Mitcheson QC and Mr Hinchliffe QC, on behalf of Premaitha, took the lead in relation to the other patents. Premaitha supported

TDL/Ariosa's challenges to validity and title of Lo 1. It advanced separate arguments as to non-infringement of Lo 1 by the IONA test.

6. Mr Purvis QC, on behalf of Illumina, summarised the position in respect of each of the Patents in a table which is reproduced below:

Patent	Priority Date	Patentee	Exclusive licensee	Relevant action	Defendant
Lo 1	4 March 1997	Sequenom	Illumina	HC-2015-001175 / HP-2016-000001	Premaitha and Ariosa
Quake 1/2	2 February 2006	Stanford University	Verinata	HC-2015-001175	Premaitha
Lo 2/3	23 July 2007	Chinese University of Hong Kong	Illumina	HP-2015-000047	Premaitha

PART A: JUDGMENT IN RELATION TO THE LO 1 PATENT

The main issues in dispute

7. With some encouragement from the Court, the parties reduced the number of issues which they chose to pursue by the time that closing speeches were exchanged. However, there was still a great deal left to argue about. The following issues remain in dispute in relation to Lo 1:

   i) Whether Lo 1 is obvious in the light of a paper by Kazakov *et al.*, Extracellular DNA in the blood of pregnant women. *Cytology* 1995 Vol 27 3 ("Kazakov").

   ii) Whether Lo 1 is entitled to its claimed priority date of 4 March 1997. It is accepted by Illumina, for the purposes of these proceedings only, that if priority is lost, then Lo 1 is invalid.

   iii) Whether the claims of Lo 1 as proposed to be amended are sufficient. Since the priority document must contain an enabling disclosure of the claimed invention, the parties agreed that sufficiency should be considered on the basis of the disclosure of the priority document.

   iv) Whether the specification of Lo 1 as proposed to be amended contains matter not disclosed in the application as filed.

   v) Whether the claims of Lo 1 relate to a discovery as such.

   vi) Whether the Harmony prenatal test (non-polymorphic and polymorphic assay) falls within the claims of Lo 1.

vii) Whether Premaitha's IONA test and/or two proposed alternative methods, in respect of which Premaitha seeks a declaration of non-infringement, fall within the claims of Lo 1.

viii) Whether Illumina is an exclusive licensee under Lo 1.

The Skilled Team

8. Lo 1 is directed to a team interested in developing non-invasive methods of prenatal diagnosis. The team would comprise a clinician and a human molecular geneticist (also called a molecular biologist). The clinical side of the team would take the lead in assessing the potential clinical or diagnostic significance of a new piece of information.

9. There was a difference of emphasis between Illumina and TDL/Ariosa as to the attributes of the skilled geneticist. Illumina contended that the geneticist would have experience in the use of a range of standard molecular genetic techniques, whereas TDL/Ariosa contended that he/she (hereafter "he") would have practical experience of the techniques involved in laboratory-based genetic analysis of patient samples in a clinical context. This dispute arose because the parties sought to match the expertise of their own experts to that of the notional skilled person.

10. The reasons that experts give for their opinions are crucial. The experience of experts is unlikely to match that of the notional skilled person, and this dispute was peripheral. The skilled geneticist would need to be familiar with analysis of patient samples in a clinical context, which is why he would be a part of the team. The skilled geneticist would be interested in clinical aspects but would not necessarily have clinical experience of the particular clinical field in question.

Illumina's expert witnesses in relation to Lo 1

Professor Hogge (clinician)

11. Professor Hogge is a Professor in the Department of Obstetrics and Gynaecology at Virginia Commonwealth University. From 1997 to 2013, he was Director of the Pregnancy Screening Laboratory at the Magee-Women's Hospital in Pittsburgh. From 2003 to 2014, he was the Director of the Center for Medical Genetics and Genomics for the University of Pittsburgh and the Chair of the Department of Obstetrics and Reproductive Sciences at the University of Pittsburgh School of Medicine. From 2010 to 2014, he was a Professor in the Department of Pathology at the University of Pittsburgh School of Medicine.

12. His clinical work has involved carrying out prenatal diagnosis procedures, such as amniocentesis and CVS, as well as counselling patients diagnosed with prenatal abnormalities by ultrasound. He has also been involved in research relating to methods of non-invasive prenatal diagnosis. He explained that at the priority date, these included the isolation of foetal cells, and the use of molecular based techniques for diagnosing foetal chromosomal aneuploidies using foetal cells obtained from amniocentesis and CVS. He is the author or co-author of 19 books and over 80 scientific publications relating to prenatal diagnosis.

13. TDL/Ariosa submitted that Professor Hogge's research relating to methods of non-invasive prenatal diagnosis was limited to trying to isolate foetal cells from maternal blood between 1994 and 1997 and to work in the mid/late 2000s with a particular focus on epigenetics. I reject any suggestion that he lacked relevant experience. On the contrary, he was highly knowledgeable about attitudes in the relevant art at the priority date. TDL/Ariosa also submitted that in giving evidence about Kazakov, Professor Hogge lacked objectivity and unduly emphasised a negative view of the underlying science. I disagree. I consider that he gave his evidence clearly and objectively.

Professor Lovett (geneticist)

14. Professor Lovett is Professor of Systems Biology at the National Heart and Lung Institute at Imperial College. His group developed direct cDNA selection and targeted sequence capture, which have found wide application in human genetics. Between 1999 and 2013 he was Professor of Genetics and Human Genetics Division Head at the Washington University School of Medicine in St Louis, Missouri, which was one of the world's five primary Genome centres. Professor Lovett is the author or co-author of over 100 scientific publications relating to mammalian molecular genetics and genomics.

15. In 1997, his research was focused on the positional cloning of genes involved in human disease using techniques such as fluorescent *in situ* hybridisation ("FISH"), expressed sequence tag ("EST") analysis, direct cDNA selection, gel electrophoresis and blotting analysis to identify genes and map cDNAs. His particular focus was on the genetics involved in processes of hearing loss and the development of craniofacial abnormalities (such as cleft lip and palette).

16. TDL/Ariosa pointed out, correctly, that Professor Lovett had not been involved in conducting prenatal genetic tests on samples from pregnant women, and did not have any involvement in work done on trying to develop non-invasive prenatal tests using foetal cells or cell-free foetal DNA. He had relied on Professor Hogge's second report for information about the history of development in the field. Insofar as it was submitted that he lacked relevant expertise, I reject that suggestion. He is a pre-eminent geneticist who was very familiar with the genetic principles and tests of relevance to Lo 1. It is correct that he familiarised himself with the prenatal field for the purposes of this case, but his extensive expertise in genetics enabled him to provide useful evidence.

17. TDL/Ariosa criticised Professor Lovett's evidence alleging that: he gave evidence about the state of the art at the priority date, about which he had no knowledge; he had a high level of self-confidence and failed to justify his views objectively; and he was extremely reluctant to address any question put on the basis of an assumption if it was one with which he did not agree. I shall bear in mind that Professor Lovett was not working in the prenatal field in 1997 when assessing his evidence, although this needs to be balanced against his experience of genetic tests of relevance to Lo 1. Although at times he expressed his views forcefully, this was because they were strongly held. I do not accept that he lacked objectivity. It is true that he was reluctant to accept assumptions, but this was because he wished to make clear that he disagreed with them. Overall, his evidence was very helpful and his intention was to assist the Court.

TDL/Ariosa's expert witnesses in relation to Lo 1

Professor Oepkes (clinician)

18. From 1988 to 1993 Professor Oepkes was a research fellow and physician-sonographer in the foetal medicine unit at the University of Leiden, and between 1993 and 1999 he was a resident in Obstetrics and Gynaecology at that University. His experience during this period covered gynaecology including fertility treatment, laparoscopies, gynaecological cancers, delivering babies and caesarean sections. He was experienced in ultrasound scanning and counselling women at risk of carrying a foetus with an abnormality, and was involved, amongst other things, in interpreting results from 16 week 'triple test' biochemical serum screening for Down's syndrome, which became available in the Netherlands in 1991, in order to advise women of their risk.

19. His research focussed on ultrasonography relating to the management of red cell alloimmunized pregnancies (i.e. those involving issues of Rhesus D incompatibility between the mother and the foetus). He was part of a group certain members of which were carrying out research in relation to foetal cells in maternal circulation, which was a joint project between the obstetrics and the clinical unit, and he followed developments in relation to that project. Since 2001 Professor Oepkes has been a Consultant Obstetrician in the Department of Obstetrics at Leiden University Medical Centre. In March 2012 he was appointed Professor of Obstetrics and Foetal Therapy at Leiden University Medical Centre.

20. Professor Oepkes was a good witness and Illumina made no criticism of his objectivity. Some comment was made on his approach to the Kazakov prior art, which I shall consider in the context in which it arises.

Ms Norbury (geneticist)

21. Between 1987 and 2001 Ms Norbury was a Clinical Scientist, and ultimately held the position of Deputy Head of Laboratory, in the Oxford Medical Genetics Laboratories at the Churchill Hospital, Oxford Radcliffe NHS Trust. She was responsible for laboratory services for diagnosis or risk assessment of a range of genetic disorders, including devising new protocols to diagnose disorders as well as carrying out the lab work (using a range of techniques including PCR) and interpreting the results. By 1997 the laboratory was providing prenatal diagnoses and risk assessments for a variety of inherited disorders. Between 2001 and 2009 she was director of the Molecular Genetics Laboratory at Great Ormond Street Hospital, which provided a diagnostic service for a number of single gene disorders. At that time, she gained more experience of quantitative genetic analysis and became involved with non-invasive prenatal diagnosis. She is currently a Consultant Clinical Scientist at the Regional Genetics Laboratories at the Guy's and St Thomas' Hospital.

22. Illumina alleged that when commenting on Kazakov in her written evidence, Ms Norbury did not set out multiple errors that were evident in that document, in particular in relation to the experiments which were claimed to support the authors' conclusions. It is true that Ms Norbury did not provide any detail of the technical flaws in Kazakov. However, it is evident from her reports that she recognised that such flaws existed. At [7.16] of her First Report she stated that:

> "Overall, the skilled person would have taken the discussion and conclusions of the paper at face value, as little supporting data or relevant control information is provided."

This is scarcely a ringing endorsement of the Kazakov experiments.

23. She expanded on this at [2.14] of her Second Report, where she said:

> "As noted in my first report at paragraph 7.16, there is little supporting data and relevant control data in Kazakov. I therefore agree with Professor Lovett that Kazakov contains various statements that are not supported by data presented in the paper. I also agree with Professor Lovett that Figures 1 and 2 do not support the conclusions which Professor Lovett says in his report they are intended to support."

24. Since Ms Norbury agreed with Professor Lovett's criticisms of Kazakov, she was plainly not seeking to justify the data or experiments in that document. I do not consider that this criticism of her evidence is justified.

25. Secondly, Illumina alleged that Ms Norbury's reaction to Kazakov was not representative of the person skilled in the art, because she was influenced by knowledge of Kazakov which she gained in 2016, when it was drawn to her attention as a disclosure of interest which pre-dated Professor Lo's findings. This is not a criticism of Ms Norbury, but it does raise an important point which I shall address when considering the case of obviousness over Kazakov.

Common general knowledge in 1997 – technical background to Lo 1

26. I shall apply the summary of legal principles in respect of common general knowledge set out by Arnold J in *KCI Licensing v Smith & Nephew* [2010] EWHC 1487 (Pat); [2010] FSR 31 at [105]-[115], which was approved by the Court of Appeal at [2010] EWCA Civ 1260; [2011] FSR 8 at [6].

27. The parties emphasised that much of the common general knowledge was agreed. However, it did not prove easy to identify precisely what was common ground. Subsequent to the trial, the parties prepared a document which summarised (subject to a few minor disagreements which I have considered but have not felt necessary to set out), common general knowledge in 1997. I shall focus on the key areas of common general knowledge addressed in that document which does not require to be set out in its entirety. This should also provide a technical background to assist in understanding some of the terms used in this judgment. There are other matters of common general knowledge which are more controversial, which I shall consider in the context in which they arise.

Blood

28. Blood cells make up approximately 45% of the blood. These cells include oxygen-carrying erythrocytes (red blood cells), immune cells called leukocytes (white blood cells) and thrombocytes (platelets). In the case of pregnant women, it was also known that there were foetal cells present in the mother's blood. Plasma, which makes up the

remaining 55% of the blood, is a straw yellow fluid which contains water, blood plasma proteins, minerals and dissolved nutrients and waste products. Serum is the name given to plasma which has had the clotting factors removed.

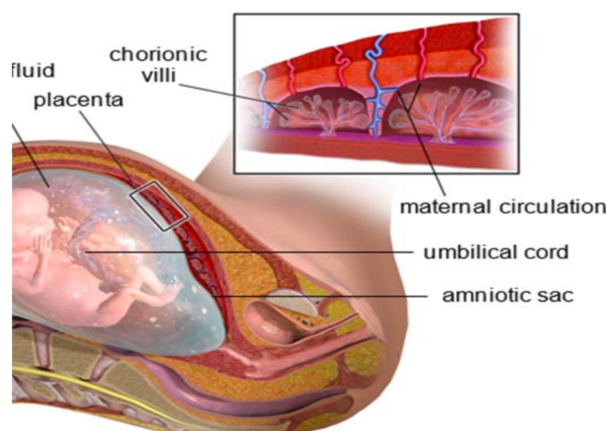
29. Whole blood can be separated by centrifugation into three layers: i) the upper plasma layer ii) the "buffy coat" layer which contains the leukocytes and thrombocytes and iii) the lower layer which contains the erythrocytes.

Prenatal development

30. Following fertilisation of an ovum (egg) by a spermatozoon in the Fallopian tubes, the resulting single cell zygote travels down the Fallopian tube and divides to form a blastocyst. Approximately 5 days after fertilisation, the blastocyst, which consists of trophoblast cells and embryonic cells, reaches the uterus and becomes embedded in the endometrium (lining) of the uterus. The trophoblast cells, which surround the embryonic cells, proliferate and embed further into the uterine lining, eventually forming the placenta. The blastocyst becomes fully implanted approximately 7-12 days after fertilisation.

Placenta

31. The placenta is a composite structure made up of maternal tissues as well as those derived from the foetus. Foetal blood vessels extend to the placenta via the umbilical cord and branch into many chorionic villi, providing a large surface area for the exchange of materials between foetal and maternal blood across a layer of tissue called the placental membrane. A variety of materials, including nutrients and oxygen, are exchanged between the maternal circulatory system and the foetus via chorionic villi in the placenta and the umbilical cord. Other materials passing from the foetus or placenta into the maternal blood circulation include foetal blood cells, proteins and hormones which form the basis of the Rh disease test and the biochemical screens of maternal serum for Down's syndrome discussed below. Likewise, waste materials are removed from the foetus to the maternal circulation.



Pre-eclampsia

32. Pre-eclampsia is a pregnancy disorder which affects about 6% of pregnancies, and is characterised by high blood pressure and elevated protein levels in the maternal urine. Pre-eclampsia generally occurs 24-26 weeks after fertilisation and often increases in

severity until birth. Untreated, pre-eclampsia may lead to eclampsia (convulsions), bleeding in the mother's brain and death of the mother. Especially the early forms of pre-eclampsia are often associated with foetal growth restriction due to placental dysfunction.

Rhesus Disease

33. Rh (Rhesus) factor (also known as the Rh D antigen) is a protein found on the surface of red blood cells in so-called Rh positive individuals. Rh negative individuals lack this protein. Lack of this protein in Rh negative individuals is caused by a deletion or mutations of the gene (*RHD*) that encodes it in both copies of chromosome 1 (which carries the *RHD* gene). If one copy of chromosome 1 contains the *RHD* gene and one does not, the individual still expresses the Rh factor and is considered Rh positive.

34. Rh disease can cause haemolytic disease of the newborn and foetus. This issue typically arises in second or subsequent pregnancies when a Rh negative mother is carrying a Rh positive foetus. In other words, the child inherits from its mother a copy of chromosome 1 in which the *RHD* gene is deleted or mutated and a copy of chromosome 1 from the father in which the *RHD* gene is present and functional. Since the child possesses one functioning copy of the *RHD* gene, the child produces Rh factor, and is thus referred to as Rh positive.

35. When a Rh negative mother carries a Rh positive foetus, the foetus expresses the Rh factor on its red blood cells. During pregnancy and birth the mother may be exposed to foetal red blood cells expressing Rh factor. The mother mounts an immune response to Rh factor, which it identifies as foreign, and thus her immune system becomes sensitised to Rh factor. A Rh negative mother sensitised to Rh factor may mount a more robust immune response destroying the red blood cells of a Rh positive foetus in subsequent pregnancies.

36. By 1997 it was routine to give all pregnant mothers a blood test to determine their Rh status. The general approach to treatment was to treat all mothers identified as Rh negative with anti-Rh factor antibodies (so called prophylactic anti-D), ensuring that any Rh positive foetal red blood cells are masked before an immune response can be raised against them by the mother's immune system, hence preventing issues with subsequent Rh positive pregnancies. This was, however, an inefficient approach as it inevitably involved treating Rh negative mothers carrying Rh negative foetuses, who did not need the treatment. There was, therefore, a desire to develop a way to screen for the Rh status of the foetus non-invasively – this would allow prophylactic anti-D to be given only to the Rh negative women who needed it (i.e. those carrying a Rh positive foetus).

Haemoglobinopathies

37. Haemoglobinopathies are genetic disorders in which the haemoglobin molecules in an affected individual's red blood cells are abnormal. Well-known examples of haemoglobinopathies are sickle cell anaemia and alpha- and beta-thalassemia. Alpha-thalassemia is considered a lethal disease, often leading to foetal death in the third trimester with maternal hydrops ('mirror') syndrome also commonly present. Sickle cell anaemia and beta-thalassemia can be treated but patients suffer from many

symptoms and often need life-long repeated blood transfusions. Many parents being confronted with a diagnosis of these foetal diseases elect for termination.

Sex-linked disorders

38. A number of diseases are known to be caused by a defective gene on the X chromosome, e.g. haemophilia. In many cases, these diseases primarily affect male foetuses (because female foetuses will have another, non-defective, copy of the X chromosome). Work was on-going in 1997 to try to find ways to identify foetuses with possible sex-linked disorders. There was, therefore, a desire to develop a way to identify the sex of the foetus quickly, accurately and as early as possible in the first trimester. Further, in cases of congenital adrenal hyperplasia, treatment with dexamethasone is needed to prevent virilisation in girls. This medication can be stopped once the foetus is known to be male. In severe X-linked diseases for which the parents would typically elect termination, having a diagnosis as early as possible in the first trimester is valuable. DNA testing for the disease in such cases (which often took a week or longer) would only be done after the sex determination and could be omitted if the foetus was known to be female. Gender determination by ultrasound only becomes reliable for establishing the sex of a foetus from 18 weeks onwards.

Aneuploidies

39. The presence of a variation in the number of chromosomes from the usual complement (i.e. 46 chromosomes) is referred to as aneuploidy. The absence of a single chromosome from a usual pair is referred to as monosomy, and the presence of an additional copy of a single chromosome to a usual pair is referred to as trisomy.

40. Aneuploidies in autosomal and sex chromosomes are responsible for a number of genetic conditions, due to abnormal dosage of genes, including Down’s syndrome (trisomy of chromosome 21), Edwards’ syndrome (trisomy of chromosome 18), Patau syndrome (trisomy of chromosome 13), Turner syndrome (full or partial monosomy of X), Klinefelter syndrome (XXY), XYY syndrome, XXYY syndrome and Triple X syndrome.

41. The most common viable autosomal trisomies are trisomies of chromosomes 21, 18 and 13. Trisomy 13 and trisomy 18 often result in miscarriage, stillbirth or, in the case of viable births, neonatal death. Trisomy 21 is not usually life-threatening but can result in significant physical and mental disability. Foetuses with aneuploidies of multiple chromosomes are unlikely to survive past the early stages of pregnancy.

42. The additional chromosome found in cases of trisomy may be paternally- or maternally-inherited. In trisomies 13, 18 and 21, the extra copy of the relevant chromosome is inherited from the mother in the majority of cases (over 91% maternal in trisomy 13, around 95% maternal in trisomy 18 and around 90% maternal in trisomy 21).

Prenatal testing for aneuploidy

43. Cytogenetic techniques were available in 1997 to analyse the number and structure of chromosomes in foetal cells, which had been extracted from the pregnant woman's

amniotic fluid, by amniocentesis, or placenta, by CVS. Each of these techniques carried with it a risk to the foetus.

44. Amniocentesis involves the collection of amniotic fluid, which contains foetal cells, using a needle which is inserted through the abdomen and uterus into the amniotic sac under ultrasound guidance. It is feasible from 15 weeks.

45. CVS is a technique for sampling cells that are likely to have the same karyotype as the foetus (although in some cases they will differ, for example where there is a confined placental mosaicism). The sample is collected from the chorionic villus of the placenta either using a catheter inserted through the vagina or using a needle inserted through the abdomen.

46. Once the foetal cells had been isolated and cultured they could be analysed by cytogenetic techniques to determine the number and structure of chromosomes. These include:

    i) Karyotyping. The “karyotype” of an individual is the number and appearance of the chromosomes in the nucleus of the cell. Traditional karyotyping involves staining chromosomes with a dye to allow them to be visualised under a microscope. This allowed foetuses possessing an abnormal number of chromosomes (such as an extra copy of chromosome 21 in Down's syndrome) or chromosomes with abnormal structures to be diagnosed.

    ii) Fluorescent in situ hybridisation (‘FISH’). FISH uses a fluorescently labelled DNA probe which is designed to bind to portions of a gene of interest. The presence of trisomy 21 may be detected by the presence of three fluorescent spots in the foetal cell, rather than the expected two.

47. While these approaches were accurate and reliable, the main drawback with amniocentesis and CVS was that both procedures were invasive and were understood to increase the risk of the mother suffering a miscarriage (in 1997 the risk was believed to be around 1% for amniocentesis and 2% for CVS).

48. Consequently, in addition to the use of maternal age to assess the risk that a pregnant woman was carrying a foetus with Down's syndrome (it has been known for decades that the likelihood of a woman conceiving a foetus affected by Down's syndrome increases as the woman gets older), biochemical screening of maternal serum was used to identify women who were at higher risk of carrying an aneuploid foetus and only those women were referred for invasive testing.

49. It was known that at around 16 weeks' gestation (in the second trimester of pregnancy), three substances (alpha-foetoprotein, free beta hCG and estriol) were often present in different amounts in maternal serum in pregnancies where the foetus was affected by Down's syndrome and pregnancies where it was not. This led to the development of what became known as the 'triple test'. Instead of involving an invasive test, measurement of the levels of these markers could be achieved using a simple blood sample from the mother at around 16 weeks' gestation. The triple test was the standard serum screening test for Down's syndrome for a long time (and was eventually offered to all pregnant women regardless of age in many countries).

50. By 1997 work had also been carried out to find new markers which could be used at 10-12 weeks' gestation (as there was a desire to enable diagnosis of Down's syndrome within the first trimester of pregnancy), leading to the discovery in the early 1990s that free beta hCG could be used in combination with pregnancy-associated plasma protein A ("PAPPA") to screen reliably for Down's syndrome during the first trimester of pregnancy using maternal serum. It had also been discovered that foetuses affected by Down's syndrome could be identified using ultrasound scanning in what was known as the nuchal translucency test. By 1997 researchers had started to consider whether combining the nuchal translucency test with serum markers might give even more accurate results.

Foetal cells in maternal blood

51. The idea that foetal cells might be present in the mother's blood had been first proposed in 1969. The possibility of being able to access whole foetal cells by taking a maternal blood sample was of great interest to those looking for a non-invasive way of obtaining information about the foetus because it would allow analysis of the foetal genome to be carried out without the need for invasive testing and the problems associated with it (all that would be needed was a blood sample from the mother's arm). As a result, a substantial amount of work was carried out in this area through the 1980s and the 1990s.

52. By 1997 it was known that several different types of foetal cell were present in maternal blood during pregnancy. These include haematopoietic stem cells (which, in the foetus, go on to make red and white blood cells), nucleated erythrocytes (which are a type of red blood cell which is typically only found in foetuses and very young children, not in adults whose red blood cells do not contain a nucleus or, therefore, chromosomes), lymphocytes and granulocytes (which are types of white blood cell) and trophoblasts (which are foetal placental cells which invade the tissue of the mother's uterine wall causing changes in its vascular structure and formation of the placenta).

53. The aims of this research included investigating the use of foetal cells from maternal blood to provide a non-invasive means of diagnosis of Down's syndrome, to determine the blood type of the foetus and enable the pregnancy to be managed accordingly, to provide a way to determine the sex of the foetus (which would be useful when trying to identify foetuses with possible sex-linked disorders), and to diagnose single gene disorders.

54. However, isolating foetal cells was not easy because they were known to occur only rarely in maternal blood and were vastly outnumbered by maternal cells in the sample. Consequently, as well as work on new or improved methods and equipment for isolating foetal cells, research was also being carried out into methods for enriching the proportion of foetal cells in a sample. However, by 1997 foetal cells could not reliably be identified from every maternal blood sample.

55. Another important issue was verifying that the cells which had been isolated were actually foetal before any analysis was carried out. Foetal cell detection had been approached using various methods, including PCR with Y-chromosome specific primers. Where the reaction successfully amplified the Y-specific target sequence, it

could be concluded that the cells in question could not have originated from the mother (who would not possess the targeted part of the Y chromosome).

56. By 1997 research had emerged suggesting that in some cases foetal cells could survive in a woman's body for many years after the birth of the baby. This caused concern that some of the foetal cells being analysed from a given sample might not be from the current pregnancy and, therefore, could not be assumed to give reliable information on the foetal genome.

57. In spite of these problems, research into foetal cells in maternal plasma was still on-going in 1997 given the significant clinical impact that would be felt if it was possible to overcome these problems to provide a means of allowing analysis of the foetal genome without the need for invasive testing. Some groups continue to do research on whole foetal cells in maternal circulation today.

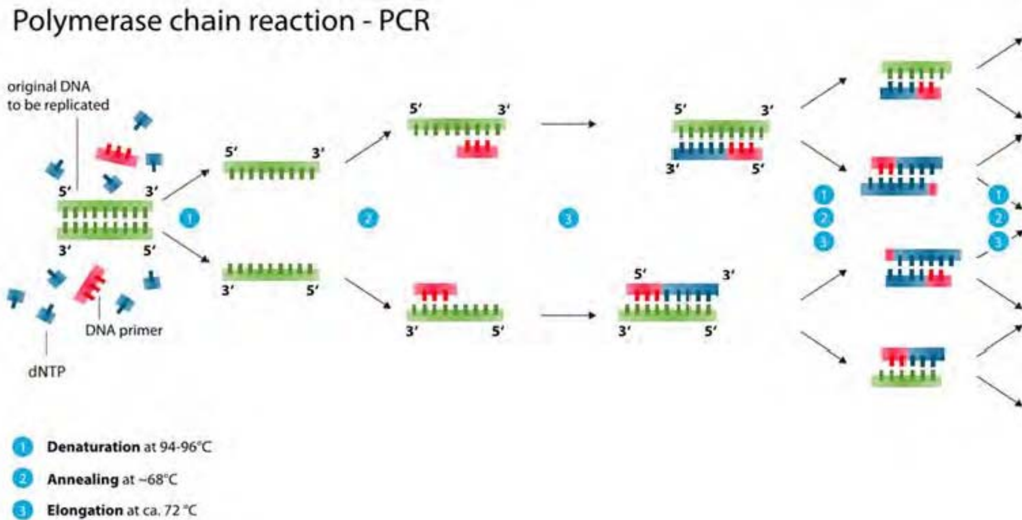
Molecular genetic diagnosis

58. Molecular genetic clinical diagnosis first became possible in the 1980s following the discovery of genetic markers (that is, known sites of variation between individuals within a population located on a particular chromosome, otherwise known as genetic polymorphisms).

59. The process of working out which allele (i.e. marker) a person had at a particular position or set of positions on a chromosome (i.e. determining the genetic make-up of the alleles at the relevant loci on an individual's chromosomes) was called genotyping. In 1997 genotyping was limited to marker analysis or determining the sequence of short sections of DNA. The two types of marker which were routinely used in molecular genetic diagnostic laboratories in 1997 were restriction fragment length polymorphisms and short tandem repeats, the details of which are unnecessary to set out.

PCR

60. PCR is a standard molecular biology technique that involves the amplification of specific sequences of DNA using repeated cycles of denaturation, primer annealing and extension, resulting (in theory at least) in exponential accumulation of DNA fragments. The basic technique is illustrated by the diagram below:



61. In 1997, standard practice was to run 30-35 cycles of amplification (i.e. to the end-point of the reaction). Running more than 40 cycles was known to result in a much higher chance of amplifying something other than the target. This can happen when the primers bind to a sequence of DNA that is very similar to the target or where there is contamination, i.e. when some foreign DNA gets into the sample and is targeted by the primers. The risk of contamination affecting the results of a PCR assay is particularly high when the target sequence occurs in low levels in the sample or when there is no separation of the pre- and post-PCR laboratory areas or where appropriate equipment is not used, such as filter tips.

62. Real-time PCR, a development of standard (or end-stage) PCR, uses fluorescent reporter molecules to monitor the amounts of PCR product present after each PCR cycle. This allows the generation of a growth curve and enables the quantification of DNA in the exponential phase by determining the number of amplification cycles necessary to achieve a specified fluorescence level. As a consequence of the exponential nature of PCR, one cycle represents approximately a doubling in template concentration. It was therefore suitable for detecting a 2-fold difference.

63. In 1997, the products of the PCR were typically analysed by gel electrophoresis as described below. Sequencing was a possible means of analysing the products of a PCR reaction but was laborious, expensive and limited to products of around 400bp or fewer at a time.

Gel electrophoresis

64. Gel electrophoresis was (and is) used to separate molecules like DNA based on their size (molecular weight). When carried out following PCR or simple restriction enzyme digestion, the reaction products would be mixed with a suitable buffer containing a dye to increase the density of the material in the sample so that it could be seen during loading into a 'well' on a gel made of agarose or polyacrylamide. It is unnecessary to set out further details in this judgment.

The Lo 1 Patent

Overview

65. Lo 1 discloses that cell-free foetal DNA can be detected in maternal serum in sufficient quantities to allow it to be used in prenatal testing. Lo 1 claims priority from GB 9704444.0 ("the Lo 1 Priority Document"). After the Lo 1 Priority Document had been filed, this finding was published in Professor Lo's 1997 paper Lo Y-MD *et al.,* Presence of foetal DNA in maternal plasma and serum. *The Lancet* 1997*;* 350: 485-7 ("Lo 1997"). Professor Hogge described this as a breakthrough, and explained at [39] of his First Report that:

> "This achievement represented an important milestone in the prenatal diagnostic field, which had previously been focused on the analysis of foetal cells. Professor Lo's finding that maternal serum contained cell-free foetal DNA in clinically significant quantities opened up an entirely new, and unexpected, avenue of enquiry with respect to non-invasive prenatal diagnostic testing."

66. Lo 1997 has received widespread acclaim and has been cited over 2,300 times in scientific publications. Professor Hogge explained, and I accept, that prior to the publication of Lo 1997, new avenues for prenatal diagnostic testing had focused on the use of foetal cells, which were either obtained by invasive procedures such as amniocentesis or from maternal blood. It was therefore normal practice for researchers to discard maternal serum/plasma as this fraction of the blood was not thought to contain useful genetic material.

67. Professor Oepkes agreed about the significance of this finding. At [12.1] of his First Report he said:

> "The first publication claiming to have found foetal DNA in maternal serum and plasma was published by Dr Lo and colleagues in the Lancet in 1997. It was viewed as a very interesting development, and the Lo 1997 paper was widely cited and the discovery was widely reported."

The Description

68. Paragraph [0001] of Lo 1 explains that the invention relates to prenatal diagnosis by detecting foetal nucleic acids in serum or plasma from a maternal blood sample. Paragraph [0002] explains that the conventional invasive techniques for obtaining foetal cells present a risk to the mother and foetus. Paragraph [0003] explains that more recent techniques for predicting abnormalities in the foetus used maternal blood or serum samples, including biochemical screening of maternal serum, and the isolation of foetal cells from maternal blood.

69. Paragraph [0006] discloses that:

> "It has now been discovered that foetal DNA is detectable in maternal serum or plasma samples. This is a surprising and unexpected finding; maternal plasma is the very material that is routinely discarded by investigators studying non-invasive prenatal diagnosis using foetal cells in maternal blood. The detection rate is much higher using serum or plasma than using

> nucleated blood cell DNA extracted from a comparable volume of whole blood, suggesting that there is enrichment of foetal DNA in maternal plasma and serum. In fact, the concentration of foetal DNA in maternal plasma expressed as a % of total DNA has been measured as from 0.39% (the lowest concentration measured in early pregnancy), to as high as 11.4% (in late pregnancy), compared to ratios of generally around 0.001% and up to only 0.025% for cellular fractions (Hamada et al 1993). It is important that foetal DNA is not an artefact of the clotting process."

70. Paragraph [0007] states that:

> "The invention provides a detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample wherein said nucleic acid is a paternally inherited sequence which is not possessed by said pregnant female. The detection may comprise quantifying the nucleic acid or determining the sequence of the nucleic acid. The invention thus provides a method for prenatal diagnosis."

71. Paragraph [0008] explains that "prenatal diagnosis" includes: sex determination; the detection of foetal abnormalities; and the detection and monitoring of pregnancy-associated conditions such as pre-eclampsia, which result in higher or lower than normal amounts of foetal DNA being present in the maternal plasma or serum.

72. Paragraph [0009] summarises the invention as follows:

> "The invention provides a method of performing a prenatal diagnosis on a maternal blood sample, which method comprises obtaining a non-cellular fraction of the blood sample and performing nucleic acid analysis on the fraction to detect the presence of a nucleic acid of foetal origin in the sample, wherein said sequence is a paternally inherited sequence which is not possessed by the mother. A method of performing a prenatal diagnosis on a maternal blood sample according to the invention may comprise removing all or substantially all nucleated and anucleated cell populations from the blood sample and subjecting the remaining fluid to a test for foetal nucleic acid indicative of a maternal or foetal condition or characteristic."

73. Paragraphs [0016] to [0019] explain that the invention can be used for the following applications:

    i) Sex determination by detecting the presence of a Y chromosome, which may be by detection of a foetal nucleic acid sequence from the Y chromosome (paragraph [0016]).

ii) Detection of a foetal nucleic acid from a paternally-inherited non-Y chromosome, for example:

a) Foetal rhesus D status determination in rhesus negative mothers by detection of rhesus D sequences (paragraph [0017(a)]).

b) Detection of haemoglobinopathies by detection of paternal mutations in the beta-globin gene, where the father and mother carry different mutations (paragraph [0017(b)]).

c) Detection of paternally-inherited DNA polymorphisms or mutations, following genotyping of the father and mother using a panel of polymorphic markers for detection of an allele which is present in the father but not the mother (paragraph [0017(c)]).

iii) Screening for Down's syndrome and other chromosomal aneuploidies, by one of two possible methods:

a) Quantifying the amount of foetal nucleic acid in maternal plasma or serum (e.g. by quantitative PCR), which may be used as a screen for foetal aneuploidy due to the demonstration that the level of foetal DNA in maternal plasma and serum is higher in pregnancies where the foetus has a chromosomal aneuploidy than in normal pregnancies (paragraph [0018(a)]).

b) Quantification of foetal DNA markers on different chromosomes, for example to detect Down's syndrome by detecting a higher quantity of foetal DNA derived from chromosome 21 than from other chromosomes (paragraph [0018(b)]).

iv) Monitoring of certain placental pathologies, such as pre-eclampsia, by detecting the concentration of foetal DNA in the maternal serum or plasma, which is elevated in pre-eclampsia (paragraph [0019]).

74. Lo 1 contains five Examples. Example 1 relates to analysis of foetal DNA for sex determination; Example 2 relates to quantitative analysis of foetal DNA in maternal serum in aneuploidy determination; Example 3 relates to non-invasive prenatal determination of foetal RhD status from plasma of RhD-negative pregnant women; Example 4 relates to elevation of foetal DNA concentration in maternal serum in pre-eclamptic pregnancies; and Example 5 relates to quantitative analysis of foetal DNA in maternal plasma and serum.

75. Examples 2-5 were not disclosed in the Lo 1 Priority Document and were first introduced in WO 98/39474 ("the PCT Application"). Since Illumina has to establish that the Priority Document is an enabling disclosure, it focused on Example 1 of the Lo 1 Patent. TDL/Ariosa referred to Example 5 as pointing to limitations on the conclusions to be derived from Example 1.

76. Example 1 at [0024] - [0030] discloses a method for analysing foetal DNA for sex determination. Samples of maternal blood were collected and centrifuged. Prior to centrifugation, the samples were divided into two tubes, one of which contained

EDTA (which inhibits clotting). After centrifugation, the supernatant (serum in the case of the clotted blood sample and plasma in the case of the unclotted blood sample) from each tube was removed and subject to a second round of purification by centrifugation. DNA was extracted from the remaining red cell pellet (in the case of the clotted blood sample) and buffy coat (in the case of the unclotted blood sample), and from the plasma and serum samples. PCR analysis was carried out on the DNA extracted from the plasma, serum and nucleated blood cells using primers designed to amplify a Y-chromosome specific foetal sequence.

77. [0030] states that, of the 30 women bearing male foetuses, Y-positive signals were detected in 24 plasma samples and 21 serum samples, but only in 5 of the samples from nucleated blood cells. None of the samples from the 13 women bearing female foetuses, nor the 10 non-pregnant female control patients, gave a Y-positive signal. Paragraph [0030] therefore concludes that "*[a]ccuracy of this technique, even with serum/plasma samples of only 10 µl, is thus very high and most importantly it is high enough to be useful*".

78. After reference to the results of Example 1 in [0075], the Lo 1 Patent says:

> "[0076] These observations indicate that maternal plasma/serum DNA may be a useful source of material for the non-invasive prenatal diagnosis of certain genetic disorders. To demonstrate that clinical applications are possible, a number of important questions need to be answered. First, foetal DNA in maternal plasma and serum needs to be shown to be present in sufficient quantities for reliable molecular diagnosis to be carried out. Second, data on the variation of foetal DNA in maternal plasma and serum with regard to gestation age is required to determine the applicability of this technology to early prenatal diagnosis."

79. The Lo 1 patent summarises Example 5 as follows:

> "[0077] In this Example we have addressed both of these issues by developing a real time quantitative TaqMan polymerase chain reaction (PCR) assay (Heid *et al.* 1996) for measuring the copy numbers of foetal DNA molecules in maternal plasma and serum. … Our data show that foetal DNA is present in maternal plasma and serum at concentrations similar to those achieved by many foetal cell enrichment protocols. We have also investigated the changes of foetal DNA concentration in maternal serum at different gestational ages. Using this plasma or serum-based approach, we show that the reliable detection of foetal DNA is achievable and therefore useful for the non-invasive prenatal diagnosis of selected genetic disorders."

80. The foetal and maternal DNA concentrations in plasma and serum determined by Example 5 are reported in Tables 2 and 3 and discussed in [0087] - [0089] on p.13 of the Lo 1 patent. In particular [0089] reports that the fraction of DNA in maternal plasma that is foetal ranges from 0.39% - 11.9% in early pregnancy and from 2.33% - 11.4% in late pregnancy.

The Claims

81. Illumina alleged that claims 1, 5, 7 and 8 are independently valid. Claim 5 is dependent on claim 4. Claim 8 is of importance, as Illumina submitted that there can be no priority, sufficiency or excluded subject matter challenges against this claim. These claims are set out below:

> "1. A detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample, wherein said nucleic acid is a paternally inherited sequence which is not possessed by said pregnant female.
>
> 4. A method according to any one of claims 1 to 3, wherein said detecting comprises amplifying said nucleic acid.
>
> 5. A method according to claim 4, wherein said amplification is by the polymerase chain reaction.
>
> 7. A method according to any one of the preceding claims, wherein the presence of a foetal nucleic acid sequence from the Y chromosome is detected.
>
> 8. A method according to claim 7, for determining the sex of the foetus."

Inventive step

82. I shall consider first the claim that Lo 1 is invalid for lack of inventive step, as if this objection is successful, all of the claims of Lo 1 are invalid.

Legal principles

83. Legal principles of relevance to the present case are as follows:

i) Obviousness must be considered on the facts of each case, and the Court must consider the weight to be attached to particular facts in the light of all the relevant circumstances. These include the motive to find a solution to the problem that the patent addresses, the number and extent of possible avenues of research and the effort involved in pursuing them; *Generics (UK) Ltd v H Lundbeck AS* [2007] EWHC 1040 at [72] *per* Kitchin J (as he then was), approved by the House of Lords in *Conor Medsystems Inc v. Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] 4 All ER 621, [2008] RPC 28 at [42].

ii) Where it is alleged that a step is obvious to try, the question is whether the skilled person would do so with a fair expectation of success; how much expectation depends on the particular facts of the case. Including something in a research project is not enough to establish lack of inventive step. There is no single standard of what amounts to a fair expectation of success; *Hospira UK Ltd v Genentech Inc* [2016] EWCA 780 *per* Floyd LJ at [13] – [16]. There are some steps which can be characterised as so routine that the skilled person

would carry them out simply because they are routine, and irrespective of any prospect of success; *Actavis Group PTC EHF v Icos Corporation* [2017] EWCA Civ 1671 per Floyd LJ at [160].

iii) The court is not constrained to make a finding of obviousness only where it is manifest that a test ought to work; *Conor v Angiotech* at [42]; *Medimmune v Novartis* at [90]-[91]; *Teva UK Ltd v LEO Pharma AS* [2015] EWCA Civ 779 at [32]; *Novartis AG v Generics (UK) Ltd* [2012] EWCA Civ 1623 at [55].

iv) It is settled law that the skilled person is deemed to have read the prior art carefully and completely; *Terrell on Patents* (18th ed.) 12-63 – 12-67; *Technograph v Mills & Rockley Ltd* [1972] RPC 346 at 361; *Asahi v Macopharma* [2002] EWCA Civ 466 at [21].

v) Having read the prior art, the skilled person may decide that it is of no interest. Kitchin J (as he then was) explained in *Eli Lilly v Human Genome Sciences* [2008] RPC 29 at [55] that:

> "… the law does not deem the skilled person to assume the prior art has any relevance to the problem he is addressing or require him to take it forward. Having considered it, he may conclude that it is simply not a worthwhile starting point and so put it to one side. "

The disclosure of Kazakov

84. Kazakov is a Russian paper which was published in an obscure journal. Its title and abstract read as follows:

> "EXTRACELLULAR DNA IN THE BLOOD OF PREGNANT WOMEN
>
> The level of extracellular DNA increases in the blood of women during pregnancy. By means of PCR, the full-size Alu repeats were observed among extracellular blood DNA repeats of pregnant women. Furthermore, with Tc65 type primer the PCR method allowed to observe in the blood DNA fragments flanked by inverted Alu repeats (inter-Alu repeats). The presence of such a type of inter Alu repeats was estimated in the blood of women being in the first trimester of pregnancy only, but was not estimated among blood DNA fragments of women of the last trimester of pregnancy. It is discussed which types of cells may serve as a source of extracellular blood DNA (either trophoblasts, lymphocytes, or decidual cells), the significance of such DNA for pregnancy being appreciated."

85. The introductory section of Kazakov states that it has been shown that extracellular DNA is contained in the blood of humans and animals. It indicates that an increase in the content of extracellular DNA in the blood of humans has been described during pathological processes taking place in various types of tissues of the body, especially during certain inflammatory processes. It states that it is believed that the high-

molecular component of extracellular DNA in the blood comes from living cells, and certain types of cells, especially lymphocytes, excrete extracellular DNA into their surroundings. It asserts that blood also contains "*low-molecular DNA*", the content of which, in the blood of rats, increases after total x-ray exposure. Kazakov says that it has been conjectured that the low-molecular DNA in the blood is a product of intensified extra-chromosomal synthesis.

86. At page 233 Kazakov states that extracellular DNA in the blood of humans and animals is of both theoretical and practical interest. Kazakov chose the blood of pregnant women to investigate extracellular DNA. The reason for this choice is said to be that:

> "According to available data, cellular proliferation, differentiation, and cell death occurs in the uterus during pregnancy… It was anticipated that these processes exert an influence on the specifics of the nucleotide composition of the extracellular DNA in the blood of pregnant women."

87. Experimental techniques used by Kazakov are described in the "*[m]aterial and method*" section on page 233. This records that Kazakov studied blood sera of men, non-pregnant women, and women in the first and third trimester of pregnancy, and those with late toxicosis of pregnancy. Two types of PCR primers were used to amplify DNA extracted from the blood sera: a pair of primers (B1 and C2) which resulted in the amplification of 239 base pair fragments from within each Alu repeat; and a single primer (Tc65) which resulted in the amplification of fragments flanked by two repeats with their 3'regions facing each other (referred to by Kazakov as "inter-Alu repeats").

88. Professor Lovett explained that Alu repeats are short repetitive sequences of DNA which are present on every human chromosome. In total, in excess of 500,000 Alu repeats are present in the human genome and they comprise approximately 10% of the human genome. Amplification of Alu repeats, or inter-Alu repeats, may be used to establish whether human DNA is present in a sample. Given that Alu repeats are so prevalent in the human genome, and the sensitivity of PCR, even a small amount of human DNA in a sample will be expected to be detected.

Figure 1

89. Kazakov's first experiment is at Figure 1. This shows a gel of the PCR amplification products obtained using primers B1 and C2 on serum samples from: (i) a man; (ii) a non-pregnant woman; (iii) a pregnant woman in the first trimester; (iv) a pregnant woman in the third trimester; and (v) a pregnant woman with pre-eclampsia.

90. On page 233 of Kazakov, the authors state that it was not their goal to study in detail the changes in the concentration of DNA in the blood serum of pregnant women. Nonetheless, in the first paragraph on page 234, Kazakov states that

> "[a]ccording to our data findings, during pregnancy there is an increase first of all in the concentration of low-molecular DNA, the increase being most pronounced during gestosis [pre-eclampsia]."

Figure 2

91. Kazakov states that:

> "[w]ith the help of the Tc65 primer, we detected inter-Alu repeats in the blood of women only in the first trimester of pregnancy (Fig. 2)."

Figure 2 of Kazakov is said to show the PCR amplification products that were obtained from DNA extracted from blood serum samples taken from 8 pregnant women in the first trimester. Kazakov states that:

> "[i]t is important that inter-Alu repeats have been detected only in the blood of women in the first trimester of pregnancy. This fact most likely reflects the difference in content of the cellular processes that are characteristic of the early and late stages of pregnancy."

92. Kazakov concludes that:

> "Thus, in the early stages of pregnancy in humans, cells of the foetus (trophoblast) and the mother (cells of the endometrium and lymphocytes) may excrete DNA … it can be conjectured that the inter-Alu repeats discovered by us in the blood serum of pregnant women may play some kind of regulatory role in the early stages of pregnancy …"

Obviousness in the light of Kazakov

TDL/Ariosa's submissions in outline

93. TDL/Ariosa submitted that the skilled team in 1997 would have been aware of the work that had been done on trying to develop non-invasive prenatal testing using foetal cells from blood, and of the various techniques used in such testing. It would have been aware of problems that had been experienced in trying to isolate foetal cells. In 1997 there was a strong motivation to find improved methods of non-invasive prenatal diagnosis.

94. Kazakov was an obscure publication and there was no suggestion that anyone in the field had actually read it. However, it would have been of interest to the notional skilled team for two reasons. First, it contained a new idea that extracellular DNA was present and detectable in the blood of pregnant women (in common with all other people). Even though the existence of extracellular DNA in human blood had been known to the scientific community for many years, this was not part of the common general knowledge of either member of the skilled team. Secondly, it contained the idea that some of the extracellular DNA in the blood of pregnant women could be of foetal origin. That would have been of significant interest to the skilled team because of its potential utility for prenatal screening and diagnosis. It provided a potential alternative to the foetal cells approach.

95. TDL/Ariosa relied on the evidence of Professor Oepkes and Ms Norbury that Kazakov would have been of interest, and that the two ideas identified above were credible. In particular, Kazakov suggests foetal trophoblast cells as one of the potential sources of extracellular DNA. Professor Oepkes considered that trophoblasts would have been seen as a reasonable cell type to propose as a potential source for the extracellular DNA.

96. Accordingly TDL/Ariosa claimed that it would have been obvious to the skilled team to have conducted a test to see whether Kazakov's idea was correct. However, it would not have tried to repeat Kazakov's experiments. The test to verify Kazakov's theories was straightforward and well established: PCR on plasma / serum from a woman carrying a male foetus using the well-known and proven primers for Y chromosome DNA, which would have been expected to detect foetal extracellular DNA if it was present. That could have been done quickly and easily, in parallel with work on foetal cells, and it would have succeeded.

Illumina's submissions in outline

97. Illumina joined issue with the key steps in this argument. It contended that the obviousness case was a classic exercise in hindsight. Kazakov did not, as claimed by TDL/Ariosa, disclose a generalised theory that extracellular DNA in the blood of pregnant women might be of foetal origin. Kazakov's idea was much more specific: that foetal cells might excrete a particular form of DNA (inter-Alu repeats), which would only occur in the first trimester of pregnancy. That idea was wholly implausible and there was nothing in the common general knowledge to support it.

98. Kazakov was a deeply flawed publication which provided no data in support of the conclusions that it reached. Figure 1 did not contain any data to support the claim that there is an increase in the concentration of low-molecular weight DNA during pregnancy. Figure 2, which was the basis for Kazakov's theory of foetal DNA excretion, was meaningless. It did not show the presence of inter-Alu repeats in the plasma in the first trimester, nor that such repeats were absent in later stages of pregnancy.

99. Illumina submitted that the natural reaction of the skilled team to such a flawed piece of research would have been to dismiss it completely. Professor Oepkes' written evidence was based on a hindsight reading of the prior art, which focused only on a few passages and ignored the rest of the disclosure. Ms Norbury came to Kazakov with prior knowledge that it was of interest, which would not have been shared by the skilled person.

Discussion

Extracellular DNA as common general knowledge

100. Professors Hogge and Oepkes agreed that the presence of cell free fragments of DNA in blood was not part of the skilled clinician's common general knowledge. However, it was positively asserted by Dr Erlich, who was called as an expert witness by Premaitha, that this information was a part of the common general knowledge of the skilled geneticist; [34] of his First Report and [14] – [17] of his Second Report. Notwithstanding this evidence, I agree with TDL/Ariosa that this information was not

common general knowledge to the skilled geneticist, as Professor Lovett and Ms Norbury both accepted during their cross-examination. However, the attitude of the skilled team to this suggestion in Kazakov depends on the credibility of its disclosure, taking account of its whole contents.

Figure 1 of Kazakov

101. Professor Lovett pointed out that the only basis for Kazakov's conclusion from Figure 1 was a reliance on differences in the visual appearance of the PCR amplification bands in lanes 4, 5 and 6 (samples from three pregnant women) compared to lane 3 (sample from a single non-pregnant woman). However, it was not possible to detect significant differences between the band in lane 3 and the bands in lanes 4, 5 and 6. He explained that even if any differences were visible, such differences would not provide a valid scientific basis for concluding that there is an increase in low molecular weight DNA during pregnancy. In particular:

   i) The PCR method used in Kazakov did not permit quantitative analysis to be performed. The authors had relied solely on a visual assessment of the apparent difference in the intensity of the bands. Insofar as any differences between the bands existed, they were too small to be reliably detected by eye, and did not provide a basis from which the conclusions in Kazakov could legitimately be drawn.

   ii) Kazakov had taken no steps to ensure that equal proportions of starting materials were put into each PCR reaction. It was therefore not possible to know whether any differences in the apparent intensity of the bands shown in Figure 1 were due to real biological differences between the patients, or to variations in the relative proportions of starting material used in the PCR reactions.

   iii) Only a single sample from each test subject had been analysed, which was contrary to good scientific practice. Since no replicates of any kind were performed, even if differences between the single samples analysed in Kazakov had been detected, it would not be possible to know if these were due to natural variations in DNA serum concentration that existed in the women irrespective of whether they were pregnant or their stage of pregnancy.

   iv) No statistical analysis on the data had been carried out by Kazakov. It was therefore not possible to know whether any differences between the bands shown in Figure 1 were statistically significant.

102. Professor Lovett's view was that Figure 1 did not contain any data to support the conclusion that there is an increase in the concentration of low molecular weight DNA during pregnancy. This was not challenged, and during cross-examination Ms Norbury agreed with Professor Lovett's reasoning. She agreed that Kazakov had not presented data to support the author's hypothesis. She said that:

> "I agree there is no evidence to show that there is an increase, and there never would have been the evidence, because he was using a qualitative technique."

She also agreed that in 1997 any competent scientist would have known that Kazakov's conclusion could not be drawn from Figure 1.

103. I accept Professor Lovett's evidence on this issue and I find that Figure 1 does not contain any data to support Kazakov's conclusion that there is an increase in the concentration of low molecular weight DNA during pregnancy.

Figure 2 of Kazakov

104. Professor Lovett was clear that Kazakov's suggestion that "*inter-Alu repeats have been detected only in the blood of women in the first trimester of pregnancy"* was not credible, for the following reasons:

   i) It is not credible to assert that inter-Alu repeats are only detectable in the blood serum of women in the first trimester of pregnancy when Alu repeats were shown to be detectable in the blood serum of all human patients studied (pregnant or otherwise). This observation does not make any sense. Inter-Alu repeats, like Alu repeats, exist in large numbers on every human chromosome. Therefore, inter-Alu repeats should be detected in all samples in which Alu repeats are detected.

   ii) Kazakov does not show the data for non-pregnant women, men, or women in the later stages of pregnancy, and there was therefore no evidence for the claim that inter-Alu repeats were not detectable in the blood of women in the later stages of pregnancy.

   iii) The use of the Tc65 primer would be expected to give rise to a smear of DNA. However, no smear can be seen in Figure 2 of Kazakov. The gel shown in Figure 2 of Kazakov would suggest that the PCR reactions using the Tc65 primers were very inefficient or did not work. Due to the lack of positive or negative controls, it was not possible to tell why a characteristic smear of DNA was not generated.

105. Professor Lovett's view was that the skilled geneticist would not have accepted Kazakov's conclusion that "*in the early stages of pregnancy in humans, cells of the foetus (trophoblast) and the mother (cells of the endometrium and lymphocytes) may excrete DNA*". He considered that it was speculation which was not supported by the data in Figure 2. The statement was based on an unsupported theory that inter-Alu repeats may have a regulatory role in the early stages of pregnancy owing to their selective excretion from cells. This theory was far-fetched. His view was that even if the suggested selective excretion were to have occurred, the data presented would not have enabled the skilled geneticist to determine the source of the inter-Alu DNA.

106. Professor Lovett was not cross-examined on this evidence and none of it was disputed by Ms Norbury. During cross-examination she agreed that the statement concerning the presence of inter-Alu repeats in the first trimester of pregnancy was based on Figure 2 and said that "*I just want to make very clear that I do not think you can make any sense at all out of Figure 2*". She considered that the experiment had failed to work. Professor Oepkes agreed that Figure 2 did not show the presence of inter-Alu repeats in first trimester pregnancies, nor their absence in the third trimester. In my

view, the skilled geneticist would have readily appreciated that no reliance could be placed upon Figure 2.

The evidence of the clinicians

107. Professor Oepkes stated in his First Report that a skilled clinician would have found the title of Kazakov interesting and would have moved on to read the abstract. The information presented in the abstract would have been interesting from the perspective of prenatal screening and diagnosis, particularly the claim that there was an increase in the levels of extracellular DNA in the blood of pregnant women during pregnancy and the suggestion that trophoblast (i.e. foetal) cells are a possible source of extracellular blood DNA in such women. He stated that the skilled clinician would not have found the introduction or methods sections particularly relevant from a prenatal diagnosis and screening perspective. He would, however, have taken more interest in the results and discussion section and would have found the final paragraph of the article of particular interest.

108. In my view, this approach to the prior art, which concentrates only on selected passages and ignores the rest of the document, is wrong in principle and in law. The notional skilled clinician would read the entirety of the document and consider its contents "warts and all", before deciding on the value of its teaching.

109. Professor Oepkes referred to the common general knowledge that foetal materials (cells, proteins and hormones) were known to enter the maternal circulation from the placenta as a reason for thinking that Kazakov's idea could well be correct. He relied upon the chorionic villi of the placenta as presenting a large surface area (10 m^2 at term) of trophoblasts in direct contact with the maternal circulation and therefore a credible source of DNA. He stated at [8.6] of his First Report that:

> "The skilled person would have found the information presented in the abstract interesting from the perspective of prenatal screening and diagnosis, particularly the fact that the authors say that there is an increase in the levels of extracellular DNA in the blood of pregnant women during pregnancy and the suggestion that trophoblast (i.e. foetal) cells are a possible source of extracellular blood DNA in such women."

110. However, whilst the surface area of the chorionic villi is around 10 m^2 at term, it is much smaller in the first trimester (around 0.5 m^2 at week 13), as Professor Hogge explained. It was common general knowledge that, at the end of the third trimester, the maternal blood was exposed to several thousand times more surface area of maternal tissue than foetal tissue. If surface area was relevant, this would refute, rather than support, Kazakov's theory. Inter-Alu repeats would be expected to increase in concentration in later stages of pregnancy, whereas Kazakov postulates that they disappear.

111. During cross-examination it was suggested to Professor Hogge that trophoblasts are shed from the chorionic villi into the maternal circulation where they then degrade and release their contents, including their DNA. He explained that the number of trophoblasts in question (100,000 per day) was incredibly small relative to the background of maternal cells. His expectation would have been that if there was DNA

in the maternal plasma, it would be almost exclusively maternal. Professor Hogge's view was that the idea that extracellular DNA in the first trimester was coming from foetal trophoblasts made no physiological sense. I accept his evidence.

112. Professor Hogge explained that the skilled clinician would look at Kazakov and immediately say that the science was bad. He considered that the skilled clinician would probably not go so far as even to show it to the skilled geneticist, since he would see no reason to expect any repeated (or new) experiments to work. He reasoned that Kazakov would not have been relied upon by the skilled team, as the data which it presented was fundamentally flawed. When questioned about the conclusions to be drawn from Figure 1, Prof Hogge, having initially agreed that Figure 1 showed the presence of extracellular DNA in the blood of pregnant women, said:

> "We should step back a moment and say that we are assuming this is good science and the skilled clinician would look at this and immediately say the science was bad. We would take it to a geneticist, who would also say the science is really bad. For us to say we can make any kind of statement from this paper, it is possible for us to speculate, but there is no data and no scientific support for anything that is in this paper."

113. I bear in mind that the skilled clinician would have been aware of problems that had been experienced in trying to isolate foetal cells, and that in 1997 there was a strong motivation to find improved methods of non-invasive prenatal diagnosis. Furthermore, I have found that it was not part of the common general knowledge of the skilled team that extracellular DNA was present and detectable in the blood, including in the blood of pregnant women. Nonetheless, I prefer the evidence of Professor Hogge to that of Professor Oepkes in relation to this issue, given the implausibility of Kazakov's theory, and the clear defects in the data which are claimed to support it.

The evidence of the geneticists

114. Ms Norbury held the view that in spite of the technical flaws in the paper, the skilled geneticist would nonetheless have been motivated to pursue Kazakov. Her opinion was that:

i) A source of foetal DNA that could be accessed non-invasively would have been of interest to the skilled person with experience of genetic testing of patient samples because of its potential for use, for example, in sex determination as part of the process of investigating X-linked disorders.

ii) On the basis that it was known that foetal cells and proteins were able to enter the maternal circulation, the idea that foetal DNA would also be present in maternal circulation was entirely credible.

iii) The skilled geneticist would have carried out an assay using well-known primers for the Y chromosome and that the experiment could have been done in a day.

115. During cross-examination, it emerged that Ms Norbury had attended a presentation by Professor Kypros Nicolaides, who was well known in respect of his work in NIPD, at a Royal Society meeting in June 2016. This was before she was given Kazakov by TDL/Ariosa's solicitors in November/December 2016. She explained that Professor Nicolaides had said that Professor Lo was not the first person to report the presence of foetal cell-free DNA and showed a slide of Kazakov.

116. I consider that Ms Norbury read Kazakov with Professor Nicolaides' claim that this paper pre-empted Dr Lo's discovery in mind. The presentation was a few months before she was shown the Kazakov paper for the purposes of this case. Ms Norbury read Kazakov with knowledge that would not have been shared by the notional skilled person in 1997. That caused her to consider that it would have been pursued by the skilled geneticist, in spite of its technical flaws.

117. Once the methodology and data in Kazakov are taken into account, there was much agreement between Ms Norbury and Professor Lovett. Professor Lovett considered that Kazakov was paradoxical nonsense and would be thrown in the bin. Ms Norbury accepted that the only data in Kazakov was that extracellular DNA was present in the blood of all humans including pregnant women and that Kazakov's theory of the presence of inter-Alu repeats only in the first trimester was implausible. Insofar as there was disagreement between them, I prefer the evidence of Professor Lovett on this issue. Even if the skilled clinician had referred Kazakov to the skilled geneticist, which I do not accept, he would rapidly have been told that it was fundamentally flawed.

Fair prospect of success

118. In my judgment, none of the expert evidence supported a conclusion of a fair prospect of success in the light of Kazakov. In particular:

    i) During his cross-examination, when faced with the clear defects in Kazakov, Professor Oepkes expressed the view that Kazakov would not have been *"binned immediately"* but would have been *"put on a pile of potentially interesting papers to share with a knowledgeable laboratory colleague from the team to see what they thought of it."* He said that the skilled clinician would have to discuss the methodology with a laboratory-based colleague but was unable to predict what the outcome of that discussion would be.

    ii) Professor Hogge's view was that there was nothing in the paper to suggest further work to do, but if one were to look for foetal DNA, the expectation would be not to find it.

    iii) Professor Lovett's view was that if the skilled geneticist had been motivated to do anything with Kazakov, he would have repeated the experiments using a properly designed experimental methodology. In cross-examination, he explained that the skilled geneticist would have no expectation of success even if (contrary to his view) he took Kazakov forward.

    iv) Ms Norbury was in agreement with the other experts, as her cross-examination revealed:

> "Q. There is no basis in Kazakov from which a skilled person could conclude that if you carried out the test that you are suggesting he might have come up with to look for foetal DNA that it would actually work to find foetal DNA, that it was likely to work."
>
> "A. But I would not have approached the experiment with a definite expectation. That is why you do experiments; to actually investigate things."

119. In my judgment the experts were correct to be extremely cautious about the likely outcome of pursuing Kazakov's theory. If, contrary to my view, the skilled team decided to do this, then the obvious course would be to attempt to improve Kazakov's experiments in order to test the authors' theory, with little expectation of success. If this failed, as it would have done, then further experiments would not have been performed with any realistic expectation of success.

Conclusion

120. I have reached the clear view that Lo 1 is not obvious in the light of Kazakov. Kazakov propounded an implausible theory, which was unsupported by any data that could be relied upon. Having read Kazakov, the skilled clinician would not refer it to a geneticist for further investigation. If consulted, the geneticist would have taken the view that Kazakov was fundamentally flawed. None of the skilled team would have considered that there was a fair prospect that tests performed in the light of Kazakov would succeed.

Lo 1 – entitlement to priority/enablement

Legal principles

121. The following is a brief summary of the basic principles in relation to priority and enablement.

<u>*Priority*</u>

i) A claim to priority of the "same invention" is referred to in Article 87(1) of the European Patent Convention. Section 5(2)(a) of the Patents Act 1977, which provides for entitlement to priority, is to be interpreted as having the same effect as Article 87(1), pursuant to section 130(7) of the Act; *Medimmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234; [2013] RPC 27 at [151].

ii) The requirement for the "same invention" means that priority is to be acknowledged only if the skilled person can derive the subject matter of the claim directly and unambiguously, using common general knowledge, from the priority document as a whole; G 2/98 *Same Invention* [2001] OJ EPO 413; [2002] EPOR 167.

iii) The approach is not formulaic: priority concerns technical disclosure, explicit or implicit. The question is whether there is enough in the priority document to

give the skilled person essentially the same information as forms the subject of the claim and enables him to work the invention in accordance with that claim; *Unilin Beheer v Berry Floor* [2004] EWCA (Civ) 1021; [2005] FSR 6 at [48].

iv) The important thing is not the consistory clause or the claims of the priority document, but whether the disclosure as a whole is enabling and directly and unambiguously gives the skilled person what is in the claim whose priority is in question. It must "give" this disclosure directly and unambiguously. It is not sufficient that it may be an obvious development from what is disclosed; *Abbott Laboratories Ltd v Evysio Medical Devices plc* [2008] EWHC 800 at [228].

Enablement

v) Plausibility, as part of the requirement of an enabling disclosure, applies to issues of priority as well as sufficiency; *Hospira UK Ltd v Genentech Inc* [2014] EWHC 1094 at [149].

vi) If the invention discloses a principle capable of general application, the claims may be in correspondingly general terms. The patentee need not show that he has proved its application in every individual instance. On the other hand, if the claims include a number of discrete methods or products, the patentee must enable the invention to be performed in respect of each of them; *Biogen Inc v Medeva plc* [1997] RPC 1 at pp. 48-49.

vii) A principle of general application simply means an element of the claim which is stated in general terms. Such a claim is sufficiently enabled if one can reasonably expect the invention to work with anything which falls within the general term; *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2004] UKHL 46, [2005] RPC 9 at [112] – [113].

viii) It must therefore be possible to make a "*reasonable prediction*" that the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible or credible; *Regeneron Pharmaceuticals Inc v Genentech Inc* [2013] RPC 28 at [95] - [103].

ix) If it is not possible to make such a prediction or if it is shown the prediction is wrong and the invention does not work with substantially all of the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution and the claim will be insufficient; *Regeneron v Genentech* at [101].

x) A reasonable prediction, in the sense of a plausible or credible assertion, is a low threshold test, requiring only that the claim must not be speculative. It is not the same test as 'reasonable prospect of success' in the context of obviousness; *Generics v. Warner-Lambert* [2016] EWCA Civ 1006; [2017] RPC 1.

The disclosure of the Lo 1 Priority Document

122. The Lo 1 Priority Document introduces its invention at page 1 lines 3-11:

> “This invention relates to prenatal diagnosis using non-invasive techniques. In particular, it relates to prenatal diagnosis by detecting foetal nucleic acids in serum or plasma from a maternal blood sample. Conventional prenatal screening methods for detecting foetal abnormalities and for sex determination traditionally use foetal samples derived by invasive techniques such as amniocentesis and chorionic villus sampling. These techniques require careful handling and present a degree of risk to the mother and to the pregnancy.”

It then acknowledges certain techniques used in the prior art, including

> “the use of foetal cells in maternal blood for non-invasive prenatal diagnosis (Simpson and Elias 1993) [which] avoids the risks associated with conventional invasive techniques."

123. At page 2 lines 5 to 14, the Lo 1 Priority Document states that:

> “It has now been discovered that foetal DNA is detectable in maternal serum or plasma samples. This is a surprising and unexpected finding; maternal plasma is the very material that is routinely discarded by investigators studying non-invasive prenatal diagnosis using foetal cells in maternal blood. The detection rate is much higher using serum or plasma than using nucleated blood cell DNA extracted from a comparable volume of whole blood, suggesting that there is enrichment of foetal DNA in maternal plasma and serum. It is important that foetal DNA is found in maternal plasma as well as serum because this indicates that the DNA is not an artefact of the clotting process.”

124. At page 2 lines 15-18 the Lo 1 Priority Document states that:

> “This invention provides a method of performing a prenatal diagnosis on a maternal serum or plasma sample which method comprises detecting the presence of a nucleic acid sequence of foetal origin in the sample.”

It then provides a broad definition of “prenatal diagnosis”:

> “The term “prenatal diagnosis” as used herein covers determination of any maternal or foetal condition or characteristic which is related to either the foetal DNA itself or to the quantity or quality of the foetal DNA in the maternal serum or plasma. Included are sex determination, and determination of foetal abnormalities which may be for example chromosomal aneuploidies or simple mutations. Also included is detection and monitoring of pregnancy-associated conditions such as pre-eclampsia which may result in differing

> amounts of foetal DNA being present in the maternal serum or plasma. The nucleic acid detected in the method according to the invention may be of a type other than DNA e.g. mRNA."

125. Page 3 line 27 – page 5 line 2 describes various ways in which foetal DNA in maternal serum or plasma might be used to obtain information about the foetus. It is disclosed from page 3 line 27 - page 4 line 4 that:

> "The method according to the invention may be particularly useful for sex determination which may be carried out by detecting the presence of a Y chromosome. It is demonstrated herein that using only 10 µl of plasma or serum a detection rate of 80% for plasma and 70% for serum can be achieved. The use of just 1ml of maternal plasma or serum resulted in a 100-fold increase in the absolute amount of foetal genetic material available for analysis. This is expected to provide a very accurate system for detecting paternally-inherited foetal DNA sequences."

126. The detail of this finding is set out from page 6 onwards, which is materially the same as Example 1 of the Lo 1 Patent.

127. As in the Lo 1 Patent, the Lo 1 Priority Document states that its method can be applied to the detection of any paternally inherited sequences which are not possessed by the mother. Examples are said to include foetal Rhesus D status (page 4 lines 8-15). The Lo 1 Priority Document says that this is possible because rhesus positive individuals possess the rhesus D gene which is absent in rhesus D negative individuals. Therefore, the detection of rhesus D gene sequences in the plasma and serum of a rhesus D negative mother is indicative of the presence of a rhesus positive foetus (with a rhesus positive father). The authors also propose the use of cell free foetal DNA in maternal plasma and serum for identifying foetal haemoglobinopathies (page 4 lines 16-21); and detection of paternally inherited DNA polymorphisms or mutations (page 4 lines 21- 5 line 2).

128. At page 5 lines 3-26 the Lo 1 Priority Document describes two approaches which it claims can be used for the screening of Down's syndrome and other chromosomal aneuploidies. The Lo 1 Priority Document suggests another potential application for its invention in the detection of pre-eclampsia. I shall consider this part of the disclosure in detail when addressing allegations of non-enablement.

Challenges to priority

129. TDL/Ariosa challenge entitlement to priority on the basis of lack of enablement and lack of disclosure. It relies upon five grounds:

i) Squeeze between infringement and validity

<u>*TDL/Ariosa's submissions*</u>

130. TDL/Ariosa argued that if the claimed detection method of Lo 1 covers the approach adopted in the Polymorphic Assay of Harmony, then since this approach is not

enabled by the Priority Document, Lo 1 is invalid. This approach does not require or use information about parental genotypes from an independent source, and avoids the need for such information by carrying out relative quantitation of alleles and, where a difference in the relative quantities is found, attributing them to the mother and the foetus.

131. It argued that the Lo 1 Priority Document did not disclose or enable any new approach to detecting the presence of foetal sequences that are paternally-inherited sequences not possessed by the mother. The approach disclosed by the Lo 1 priority document was the standard one of using information about parental genotypes to identify a sequence that it was known would, if found, be paternally-inherited rather than maternally-inherited, and so would be foetal, followed by using PCR to determine whether such a sequence was present in the sample. Its contribution to the art was limited to the discovery that foetal Y chromosome DNA could be detected in the plasma and serum of women carrying male foetuses using standard, well-established techniques.

132. It submitted that the only Example of the invention in the Lo 1 Priority Document (which became Example 1 in the Patent) used this conventional approach. It showed no more than that Y chromosome foetal DNA was detectable in maternal serum or plasma samples, and did not disclose the level of foetal DNA or the presence or level of maternal DNA. The first disclosure as to the relative levels of foetal and maternal DNA in maternal serum and plasma was in Example 5 of the PCT Application, which demonstrated for the first time that foetal DNA is present in plasma/serum in sufficient quantities that it may potentially be useful for non-invasive prenatal diagnosis of selected genetic disorders.

133. TDL/Ariosa submitted that the Lo 1 Priority Document did not disclose a principle of sufficiently general application to support a claim that extends to detecting the presence of a paternally inherited foetal sequence not possessed by the mother without an independent source of information about parental genotypes. It argued that if the scope of the claims of the Lo 1 Patent is such that it encompasses the approach used in the Harmony test, then it must be invalid for lack of enabling disclosure by the Priority Document.

Illumina's submissions

134. Illumina submitted that the Lo 1 Patent claims a principle of general application. Claim 1 includes elements stated in general terms, namely 'nucleic acid of foetal origin' and 'a paternally inherited sequence'. The claim is amply justified by the technical contribution of the Patent, which was also disclosed in the Priority Document. The invention of Lo 1 was not merely plausible; it was regarded by the NIPD field as revolutionary and it opened up an entirely new, and unexpected, avenue of enquiry.

135. It submitted that it is sufficient for a patentee who has invented a new principle of general application to disclose at least one method of exploiting it which could be achieved without undue burden. There is no dispute that this has been done in the Lo 1 Priority Document in respect of the detection of the Y chromosome and the detection of other paternally-inherited conditions such as RhD-positive foetuses in RhD-negative women.

136. Illumina argued that the Harmony assay was an improvement to the invention which utilised the principle of general application which it claimed in Lo 1. Lo 1 did not have to enable such improvements, nor anticipate future technology.

137. Alternatively, Illumina claimed that performing the method without an independent source of information about parental genotypes was in fact plausibly enabled at the priority date using semi-quantitative PCR analysis to identify the paternally-inherited foetal allele. This argument is based upon an explanation given by Professor Lovett of how this could have been done at the priority date, which he illustrated by a sketch which became 'X2'.

Discussion

138. This is a key issue which requires a detailed analysis of the relevant legal principles. In *Kirin-Amgen Inc v Transkaryotic Therapies Inc* [2004] UKHL 46; [2005] RPC 9 at [102] Lord Hoffmann stated that the law required that "*the disclosure must enable the invention to be performed to the full extent of the monopoly claimed*." At [103] he said that:

> "…whether the specification is sufficient or not is highly sensitive to the nature of the invention. The first step is to identify the nature of the invention and decide what it claims to enable the skilled man to do. Then one can ask whether the specification enables him to do it."

139. The principle of enablement across the breadth of the claim is of considerable importance, but it is not absolute. It does not require a patentee who has claimed a principle of general application to anticipate inventive improvements which make use of that principle, nor future advances in technology, which would be an impossible task. The case-law on this issue is summarised in *Terrell on Patents* (18th Ed.) at [13.30] – [13.37]. The point was expressed succinctly by Aldous LJ in the Court of Appeal in *Kirin-Amgen*; [2002] EWCA 1096; [2003] RPC 3 at [69]:

> "The law contemplates that patents will not lack sufficiency even though the claims cover inventive improvements. If the law were otherwise there would be no room for patents which disclosed a principle of general application unless the specification described how to carry out later inventions using the principle."

140. When considering (*obiter*) that passage in the Court of Appeal judgment, Lord Hoffmann said at [117] of *Kirin-Amgen* that:

> "As for the point made by the Court of Appeal, it is of course correct so far as it goes. The choice of a particular form of an integer falling within the terms of the claim may improve the way the invention works and be in itself an inventive step. The specification is not insufficient merely because it does not enable the person skilled in the art to make such an invention. The use of the improvement is still a way of working the original invention. But TKT does not rely upon the fact that the use by TKT of an endogenous EPO gene was inventive.

> Their objection is that it is not a way of making EPO which is disclosed, even in the most general terms, by the specification. …"

I do not read that comment as disapproving the principle set out by Aldous LJ. On the contrary, Lord Hoffmann expressed the same view in his own words.

141. TDL/Ariosa also relied upon [114] of Lord Hoffmann's judgment in *Kirin-Amgen*, where he rejected the submission that the patent would be saved by the disclosure of a principle of general application and said:

> "In my opinion the facts did not support the application of this principle. Assuming the claims can be read, as the judge thought, to include any way of making EPO by recombinant DNA technology, the specification does not disclose a way of making it in sufficiently general terms to include the TKT process. It discloses only how to make EPO by introducing exogenous DNA coding for EPO into a host cell. The TKT method is not a version of this process which, although untried, could reasonably be expected to work as well. It is different."

142. Both of the cited passages from Lord Hoffmann's judgment emphasise the need to have regard to the nature of the invention, and its technical contribution, when considering a breadth of claim objection. Otherwise, they are specific to the facts of the *Kirin-Amgen* case.

143. In *Actavis v Eli Lilly* [2017] UKSC 48, Lord Neuberger stated at [51] that helpful guidance concerning the approach to variants could be found in a lecture given in 2016 by Judge Rian Kalden, the head of the IP division in the Court of Appeal in The Hague; *"Article 69 EPC – the Scylla and Charybdis of the European Patent Convention – which route did the Dutch courts take?*". He cited the following passage from Judge Kalden's lecture:

> "Variants that are not foreseeable at the priority date may well, due to later developments, become an obvious variant at a later date. This may happen in case of a pioneer invention, where at the priority date the full breadth of the possible applications could or has not been fully recognised and therefore was not sufficiently taken into account when drafting a claim. Another possibility is that a new technique becomes available after the patent was granted, which makes available an obvious variant. It would be harsh and contrary to fair protection for the patentee to deny him the right to attack those, again provided such variant falls within the inventive concept and reasonable legal certainty is taken into account. So infringement by equivalence is not limited to foreseeable variants only."

144. In summary, fairness to the patentee may require that unforeseeable variants, enabled for the first time by new technology, fall within the scope of protection, although the patentee is less likely to succeed where the variant was unforeseeable at the priority date. A variant which represents an inventive step may nonetheless infringe; *Actavis v*

Eli Lilly at [63] – [64]. It would not make sense if, in those circumstances, the patent was found to be insufficient solely because such an inventive variant, which it did not enable, fell within the scope of its claims.

145. This same principle is well-established by decisions of the Board of Appeal in the EPO. In *Genentech I/Polypeptide Expression* (T292/85), the Board of Appeal allowed broad functional terminology to be used in a claim, even though it embraced the use of "*unknown or not yet envisaged possibilities, including specific variants which might be provided or invented in the future*." The Board said that:

> " In appropriate cases such as the present it is only possible to define the invention … in a way which gives fair protection having regard to the nature of the invention which has been described by using functional terminology in the claims …"
>
> " … the need for a fair protection governs both the consideration of the scope of claims and the requirement for sufficient disclosure. Unless variants of components are also embraced in the claims, which are, now or later on, equally suitable to achieve the same effect in a manner which could not have been envisaged without the invention, the protection provided by the patent would be ineffectual …"

146. Similarly, in *Erythropoietin II/Kirin Amgen* (T0636/97) the Board of Appeal stated at [4.5] that:

> "For the board it is a fundamental principle of patent law that a claim can validly cover broad subject matter, even though the description of the relevant patent does not enable every method of arriving at that subject matter to be carried out. Otherwise no dominant patent could exist, and each developer of a new method of arriving at that subject matter would be free of earlier patents. In many cases in the field of biotechnology, patent protection would then become illusory. This is not to say that some claims might not be too broad in scope and not be enabled over their whole scope for the purposes of Article 83 EPC… The boards have considered this question of allowability of broad claims versus the requirements of Article 83 EPC, strictly on a case-by-case basis, influenced by the extent to which the information in the patent could be used to develop further embodiments without a major conceptual leap."

147. In summary, this case law establishes that a patentee may claim a principle of general application. He cannot anticipate future inventive improvements or future developments in technology which will fall within his claim. The fact that such improvements or developments fall within the claim, because they adopt the principle of general application, may well not mean that the patent is invalid for insufficiency. But this conclusion depends upon the facts of the case, including the nature of the invention and its technical contribution.

148. The Lo 1 Priority Document clearly and unambiguously discloses that cell-free foetal DNA is present in detectable amounts in the maternal plasma and serum of a pregnant female. It discloses a principle of general application for detection of such nucleic acid sequences using paternally inherited cell-free foetal DNA as the source material to be analysed. The "*nucleic acid of foetal origin*" in claim 1 is stated in general terms, and represents a principle of general application. So long as that nucleic acid has the property required by the claim, namely that it is "*a paternally inherited sequence which is not possessed by said pregnant female*" the identity of the nucleic acid is otherwise general in nature.

149. The Lo 1 Priority Document discloses certain methods of exploiting its invention which could be put into practice without undue burden, namely use of the method of claim 1 for detection of foetal sequences of the Y chromosome, allowing sex determination of the foetus, and of foetal nucleic acid sequences from a paternally inherited non-Y chromosome for detection of paternally-inherited conditions such as RhD-positive foetuses in RhD-negative women.

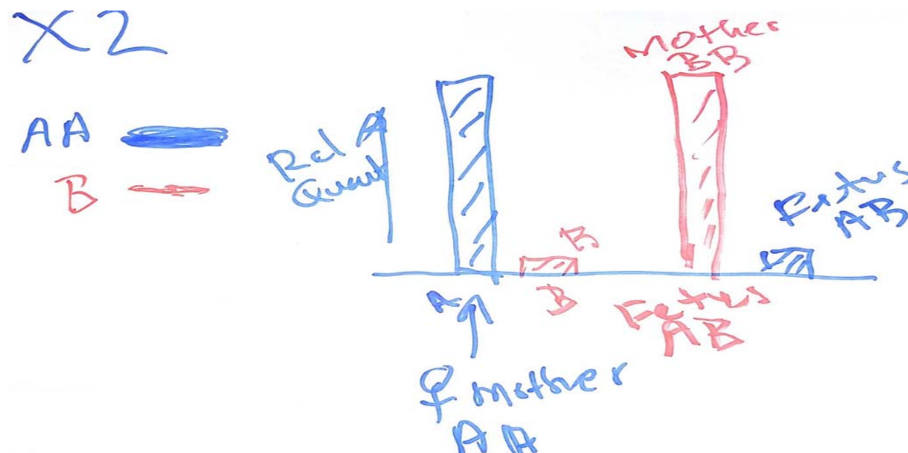
150. I accept TDL/Ariosa's submission that the method specifically disclosed by the Lo 1 Priority Document was the standard one of using information about parental genotypes to identify a sequence that it was known would, if found, be paternally-inherited rather than maternally-inherited, and so would be foetal, followed by using PCR to determine whether such a sequence was present in the sample. However, the skilled geneticist would have appreciated that insofar as new techniques for the detection or quantification of nucleic acid sequences were developed in the future, these could also be used to implement the general principle disclosed in the Lo 1 Patent and Priority document of using paternally inherited cell-free foetal DNA as the source material to be analysed; Lovett (1) at [75].

151. Furthermore, the principle of general application disclosed in the Lo 1 Priority Document was credible at the priority date. It revolutionised the approach to non-invasive prenatal testing, as shown by the reaction in the art to the publication of Lo 1997, which, like the Priority Document, disclosed Example 1, but not Example 5, of the Lo 1 Patent.

152. In my judgment, the approach used in the Harmony Test is an inventive improvement over the Lo 1 Priority Document and the technology for putting it into effect did not exist at the priority date. It could not have been predicted at the priority date and is not referred to in the Lo 1 Priority Document or the Lo 1 Patent. Ms Norbury explained in her Third Report that in 1997, the Harmony Prenatal Test's approach would not have been thought possible, nor in fact would it have been possible with the technology available at the time, and that it has real clinical benefits. I accept this evidence. This does not deprive the Lo 1 Patent of priority, nor render any of its claims insufficient.

153. It is therefore strictly unnecessary for me to consider Illumina's alternative case of enablement based upon X/2, but since I have heard arguments on this issue I shall do so. During his cross examination, Professor Lovett suggested an approach to performing the method of the Lo 1 Priority Document without an independent source of information about parental genotypes which he believed would have been obvious at the priority date. This involved the choice of a polymorphism (or set of polymorphisms) known to be bi-allelic amongst the population. The relative quantities of the two alleles at the polymorphic locus could be measured. If one allele

is observed in excess compared to the other then, if the relative levels of foetal and maternal DNA are known, it can be deduced that the minor allele came from the foetus and not the mother (and hence that it was paternally-inherited). This approach works where the mother is homozygous (AA or BB) and the foetus is heterozygous (AB). Professor Lovett illustrated this by a rough sketch (X/2), reproduced below. By this method, he suggested that the skilled team could, in one step, carry out the assay and obtain information about the genotype of the mother, the foetus and the father.



154. I do not accept Illumina's alternative case of enablement based upon X/2. Professor Lovett's approach is not referred to in the Lo 1 Priority Document and no other expert suggested it. The detail of this approach was not set out in Prof Lovett's written evidence, and therefore, if it was to be relied upon, it needed to be put to Ms Norbury and Professor Oepkes. Neither expert was cross-examined about X/2.

ii) Detecting foetal SNPs in maternal plasma/serum

155. TDL/Ariosa submitted that from the disclosure of [0017] of the Lo 1 Patent, and the equivalent passage in the Lo 1 Priority Document, the skilled team would be aware that haemoglobinopathies are caused by mutations ranging from large-scale changes to single point mutations, and that the group in [0017(c)] would include a range of such polymorphisms and mutations. It submitted that the Patent and the Priority Document were representing that all such polymorphisms and mutations could be detected so long as they were paternally inherited and not possessed by the mother.

156. TDL/Ariosa acknowledged that the approach of the Priority Document could easily be used to detect the Y chromosome and RhD negative mothers, where the differences between the sequence to be detected and the maternal sequence present in maternal plasma or serum were substantial. However, it submitted that this was not the case in respect of the detection of single nucleotide polymorphisms ("SNPs") where the difference between the sequence to be detected and the maternal background was much smaller.

157. In support of this contention, TDL/Ariosa relied upon Lo YMD *et al.*, Prenatal diagnosis: progress through plasma nucleic acids. *Nature Reviews Genetics* 2007; 8: 71-77. The authors considered attempts to implement the approach of the Lo 1 Patent. They indicated that the technical challenge of distinguishing between foetal and maternal circulating DNA to a single nucleotide had only recently been overcome by the development of a single-allele base extension reaction protocol for mass-

spectrometry analysis. In the light of this publication, Professor Hogge accepted that whilst it proved possible at the priority date to detect paternally inherited sequences that were significantly different from the maternal background, where the difference was a single point mutation, that was generally not possible until the development of new technology.

158. Therefore, TDL/Ariosa submitted that neither the Priority Document nor the Patent enabled the skilled person to detect polymorphisms and mutations on a non-Y foetal chromosome without undue burden across the scope of the claims. It was not possible to detect the group of foetal sequences with single based differences from the maternal background without the development of new technology.

159. I do not accept TDL/Ariosa's case on this issue for the following reasons. Illumina was not given proper notice of this specific allegation and it was not mentioned in TDL/Ariosa's expert reports. The SNP issue was put to Professor Hogge during his cross-examination and he repeatedly indicated that questions about the ability to detect a single base change should be directed to Professor Lovett, as it was within his area of expertise rather than that of Professor Hogge. However, TDL/Ariosa did not direct any questions on the subject to Professor Lovett. In my judgment, the point on SNP detection was a matter for the geneticists. Professor Lovett and Ms Norbury had dealt with detection of polymorphisms in their reports. Ms Norbury had not raised any difficulty with SNP detection. Professor Lovett set out methods that were used for SNP detection in his first report at [27] to [30]. In the circumstances, if the point was to be pursued, it needed to be put to Professor Lovett.

160. Furthermore, although it appears that the development of new technology, subsequent to the priority date, enabled the identification of further polymorphisms and further ways of detecting them, this does not, in my judgment, give rise to a loss of priority or insufficiency, for the reasons which I have explained when considering the alleged squeeze between infringement and insufficiency.

iii) Detecting aneuploidies and pre-eclampsia

161. The Lo 1 Priority Document represents that the plasma or serum based non-invasive prenatal diagnosis method according to the invention can be applied to the screening of Down's syndrome and other chromosomal aneuploidies (page 5 lines 3 to 6). It also represents that another potential application of the accurate quantitation of foetal nucleic acid levels in the maternal serum or plasma is in the molecular monitoring of certain placental pathologies, such as pre-eclampsia (page 5 line 27- page 6 line 2).

162. The first approach disclosed for achieving this is based on the hypothesis that the level of foetal DNA in maternal plasma and serum will be higher in aneuploid pregnancies than in normal pregnancies. Therefore, it is suggested that quantitative detection of foetal nucleic acid in the maternal plasma or serum could be used to screen pregnant women for aneuploidies (page 5 lines 7-18). Prof Oepkes explained at [9.41] of his first report that there is no evidence to support this hypothesis and the skilled person would not regard it as reasonably credible. Furthermore, the suggestion that levels of foetal DNA are higher in aneuploid pregnancies than normal ones has not been reliably and reproducibly established. He also explained at [12.2] – [12.4] that, despite the desire to use maternal plasma or serum as a means for detection of

aneuploidies, this approach has not been successfully put into practice. I accept this evidence.

163. The second approach in the Priority Document proposes the identification of a foetal marker on the chromosome of interest, and a foetal marker on a reference chromosome, and determination of the relative quantity of the two. The relative quantity will be different depending upon whether the pregnancy is normal or aneuploid. Ms Norbury and Professor Oepkes gave evidence that an attempt to use this approach for the detection of aneuploidies, using sequences that are paternally inherited and not possessed by the mother, would only be capable of working, if it worked at all, in detecting aneuploidies in which the extra chromosome was inherited from the father, which account for less than 10% of trisomy 13, 18 and 21. Even then, there would be very considerable difficulties in trying to put this approach into effect in identifying suitable foetal markers, and in carrying out successful quantitative assays. Professor Oepkes' opinion, which I accept, was that this method would have been regarded as unworkable and implausible in practice. It has never been put into practice in spite of the desire to use maternal plasma or serum as a means for detection of such aneuploidies.

164. As to pre-eclampsia, there is nothing in the priority document to support the assertion that it is likely that pre-eclampsia may result in alterations in foetal DNA concentration in maternal serum and plasma. Professor Oepkes explained that this hypothesis was not credible, and the skilled person would not have regarded it as plausible that the proposed method could have been used to detect pre-eclampsia. I accept his evidence.

165. Illumina does not maintain (for the purposes of these actions only) that the applications set out in [0018] of Lo, which include the detection of Down's syndrome and pre-eclampsia, were enabled at the filing date. It follows that there was no enabling disclosure of those applications in the Lo 1 Priority Document, in spite of its assertions concerning use of its invention in Down's syndrome and pre-eclampsia applications.

166. In order to address this problem, Illumina applied unconditionally to amend the Lo 1 Patent by deleting claims 14 to 17 of the Lo 1 Patent, which relate to such applications. Furthermore, it made a conditional application to delete [0018] to [0020].

167. It is apparent, and is accepted by Illumina, that these amendments cannot affect the scope of claim 1. Illumina accepted that use for detection of aneuploidy remains within the scope of claim 1 if the unconditional application to amend is allowed. Furthermore, TDL/Ariosa pointed out that [0007] – [0008] of Lo 1 state that the invention provides a method for the detection of aneuploidies and pre-eclampsia. In response, at the end of the trial, Illumina applied to delete these paragraphs as well. Because of further references to these clinical applications in the specification, Illumina also indicated that it would be willing to delete Examples 2 and 4 if necessary.

168. Illumina relied upon the proposition that where the patent discloses a principle of general application it does not have to disclose every way of carrying the invention into effect; nor is it the case that every way of carrying the invention into effect that

might be developed using new technology in the future must be plausible at the date of the patent. It also submitted that its amendments, if allowed, would be retrospective and the deleted passages would be deemed never to have been there. Without them, it could not be suggested that there was any insufficiency by failure to enable a future application of the invention which was not set out as a possibility in the specification.

169. Illumina's fall-back position was that at least claim 8 could not be the subject any of these objections since it was limited to determination of the sex of the foetus, and did not include detection of aneuploidies or pre-eclampsia. TDL/Ariosa accepted that claim 8 is limited to sex determination and therefore is not subject to these objections.

170. In my judgment, apart from claim 8, Illumina's various applications to amend do not solve the problem. The Priority Document and the Patent both contain a non-enabling disclosure of use of the invention in certain discrete clinical applications. The disclosure was implausible in these respects and it will not work. In spite of the proposed amendments, claims 1 and 5 include these applications within their scope.

171. Illumina submitted that claim 7, which is limited to detection of the presence of a foetal nucleic acid sequence from the Y chromosome, was not subject to these objections. I do not agree. Chromosomal aneuploidies include sex chromosome aneuploidies and the sex chromosome aneuploidies include XXY, XYY and XXYY. The Lo 1 Patent and Priority Document do not enable detection of such aneuploidies.

172. It is correct that, were the amendments to be allowed, they would be retrospective. However, given the efforts at the priority date to find a non-invasive prenatal test for the detection of aneuploidies and pre-eclampsia, these applications would be at the forefront of consideration by the skilled team when reading the Priority Document and the Patent. Since the Lo 1 Patent discloses a principle of general application for NIPD, it would be clear that these applications fall within the scope of the claims.

173. In those circumstances, in my judgment, claims 1, 2, 5 and 7 are not entitled to priority and are insufficient. However these objections do not apply to claim 8, and I shall proceed on the basis that Illumina will incorporate the limitations of claim 8 into claim 1. I shall consider the precise form of this amendment by deletion, and any other claims which are said to be valid in the light of the amendment, at the form of order hearing.

iv) *Method of detection*

174. TDL/Ariosa pointed out that whereas the claimed invention is a "*detection method*" having the characteristics specified in the claim, the invention disclosed in the Priority Document is "*a method of performing a prenatal diagnosis*". It said that a detection method is broader than a method of performing a prenatal diagnosis, and the former is not clearly and unambiguously disclosed in the priority document.

175. In assessing this objection, I shall consider the whole contents of the document and avoid the application of a formulaic approach, whilst bearing in mind the need for any generalisation to be directly and unambiguously derivable from the disclosure of the priority document.

176. The Priority Document discloses on page 2 lines 5-6 that "*It has now been discovered that foetal DNA is detectable in maternal serum or plasma samples*". At page 2 lines 15-18 it discloses that "*This invention provides a method of performing a prenatal diagnosis on a maternal serum or plasma sample, which method comprises detecting the presence of a nucleic acid sequence of foetal origin in the sample".* In my view, this is a clear and unambiguous disclosure of a general concept of detection of foetal DNA in maternal serum or plasma, which includes its application in a method of performing a prenatal diagnosis.

177. It is also important to have regard to the meaning of the term "*prenatal diagnosis*" in the Lo 1 Priority Document. It is stated at page 2 lines 19-29 that "*prenatal diagnosis*" is a broad term that "*covers determination of any maternal or foetal condition or characteristic which is related to either the foetal DNA itself or to the quantity or quality of the foetal DNA in the maternal serum or plasma.*" Examples of prenatal diagnosis listed include "*sex determination*" and "*detection of … simple mutations.*" This broad meaning of the term is reinforced at page 4 lines 5-7, which discloses that the "*method according to the invention*" covers "*detection of any paternally-inherited sequences which are not possessed by the mother.*"

178. In my judgment, this disclosure is commensurate with, and supports, claim 1 of the Lo 1 Patent, and is not an impermissible combination of features from the Priority Document. I note that the Opposition Division rejected this challenge to priority. The decision states at [6.1] that:

> "the Opponent considered that claim 1 as granted is broader than the disclosure of the priority document because the more general concept of "detection" (as opposed to prenatal diagnosis) would not be disclosed in the priority document. The Opposition Division considers that the passage on page 2 lines 5 and 6 of the priority document discloses explicitly said more general concept of "detection"."

179. In my judgment, the Opposition Division was correct, and there were additional reasons for supporting its conclusion. The point was not pursued on appeal.

180. In any event, this objection cannot apply to claim 8, which is limited to one of the specific examples of prenatal diagnosis disclosed in the Priority Document at page 3 line 27 – 4 line 4.

v) Screening for chromosomal aneuploidies

181. TDL/Ariosa contended that there is no disclosure in the Priority Document that screening for Down's syndrome or other chromosomal aneuploidies can be carried out using a method which involves the detection of a paternally inherited sequence which is not possessed by the mother. The disclosure on page 5 contemplates detecting the presence of a nucleic acid sequence of foetal origin in the samples. Therefore, it is said that the subject matter of the claims of the Lo 1 Patent, which includes a detection method which relies on a paternally inherited sequence which is not possessed by the mother for the detection of Down's syndrome and other chromosomal aneuploidies, is broader than the support provided by the Priority Document.

182. I have accepted TDL/Ariosa's case in relation to non-enablement of the Priority Document in respect of claims 1, 2, 5 and 7. This objection cannot apply to claim 8 which does not include screening for Down's syndrome or other chromosomal aneuploidies. Therefore, it is not necessary for me to determine this objection. However, in case I am wrong, I shall briefly express my conclusions.

183. The Priority Document discloses that the method according to the invention can be used or applied in various ways. These include use for: (i) sex determination by detecting the presence of a Y-chromosome; (ii) detection of paternally inherited sequences which are not possessed by the mother; and (iii) screening of Down's syndrome and other chromosomal aneuploidies. The disclosure of the Priority Document in relation to paternally inherited sequences which are not possessed by the mother is in respect of (i) and (ii) and there is no disclosure on page 5 of any need to look for a paternally inherited sequence which is not possessed by the mother. Indeed, the Priority Document draws a distinction between the detection of paternally inherited sequences not possessed by the mother (page 4) and the screening for chromosomal aneuploidies and pre-eclampsia (page 5). In those circumstances, there is no scope for implicit disclosure which was not, in any event, supported by evidence. This is a further reason why claims 1, 2, 5 and 7 are not entitled to priority.

Discovery as such

Legal principles

184. Pursuant to section 130(7), section 1(2) of the Patents Act 1977 is framed so as to have, as nearly as practicable, the same effect as the corresponding provisions of Articles 52(2) and (3) of the European Patent Convention. Section 1(2)(a) and Articles 52(2)(a) and (3) declare that discoveries "*as such*" are not inventions. Lord Hoffmann explained in *Kirin-Amgen* at [77] that: "*An invention is a practical product or process, not information about the natural world.*"

185. It is necessary to distinguish substance from form, as emphasised by Lewison J (as he then was) in *Tate & Lyle Technology Ltd v Roquette Freres* [2010] FSR 1 at [75]: "*The claim is not saved from unpatentability simply by the addition of the phrase ''the use of''. What matters is the substance of the claim rather than its form.*"

186. A four-part structured approach to objections of excluded subject matter was set out by the Court of Appeal in *Aerotel Ltd v Telco Holdings Ltd; Macrossan's Application* [2007] RPC 7, and further explained by the Court of Appeal in *Symbian Ltd v Comptroller General of Patents* [2009] RPC 1. This requires the Court to:

(i) properly construe the claim;

(ii) identify the actual contribution;

(iii) ask whether the identified contribution falls solely within the excluded subject matter; and

(iv) check whether the actual or alleged contribution is actually technical in nature.

187. TDL/Ariosa submitted that, on Illumina's construction, claim 1 is in substance a claim to any method involving the discovery that foetal DNA that is paternally inherited and not possessed by the mother is detectable in maternal serum/plasma. There are no technical limits imposed on the method of detection. Nor, on Illumina's case, is there any requirement that the method of claim 1 results or enables any meaningful technical effect. It submitted that the claim, in substance, claims the discovery disclosed at page 2 lines 4 to 5 of the Priority Document, dressed up as a method claim. The contribution is simply the discovery that certain foetal nucleic acids that are paternally inherited and not possessed by the mother are detectable in maternal serum or plasma samples. That contribution is a mere discovery and is not technical.

188. TDL/Ariosa accepted that claim 8 does not relate to excluded subject matter, and I have accepted its case that claims 1, 2, 5 and 7 are invalid. Therefore, it is unnecessary for me to resolve this issue. Nonetheless, in case I am wrong, I shall briefly express my conclusions.

189. I do not accept that, properly construed, claim 1 is a claim to a discovery as such. The claims are not directed to information about the natural world, but rather to a practical process, namely a "*detection method*" which uses information about the natural world. Claim 1 is directed to the detection of foetal DNA in a sample of plasma or serum. Such samples do not exist in the natural world and must be artificially created. The claimed method of detection is also an artificial process which does not exist in the natural world. The claim is to a practical process of implementing a discovery, for practical applications. The actual contribution, as a matter of substance, does not fall solely within the excluded subject matter and is technical in nature.

Confidentiality and the principle of open justice

190. CPR Part 39.2 sets out the general rule that a hearing is to be in public. It is provided by CPR Part 39.2 (3)(c) that a hearing, or any part of it, maybe in private if it involves confidential information (including information relating to personal financial matters) and publicity would damage that confidentiality. In a recent lecture delivered at the Singapore Sentencing Conference on 26th October 2017: Perspectives on Open Justice: Anonymity and Confidentiality, the Chancellor, Sir Geoffrey Vos, made clear that the exceptions to the general rule in Part 39.2, including the confidentiality exception, "*must be applied restrictively if injustice and secret justice are to be avoided.*" He also said that:

> "… the judges themselves should be astute to ensure that they decide cases openly, transparently and in public and that their reasons are published in full and made available as widely as can be."

191. In patent cases, it is common for parties to be required to disclose highly confidential information to enable issues of infringement to be decided. The court needs the full picture, and fears about loss of confidentiality should not act as a deterrent to disclosure. The confidentiality exception in Part 39.2(3)(c) is very useful in this context. Nonetheless, hearings, including cross-examination, normally take place in public. Counsel are able to cross examine by referring the witnesses to confidential information without reading it out. In the present case, I was told by Counsel (with justification) that issues of infringement would involve detailed discussion of certain

aspects of the Harmony and Iona tests which are highly confidential, and which could not be heard in public without damaging confidentiality. Therefore, certain parts of the hearing were conducted in private.

192. Where the court has heard a case in private it may nonetheless decide to give a public judgment. It is fundamental to open justice, and public confidence in the judiciary, that the reasons for a judicial decision are public. *In R. (Mohamed) v Secretary of State for Commonwealth Affairs* [2010] EWCA Civ 65 Neuberger M.R. said at [41]:

> "41 …where litigation has taken place and judgment given, any disapplication of the principle of open justice must be rigidly contained, and even within the small number of permissible exceptions, it should be rare indeed for the court to order that any part of the reasoning in the judgment which has led it to its conclusion should be redacted. As a matter of principle it is an order to be made only in extreme circumstances."

193. If a party requests that parts of a judgment should be kept confidential, it must satisfy the court that a sufficiently strong case has been made out to override the basic principle of open justice. In the present case, I released this judgment in draft, with four "confidential" appendices which I asked the parties to review and justify. Appendix 4 contained terms of certain licence agreements. Illumina was concerned during the trial that the terms were confidential to third parties. Confidentiality is no longer maintained, and I have included this section in the public parts of this judgment. There was no dispute about the confidentiality of Appendices 2 and 3. As to Appendix 1, Illumina submitted that several features, claimed to be confidential, had been publicly disclosed by TDL/Ariosa at a hearing in the Barcelona Mercantile Court in May 2017, and the remaining features could be inferred from that public disclosure. TDL/Ariosa accepted that certain aspects were disclosed, disputed that some information would be accessible to competitors from the court file, and denied that certain features which were not disclosed could be inferred. The account of what was disclosed in the Spanish proceedings was anecdotal, and did not establish that a competitor of TDL/Ariosa could gain access to a clear description of the features of the IONA process as set out in Appendix 1. I accept TDL/Ariosa's submission that nowhere has the information in Appendix 1 been disclosed as a combination; that it would be highly detrimental for its competitors to have access to this information; and that it is not practical to divide up the reasoning in Appendix 1 into public and private sections.

194. Therefore, I am satisfied, on the basis of submissions and evidence received subsequent to release of the draft judgment, that Appendices 1-3 contain information which Premaitha and TDL/Ariosa (respectively) have demonstrated is highly confidential, and which justify an exception to the general rule.

195. I emphasise that where a party requests the court to sit in private for any part of a hearing, or to keep any part of a judgment confidential, it must be prepared to justify such request as a rare exception to the general rule of open justice.

Issues of infringement in relation to the Harmony test

196. Information as to the way in which the Harmony test works, which I am satisfied is confidential and which is required to decide infringement, is summarised in Confidential Appendix 1. Much information about the Harmony test is not confidential. The Harmony test is a non-invasive prenatal test carried out using maternal plasma samples. It estimates the risk that the foetus has a trisomy of chromosome 13, 18 and/or 21 and (if requested) certain sex chromosome aneuploidies, and likely foetal gender. The Harmony test uses the maternal plasma sample alone to produce risk estimates. No independent source of genetic information from the mother or the father is required or obtained.

197. The Harmony test consists of a "Non-Polymorphic Assay" and a "Polymorphic Assay". The Non-Polymorphic Assay interrogates loci on particular chromosomes of interest including loci on the Y chromosome. It is concerned with analysing the relative dosage of certain target loci on chromosomes, including chromosomes 13, 18 and 21 and the X and Y chromosomes.

198. The Polymorphic Assay interrogates hundreds of pairs of bi-allelic SNPs within loci on particular chromosomes. The SNPs are chosen on a population basis, rather than based on genotypes of the individuals involved. The Polymorphic Assay involves detecting 'informative loci' where the mother is homozygous for a SNP allele (AA or BB) and the foetus is heterozygous (AB). The purpose of the Polymorphic Assay is to determine the Foetal Fraction and it is not used for genotyping. The Polymorphic Assay involves looking at the relative quantities of the alleles in the sample at each SNP, and relies on the detection and quantification of maternal DNA as well as foetal DNA. It also relies on the knowledge that maternal DNA is present in greater quantities than foetal DNA.

199. Both assays work by initially interrogating the cell-free DNA in the sample using "triplets" of oligonucleotides. If all three of the triplet of oligonucleotides successfully anneal to a targeted locus in adjacent fashion, they are then ligated together to form a single oligonucleotide called a ligation product. These ligation products are then amplified by PCR.

Legal principles

200. I shall apply the principles set out by the Supreme Court in *Actavis v Eli Lilly* [2017] UKSC 48, which may be summarised as follows:

    i) A problem of infringement is to be determined by addressing two issues through the eyes of the skilled person:

        a) Does the product or process in question ("the variant") fall within any of the claims as a matter of normal interpretation, i.e. applying the normal principles of interpretation of documents?; [54] and [58].

        b) If not, does the variant vary from the invention in a way or ways which is or are immaterial? That raises a question that normally would have to be answered by reference to the facts and expert evidence; [54].

    ii) In deciding whether a variation is immaterial, one should ordinarily ask three questions; [66]:

a) Notwithstanding that is it not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve substantially the same result in substantially the same way as the invention, i.e. the inventive concept revealed by the patent?

b) If yes, would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?

c) If yes, would a reader of the patent have concluded that the patentee nevertheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?

201. The use of the word 'literal' may be confusing. In *Generics (UK) Ltd (t/a Mylan) & Anor v Yeda Research and Development Company Ltd* [2017] EWHC 2629 at [134] – [139] Arnold J rejected a submission that a patent claim should be interpreted in the same way as a commercial contract. He referred to (amongst others) the following paragraphs in the judgment of Lord Neuberger: [22], where he said that "*a patent is to be interpreted on the basis that it is addressed to a person or group of persons who is or are likely to have a practical interest in the claimed invention*"; [54], where he said that both the issues of (i) "*normal interpretation*" and (ii) infringement by immaterial variants should be "*considered through the eyes of a notional addressee*" of the patent; and [56], where he referred to issue (ii) involving "*not merely identifying what the words of a claim would mean in their context to the notional addressee*". Arnold J held that normal interpretation involves interpreting the words in context and the context must include "*the very purpose for which the document exists, namely to describe and claim an invention*."

202. I agree with Arnold J. The Protocol on the Interpretation of Article 69 precludes a strict, literal interpretation, where the description and drawings are used only to resolve an ambiguity in the claims. This applies generally to interpretation of claims and is not confined to consideration of equivalents. Normal interpretation means purposive interpretation.

Claims which are alleged to be infringed

203. The Polymorphic Assay is alleged to infringe claim 1, but not claim 8. Since I have held that claim 1 is invalid, the Polymorphic Assay does not infringe any valid claim. In case I am wrong in my conclusions on validity, I will consider TDL/Ariosa's arguments of non-infringement of claim 1. The Non-Polymorphic Assay is alleged to infringe claim 8, insofar as it is used for sex determination. Therefore, it requires separate consideration.

i) <u>Is the polymorphic assay a detection method in accordance with claim 1?</u>

204. TDL/Ariosa contended that on a normal interpretation, the skilled team would understand that when the Lo 1 Patent refers to a "detection method" that comprises "detecting the presence of a nucleic acid of foetal origin" which was "a paternally

inherited sequence which is not possessed by [the mother]", it is referring to a method of the type that was known in the common general knowledge and described in the Patent in which the sequence to be detected has been identified as one which (if present) will be *known* to be paternally inherited and not possessed by the mother.

205. It further contended that the skilled team would not, on a normal interpretation, understand claim 1 to be referring to a method which involved no independent source of information about parental genotypes, nor would be agnostic as to whether the foetal DNA was paternally inherited, nor which involved relative quantitation of maternal and foetal DNA.

206. I do not accept these submissions. A detection method is not a term of art. It is not limited to a particular method of detection which was known at the priority date. Nor does it require knowledge as to whether the method is looking at a foetal SNP of paternal origin. There are no such limitations in the claim. Claim 1 requires detection of the presence of a nucleic acid of foetal origin in the maternal serum or plasma sample. To fall within the claim, the nucleic acid so detected must be a paternally inherited sequence which is not possessed by the pregnant female. A method which is capable of detecting such a nucleic acid in the sample which has that property is covered by the claim and no element of knowledge is required.

207. Nor does the claim require an independent source of information about parental genotypes. There is no such limitation in the claim and there are instances in the specification which do not require such an independent source of information. For the purposes of [0017(a)] and Example 3 (described at [0047] – [0064]), the paternal genotype is not obtained at all. These passage concern Rhesus D determination, where the maternal genotype has been determined and the presence of the Rhesus D gene in maternal plasma or serum indicates the foetal genotype. There is no genotyping of the father except by deduction from the foetal genotype. [0017] discloses this as one example of use of the method of the invention "*to detect the presence of a foetal nucleic acid from a paternally inherited non-Y chromosome, for the detection of any paternally inherited sequences which are not possessed by the mother*". Accordingly, it is clear from the disclosure of Lo 1 that detection of a paternally inherited sequence not possessed by the mother does not require paternal genotyping, and can be satisfied by deduction from what has been detected in maternal plasma or serum.

ii) Do the Harmony test assays use a method comprising "detecting the presence of a nucleic acid of foetal origin in the [maternal plasma] sample"?

208. This argument of non-infringement applies to both the polymorphic and non-polymorphic assays. I have not found it possible to deal with the rival contentions without discussing information which is confidential to TDL/Ariosa. My assessment of this issue is in Confidential Appendix 1. I do not accept TDL/Ariosa's case on this issue, for the reasons given in Appendix 1.

209. In summary, the Harmony prenatal test (non-polymorphic assay) infringes claim 8 of Lo 1 insofar as it is used for sex determination. The Harmony prenatal test (polymorphic assay) would have infringed claim 1 of Lo 1 had this claim been valid.

Premaitha-specific issues in relation to Lo 1

210. In addition to the issues raised by TDL/Ariosa which I have addressed above, the following Premaitha-specific points require determination:

   i) whether the claims of Lo 1 are infringed by the IONA test, either as a matter of normal interpretation or as equivalents;

   ii) whether Premaitha should be granted declarations of non-infringement in respect of two proposed alternative methods;

   iii) whether the claims of the Lo 1 Patent are insufficient if they extend to cover the IONA test.

Whether the claims of Lo 1 are infringed by the IONA test, either as a matter of normal interpretation or as equivalents

Versions of the IONA test

211. There are several versions of the IONA test. These are:

   i) The IONA test as originally implemented. This has two versions:

      a) Version 1 of this test is a prenatal screen to detect the risk of aneuploidy of chromosomes 13, 18 and 21;

      b) Version 2 (available since Dec 2015) adds foetal sex determination to the aneuploidy detection of version 1.

   ii) The modified version of the IONA test. This is the current version and was rolled out between July and September 2016. The modified version of the IONA test has the Y chromosome removed from the reference genome. Both versions 1 and 2 above are available for the modified IONA test.

   iii) The Alternative Proposed Process. This is the same as the current version of the IONA test. However, the data processing steps are performed in Taiwan.

   iv) The Additional Alternative Proposed Process. This proposed process, according to Premaitha, does not involve any alignment to a reference genome.

212. Infringement is alleged for the original and modified IONA tests. There is a claim for a declaration of non-infringement in respect of each of the two proposed versions. Insofar as the IONA test includes sex determination, it infringes claim 8 if it infringes claim 1. The issue turns upon the proper construction of “detecting” and “detection” of a nucleic acid sequence that is paternally inherited and not possessed by the pregnant female. In particular, does the IONA test detect the Y chromosome in a male foetus? That depends upon whether the claim requires direct detection, or whether indirect detection is sufficient.

Legal principles

213. Illumina argued, in the alternative, for infringement by equivalence, as explained by the Supreme Court in *Actavis v Eli Lilly*, summarised above. Some further detail is now required.

214. Consideration of the first question, and in particular 'how the invention works' requires the court to focus on the inventive concept of the patent; *Actavis v Eli Lilly* at [60]. The second question applies to variants which rely on or are based upon developments which have occurred since the priority date. Whether the variant represents an inventive step over the patent is not determinative of non-infringement, but is a relevant factor and may render it less likely that the patentee will succeed; [63] – [64]. The fact that the claim cannot on any sensible interpretation cover the variant is not enough to justify holding that the patentee does not satisfy the third question. In answering the third question it is material to ask whether the component at issue (or more generally the claim feature at issue) is an essential part of the invention [65].

215. As to prosecution history, at [87] – [88], Lord Neuberger held that the court should take a sceptical, but not absolutist, attitude to the suggestion that the contents of a prosecution file of a patent should be referred to when considering a question of interpretation or infringement. Whilst not limiting the circumstances in which reference to the file would be appropriate, he identified two circumstances in which it would be appropriate to refer to the prosecution history. These were:

i) First, where the point at issue is truly unclear if one is confined to the consideration of the specification and the claims of the patent alone, and the contents of the file unambiguously resolves the point.

ii) Secondly, where it would be contrary to the public interest for the contents of the file to be ignored. This second circumstance is exemplified by a case where the patentee has made it clear to the EPO that he was not seeking to contend that his patent, if granted, would extend its scope to the sort of variant which he now claims infringes.

"Detecting" and "detection"

Premaitha's submissions in outline

216. Premaitha's case was that the foetal sex determination element of the IONA test does not detect or quantitate any Y chromosome fragments. The foetal sex determination element quantitates sequences mapping to the X chromosome. This is a sequence that is possessed by the mother. Premaitha submitted that the Y chromosome is neither detected nor quantitated.

217. Premaitha submitted that the skilled team would understand "detecting" in the context of the specification and claims of Lo 1 to require the physical observation of an entity, or a positive signal directly indicating the presence of that entity. Therefore, the skilled team would understand detecting a nucleic acid that is a paternally inherited sequence which is not possessed by said pregnant female would require the observation of such a sequence by PCR amplification or the observation of some other positive signal that directly indicates the presence of that sequence, for example binding of a fluorescent probe, to a sequence that is paternally inherited and not possessed by the mother.

218. It submitted that the skilled team would not understand "detecting" a paternally inherited nucleic acid sequence to include making an inference about the presence or

absence of such a sequence based on the detection and quantitation of sequences that are possessed by the pregnant mother. It suggested that there was nothing in the specification to suggest that detection by inference was intended, and relied upon the evidence of Dr Erlich, a distinguished geneticist, that the skilled person would know that such inferences could be confounded.

Illumina's submissions in outline

219. Illumina submitted that the claims of Lo 1 are infringed by the indirect detection of the presence of Y chromosome sequences by the IONA test. The claims require a detection method which comprises detecting the presence of a paternally inherited nucleic acid of foetal origin, and the IONA test does this, by looking for a 'Y-shaped hole' in the quantity of X chromosome sequences in the sample.

Discussion

220. 'Detection' is not a term of art. Therefore, although Dr Erlich's views on its meaning were interesting, this evidence was not admissible. Although I accept that, in the examples of the Lo 1 Patent, the methods disclosed directly detect the presence of a paternally inherited nucleic acid of foetal origin, I do not believe that the claims, when read in the context of the specification, are limited so as to exclude indirect detection.

221. The IONA test identifies whether the level of sequences from the X chromosome is high or low. If it is low, this is because of the presence of the Y chromosome, occupying the space in the foetal genome which would otherwise be occupied by a second X chromosome. By identifying a low number of X chromosome fragments, the IONA test therefore indirectly detects the presence of the Y chromosome in the maternal sample and thus enables a confident prediction that the foetus must be male.

222. Claim 1 requires a detection method which comprises "detecting the presence of nucleic acid of foetal origin". This may be the Y chromosome, which is a requirement of claim 7. The IONA test does this, through the indirect means of spotting a particular level of X chromosome which is determined only to be consistent with the 'presence' of the Y chromosome, which is paternally inherited.

223. I accept Dr Erlich's evidence that the indirect detection method using the IONA process cannot provide precisely the same degree of certainty as direct detection, which reads a sequence from the Y chromosome. However, I do not accept that this difference in reliability is significant. The XO syndrome, which, in the IONA method, could lead to an incorrect sex determination, is extremely rare. The IONA method is used to make a sex determination, which is provided to the mother, and is intended to be relied upon. Prof Avent explained that although XO syndrome occurred in about 3% of pregnancies, these were spontaneously lost very early in pregnancy within the first trimester. The IONA test is only given to women who are at least 10 weeks pregnant. Therefore the instances of XO syndrome amongst women to whom the test is administered is likely to be extremely small. If that were not the case, the test could not be relied upon.

224. I do not accept Premaitha's case that Illumina's construction does not equate with the technical contribution of the patent. I have found that the Lo 1 Patent discloses that cell-free foetal DNA is present in detectable amounts in the maternal plasma and

serum of a pregnant female. It discloses and claims a principle of general application for detection of such nucleic acid sequences using paternally inherited cell-free foetal DNA as the source material to be analysed. That technical contribution was very significant in the art at the priority date, and a construction of claim 1 which includes both direct and indirect detection is commensurate with that contribution.

225. Since I have concluded that, according to its normal interpretation, both direct and indirect detection are included within the scope of claim 1, it is unnecessary for me to determine Illumina's alternative case of infringement by equivalents. However, in case I am wrong, I will briefly summarise my view on this issue. Had I rejected Illumina's primary case, it would have been on the basis that the Lo 1 Patent was limited to direct detection. On that basis, I would not have been satisfied that the variant of indirect detection achieved substantially the same result in substantially the same way as the invention, nor that this would have been obvious to the person skilled in the art at the priority date. No evidence was directed to this issue by Illumina, and I would have required evidence in the circumstances of this case.

Prosecution history

226. Premaitha submitted that this is a case where it would be contrary to the public interest for the contents of the prosecution history to be ignored. It referred to claim 1 as originally granted, which was wider than the current claim and covered detection of any nucleic acid of foetal origin, regardless of whether that sequence was also possessed by the mother. During the Opposition, the Opponents alleged the claim was insufficient because it was not enabled for sequences that were possessed by the mother. The Opposition Division held that the patent specification did not disclose adequate information to enable this and the deficiency was not remedied by the common general knowledge. The Opposition Division recorded on page 5 of its Decision that:

> "During the oral proceedings, the Representative of the Proprietor admitted that she was not aware of a method allowing to detect sequences which do not differ from the maternal DNA."

227. The Opposition found, at pages 6 – 7, that claim 1 as granted was insufficient because it embraced detection of nucleic acids of foetal origin having sequences which do not differ from the sequences corresponding to maternal DNA. The auxiliary request, which amended the claim to its current form, was made to overcome this finding of insufficiency.

228. Accordingly, Premaitha submitted that the infringement argument now advanced by Illumina (that Lo 1 is infringed by detection and quantification of X chromosome sequences which are possessed by both the foetus and the mother) is the very type of detection that was found by the EPO to be insufficient and which the claim was limited to exclude. It argued that it would be wrong, and contrary to the public interest, to find that such a process infringes the claim after that amendment.

229. Initially, I thought that this was a powerful argument. However, as is often the case with arguments based on prosecution history, greater knowledge of the contents of the file suggested otherwise. The claim limitation which was made during the opposition

proceedings excluded the detection of the presence of foetal sequences which are indistinguishable from those of the mother, which fell within the scope of claim 1 as originally granted. That was the context in which the Patentee's representative made the statement cited above. The IONA test does not perform a method which detects the presence of foetal sequences which are indistinguishable from those of the mother. Instead, by looking at the total quantity of X chromosome sequences (without distinguishing those of the mother from those of the foetus) it detects the presence of the paternally inherited Y chromosome sequences, which are not possessed by the mother. No attempt is made by the IONA test to detect the presence of maternally inherited foetal sequences, which gave rise to the objection of insufficiency. Therefore, I do not accept Premaitha's argument based on the prosecution history of the Lo 1 Patent.

Conclusion

230. I conclude that sequences of foetal origin which are paternally inherited and not possessed by the mother are detected in the IONA test, which therefore falls within claim 1 of the Lo 1 Patent and claim 8 insofar as the IONA test includes test determination.

Foetal fraction estimation

231. Following release of this judgment in draft, Illumina asked me to deal with its case that claims 1 and 7 of Lo 1 (if valid) would be infringed by the IONA test's foetal fraction estimation by sex chromosome analysis. Premaitha indicated that it has no objection to findings being made on this issue.

232. Although I have held that these claims are invalid, Illumina submitted that this point could be of importance because, if infringed by claims found valid on appeal, the IONA test would infringe not only because of the inclusion of sex determination in version 2 of the IONA test but also because of the use of foetal fraction estimation by sex chromosome analysis in both versions 1 and 2.

233. I have set out in Confidential Appendix 2 further detail as to the way in which, as part of its trisomy analysis, the Iona test establishes the percentage of DNA fragments being tested that originate with the foetus. This is known as the foetal fraction. The foetal fraction needs to be determined so that the test does not produce a false negative result, where it misses a trisomy because there is too little foetal DNA to give a reliable result.

234. Premaitha accepted that the Iona test draws inferences about the sex of the foetus and the foetal fraction from the number of reads that align to the X chromosome. However it submitted that it does not do that by detecting or quantitating any Y chromosomes, or any other sequences of paternal origin not possessed by the mother. Rather, it does it by detecting and quantitating sequences that align to the X chromosome, on the basis that a female foetus contributes two X chromosomes to the maternal and foetal mixture in the maternal plasma whereas male foetus contributes just one.

235. The Iona test makes a determination of gender from counting the amount of reads in from the X chromosome in the maternal plasma and, if the number is below a certain level, infers that the foetus is male. It uses an 'informativeness filter' to strip out

results which cannot be relied upon because they are only consistent with the foetus being female. Premaitha argued that these inferences come not from detecting the Y chromosome but from detecting and quantitating the X chromosome.

236. I do not accept this argument. The informativeness filter in the foetal fraction estimation falls within claims 1 and 7 of Lo 1 for similar reasons to those explained in relation to the sex determination process. It indirectly detects the Y chromosome, and this is a "method of detection" within the scope of those claims. Had claims 1 and 7 been valid, they would have been infringed by the IONA test's foetal fraction estimation by sex chromosome analysis.

Declarations of non-infringement in respect of two proposed alternative methods

Premaitha's first declaration of non-infringement

237. Premaitha seeks a declaration of non-infringement based on a proposed 'workflow' where some steps of the invention are performed outside the jurisdiction. This alternative workflow (which it termed "the Alternative IONA Process") is alleged by Premaitha not to infringe any of the Patents, and it is convenient to address it when I have considered infringement of the Quake and Lo 2/3 Patents by the IONA test.

Premaitha's second declaration of non-infringement

238. Premaitha seeks a declaration of non-infringement in respect of a further alternative process, which it termed "the Additional Alternative IONA Proposed Process", details of which were provided to Illumina shortly before the pre-trial review, on 7 June 2017. It is now accepted by Illumina that the Additional Alternative IONA Proposed Process does not infringe the Lo 1 Patent, and, subject to submissions at the form of order hearing, I intend to make a declaration of non-infringement in respect of it. I shall consider allegations of infringement of the Quake and Lo 2/3 Patents by this process later in this judgment.

Insufficiency

239. Premaitha's case is that if, as I have found, the claims of the Lo 1 Patent include a method of indirect detection, then the Lo 1 Patent is insufficient since it did not enable such a method.

240. Premaitha submits, and I accept, that the Lo 1 Patent does not disclose a method of indirect detection. This is unsurprising, because, as Dr Erlich said, such a method could not have been made to work at the Lo 1 priority date since the available techniques were not sensitive enough at the time. He stated at [185] of his First Report, and I accept, that the method of indirect detection used in IONA "*would have been impossible at the Lo 1 application date, due to the limitations of the available quantitative technology…*"

241. Premaitha submitted that the Lo 1 Priority Document does not contain the disclosure of a principle of general application to enable the IONA test approach, and therefore does not support a claim that could cover it. I do not accept this submission, for the reasons which I have discussed in detail when considering TDL/Ariosa's alleged squeeze between infringement and enablement. In the circumstances of this case,

where the Priority Document discloses a principle of general application, and discloses certain methods of exploiting that principle without undue burden, the patentee is not required to predict or enable inventive improvements, or future developments in technology, which are subsequently adopted when using that principle of general application. I reject Premaitha's insufficiency allegation.

Title issues in relation to Lo 1

The parties' submissions in outline

242. Premaitha and TDL/Ariosa challenged Illumina's title to sue as exclusive licensee in respect of Lo 1. Although the proprietor of Lo 1 is a claimant, this issue could be of relevance to quantum of damages.

243. Lo 1, and the other Patents, are subject to a Pooled Patents Agreement dated 2 December 2014 between Illumina and Sequenom ("the PPA"), which concerns intellectual property relating to NIPD. Illumina alleged that an exclusive licence under the Lo 1 Patent was granted by Sequenom to Illumina under Section 2.3 of the PPA. The Defendants submitted that this does not amount to an exclusive licence within the meaning of the Patents Act 1977 on the basis that the exclusive licence was granted to Illumina "and its affiliates". The Defendants alleged that the inclusion of "affiliates" means that the licence is not exclusive.

Discussion

244. Section 130 of the Patents Act 1977 defines an exclusive licensee as:

> "a licence from the proprietor or applicant for a patent conferring on the licensee, or on him and persons authorised by him, to the exclusion of all other persons (including the proprietor or applicant), any right in respect of the invention to which the patent or application relates."

245. Section 1.1 of the PPA contains the following, amongst other, definitions:

> "**"Affiliate"** means, with respect to a Person, any other Person directly or indirectly controlling, controlled by, or under common control with, such Person at any time during the period for which the determination of affiliation is being made. For purposes of this definition, the term "control" means, with respect to any Person, the possession, directly or indirectly, of the power to direct or cause the direction of management policies of such Person, whether through the ownership of voting securities or by contract or otherwise."
>
> "**"Illumina Parties"** means, collectively, Illumina and its Affiliates"

246. Section 2.1 of the PPA does not grant any licence, but rather indicates the overall purpose of the grant. Clause 2.1(a) provides that the Illumina Parties will have:

> "The exclusive (even as to the Sequenom Parties), worldwide, sub-licensable right under the Pooled Patents to exploit NIPD IVD Products in the NIPD IVD Field."

247. The material part of Clause 2.3(a) of the PPA provides:

> "On the terms and conditions of this Agreement, Sequenom, on behalf of itself and its Affiliates, hereby grants to Illumina and its Affiliates an exclusive, irrevocable and perpetual (subject to Section 2.3(b)), non-transferable and non-assignable license (except as permitted under Section 9.1) worldwide license, with the exclusive right to grant sublicenses, under the Sequenom Owned Patents and Isis Patents, to Exploit NIPD LDT Tests in the NIPD LDT Field and to Exploit NIPD IVD Products in the NIPD IVD Field …"

248. Section 2.3(b) provides:

> "The license rights set forth in Section 2.3(a) granted to any Affiliate of Illumina shall automatically terminate with respect to such Person when it ceases to be an Affiliate of Illumina. Persons that become Affiliates of Illumina after the Effective Date shall be licensed under the license rights set forth in Section 2.3(a) only for those licensed acts that occur on or after the date it becomes an Affiliate"

249. Illumina submitted that, in practice, because Illumina exercises effective control over its affiliates, none of them can operate the licence without its authority. It submitted that the relevant affiliates were persons authorised by Illumina within the meaning of section 130(1). Illumina relied on the first witness statement of Mr Welland, commercial and IP counsel of Illumina. He explained that Illumina has no 'Persons' within the definition of 'Affiliate' over which it does not exercise control, and therefore no Affiliate may operate the licence without its authority. He further explained that there is no Person who exercises control over Illumina, since it is a publicly quoted company with no shareholder who has a controlling interest. Therefore, Illumina argued that there is no Person over whom Illumina might not exercise control, or who might themselves exercise control over Illumina, who could claim to be an Affiliate under the agreement.

250. By his second witness statement, Mr Welland dealt with the relationship between Illumina and its wholly-owned subsidiary, Illumina Cambridge Ltd, through which it exploits third party intellectual property rights in the NIPD IVD field in the United Kingdom. Mr Welland stated that Illumina Inc has substantive control over the business decisions of Illumina Cambridge Ltd. Illumina submitted that, to the extent that Illumina Cambridge can and does use the method of the Lo 1 Patent, it does so under the authority and direction of Illumina Inc. In spite of a challenge to Mr Welland's evidence based on the articles of association of Illumina Cambridge, I accept that Illumina Inc exercises *de facto* control over the activities of Illumina Cambridge.

251. Illumina argued that in the circumstances, the PPA is a licence conferring rights on Illumina Inc, and persons authorised by Illumina Inc, (to the exclusion of all other persons), as required by section 130(1). It argued that it makes no difference under the section whether an exclusive licence is granted to a parent company which can then sublicense to subsidiaries authorised by it, or whether the exclusive license agreement itself makes clear that the licence extends to those authorised subsidiaries.

252. I do not accept Illumina's submissions on this issue, for the following reasons. First, the PPA expressly confers a licence on Illumina and its Affiliates. Pursuant to the PPA, Affiliates of Illumina do not need authorisation from Illumina to operate the licence in respect of the Lo 1 Patent, because they are licensees in their own right. This appears clear from the wording of section 2.3(a). It is confirmed by section 2.1(a), which provides that the Illumina Parties, which means Illumina and its Affiliates, are to have an exclusive licence under the Pooled Patents. It is further confirmed by section 2.3(b) that the PPA is not a grant of an exclusive licence to Illumina alone, with a power to sub-license its Affiliates. Illumina and each of its Affiliates, from time to time, are licensees. Therefore, Affiliates do not require an authorisation from Illumina Inc to exploit the Lo 1 Patent. Affiliates licensed by the PPA include not only Illumina Cambridge, but all other Affiliates of Illumina Inc, from time to time.

253. Secondly, in *Dendron v University of California* [2004] FSR 43 at [11] Pumfrey J (as he then was) considered the definition of exclusive licence in section 130(1). He said:

> "The words 'or on him and persons authorised by him' seem to me to contemplate a licence which confers upon the exclusive licensee a power to sub-licence. The essential element of the transaction appears to be the exclusion of all other persons including the patentee or applicant."

254. Accordingly, a licence is only exclusive under section 130(1) if it is granted to a single person, although he may grant sub-licences to "*persons authorised by him*". The PPA does not comply with this definition, as it is a licence granted by the proprietor to a number of persons, even though one of them is in *de facto* control of the others.

Conclusion

255. Illumina is not an exclusive licensee of the Lo 1 Patent within the meaning of section 130(1) of the Patents Act 1977. However, there is no challenge to Sequenom's title to sue, and insofar as the claim against TDL/Ariosa and Premaitha has succeeded in respect of Lo 1, Sequenom is entitled to relief.

PART B: JUDGMENT IN RELATION TO THE QUAKE PATENTS

Issues in dispute

256. Although I deal separately with the Lo 2 and 3 Patents, some issues are common. The issues remaining in dispute at the end of the trial in relation to the Quake Patents are:

i) Obviousness in the light of US Patent Application US 2005/0221341 A1 ("Shimkets").

ii) Insufficiency.

iii) Added Matter.

iv) Infringement by the IONA test and non-infringement by the two proposed alternative methods.

v) Further issues as to whether the Claimants have title to bring these proceedings.

The skilled team

257. The Quake and Lo 2 and 3 Patents have similar subject matter and would have had the same skilled team. As with the Lo 1 Patent, the skilled team includes a clinician and a geneticist. For the purposes of the Quake and Lo 2 and 3 Patents, Premaitha contended that a skilled biostatistician would have been a member of the team. Illumina agreed that once the skilled clinician and skilled geneticist were in a position to test and implement the non-invasive tests they would consult a skilled biostatistician for the purpose of study design and data collection. Premaitha submitted, and I accept, that the biostatistician would be involved at any stage when the issue of the sensitivity or precision of a proposed test was considered. I accept that whenever his expertise was required, the other members of the team would consult the biostatistician.

The expert witnesses

Professor Hogge

258. Professor Hogge also gave evidence in respect of the Quake and Lo 2 and 3 Patents. Premaitha made similar criticisms of his evidence to those advanced by TDL/Ariosa, and I reject them for similar reasons. Premaitha submitted that Professor Hogge had no relevant experience in seeking to develop tests using cell-free foetal DNA before the Quake/Lo 2 and 3 priority dates. I reject the suggestion that he lacked the relevant expertise to give evidence about these patents. In particular, Professor Hogge had considerable experience in prenatal diagnosis, having joined the International Fetoscopy Working Group in 1983. This was a think-tank for researchers interested in discussing ways of performing prenatal diagnosis, who shared unpublished information and ideas. He interacted regularly with leaders in the field, both through meetings of the International Fetoscopy Working Group and of the International Society of Prenatal Diagnosis.

259. Professor Hogge had personally embarked on a research project using foetal cells in 1994, which continued well into the 2000s. He started working on cell-free foetal DNA before the Lo 2007 paper, with discussions beginning in around 2005 and work starting in late 2006 or 2007. From about 2004/2005, Professor Hogge served as a clinical advisory member of the board of Sequenom, in relation to implementation of Prof. Lo's *PLAC4* foetal mRNA work for aneuploidy. I found that his evidence was of

assistance in relation to the Quake and Lo 2/3 Patents, and he was clearly well qualified to provide it.

Professor Lovett

260. Professor Lovett also gave evidence in respect of the Quake and Lo 2/3 Patents. Premaitha made similar criticisms of his evidence to those advanced by TDL/Ariosa, and I reject them for similar reasons.

261. Premaitha submitted that Professor Lovett showed signs of having spent too long with the lawyers in the case, and at times his evidence veered into advocacy. It alleged that his desire to remain "on message" resulted in inconsistencies between his evidence and that of Professor Holmes, and that his attitude to the Patents was inconsistent with his attitude to the prior art. For example, Premaitha contended that his idea of genotyping the plasma in the absence of maternal or paternal DNA (X/2), which he suggested was routine, was an example of searching for arguments in favour of the patentee, and that he changed his mind during cross-examination as to the inventive concepts of the Quake and Lo 2/3 Patents.

262. I have not accepted Illumina's case based upon X/2, but that is no reason to criticise Professor Lovett for advancing an opinion which he genuinely held. It is unsurprising that he did not always answer questions which sought to characterise the inventions of the patents in exactly the same language – it would have been of more concern if he had stuck to a set form of wording.

263. Premaitha submitted that where there is any conflict between them, Dr Erlich's evidence should be preferred to that of Professor Lovett. Where Professor Lovett gave evidence in conflict with Professor Avent, Premaitha submitted that Professor Avent's evidence should be preferred because he was the only expert who was active in the field of NIPD at the priority date.

264. I do not accept Premaitha's submissions about Professor Lovett's evidence. It is true that he was at times somewhat forceful in his answers, and unwilling to accept assumptions that he believed were incorrect, but that was because his views were strongly held. The submission that I should reject all of his evidence which was in conflict with that of Premaitha's experts is too simplistic. The experts have given evidence about issues which are difficult, where it is reasonable to hold differing opinions. On each issue, I need to consider and weigh the reasons that they put forward for their views, rather than giving a blanket rejection of one expert's views in favour of another.

Professor Holmes (biostatistician)

265. Professor Holmes is Professor in Biostatistics at the Department of Statistics, and the Nuffield Department of Medicine, at Oxford University, where he is also a Professorial Fellow at St Anne's College and an Affiliate Member of the Li Ka Shing Centre for Health Information and Discovery. In addition, he is a Faculty Fellow of the Alan Turing Institute in London, which is the national centre for data science. He has received several awards and prizes for his research.

266. There was a difference of opinion between Professor Holmes and Professor Marchini (the biostatistician called on behalf of Premaitha) about whether a power calculation would be performed before having results of pilot studies. Premaitha criticise Professor Holmes for expressing this view for the first time in cross-examination. I do not think that this is a legitimate criticism. Professor Holmes answered the questions that were put to him, and was not required to confine himself to information that appeared in his expert report.

Premaitha's experts

Dr Erlich (molecular biologist)

267. Dr Erlich is a senior scientist at the Children's Hospital and Research Centre at Oakland California. His research focuses on quantitative and qualitative molecular biology, with specific interest in the application of PCR techniques to medical genetics, forensic genetics and anthropological genetics. He worked at Cetus Corporation from 1979-1991 and during this time he was heavily involved in the discovery and development of the technique of PCR with Nobel Prize winner Kary Mullis, co-authoring the first paper on the subject. By 1997 he had played a central part in the development of the use of Taq polymerase, which made PCR a practical reality.

268. Dr Erlich was a very impressive witness. Illumina have certain comments on his approach to obviousness, none of which amount to personal criticisms. Mr Purvis submitted that Dr Erlich found it very difficult to exclude the effects of hindsight, and also tended to refer to matters that he thought (10 years after the priority date) might have been obvious to him, as an outstanding innovator in his field, as opposed to what would have been obvious to the ordinary unimaginative skilled person. I shall consider these points when dealing with the allegation of lack of inventive step in the light of Shimkets.

Professor Avent (molecular biomedical scientist)

269. Professor Avent has been Professor of Molecular Diagnostics and Transfusion Medicine at Plymouth University since 2009, where he was Head of School for the Biomedical and Healthcare Sciences from 2010-2015. His research relates to DNA-based blood grouping and non-invasive prenatal diagnosis. Professor Avent was working in the NIPD field at the priority date of the Quake and Lo 2/3 Patents, although he did not particularly focus on aneuploidy. Illumina made detailed criticisms about his approach to obviousness, including the accuracy of his recollection about discussions in which he participated before the priority dates. I shall consider these points when dealing with the allegation of lack of inventive step in the light of Shimkets. However, I should make it clear that there was no attack on the credibility of Professor Avent.

Professor Marchini (biostatistician)

270. Professor Marchini is Professor of Statistical Genomics in the Department of Statistics and group leader at the Wellcome Trust Centre for Human Genetics at Oxford University. He has worked on a number of high-profile international collaborative projects in Human Genetics over the last 15 years, which have involved

developing a range of distinct statistical approaches for the analysis of biological datasets.

271. Mr Purvis pointed out that Professor Marchini said at [123] of his First Report that "*a standard statistical threshold is 5.0% as that enables a statistician to be reasonably certain that the effects are not simply by chance*" but suggested during his cross-examination that p-value thresholds were arbitrary. It is unnecessary to explore whether these statements can be reconciled, as Professor Holmes was cross-examined on the basis that a p-value of 0.05 is used as a standard threshold to indicate significance.

Common general knowledge in 2006 – technical background to the Quake Patents

272. Subsequent to the trial, the parties prepared a document setting out common general knowledge at the priority date of the Quake Patent which, subject to a few minor issues, was agreed. Premaitha included certain references (not agreed by Illumina) which it stated were not challenged. This applies to a large amount of material in a case of this size. I have considered these references, but I have not felt it necessary to set them out in this judgment. I set out below the way in which common general knowledge progressed between 1997 and 2006, which provides a technical background the Quake Patents. There is a significant area of dispute as to common general knowledge, which I will consider separately.

The discovery of cell free foetal DNA

273. By 2006, the existence of extracellular foetal DNA in maternal plasma, which was used more regularly than serum, was part of the common general knowledge, as was Lo 1997 (published in the Lancet).

274. Extracellular foetal DNA was being used as the starting point for NIPD experiments by a significant number of researchers. By 2006, 75% of researchers were using extracellular foetal DNA, with only 25% continuing research into foetal cells. This was in part because foetal cells are rare and difficult to isolate in the maternal circulation and the sensitivity and specificity of the approaches using foetal cells was not good.

275. The level of extracellular foetal DNA (referred to as the "foetal fraction") was calculated by Professor Lo in a 1998 paper as about 3% in early pregnancy and about 6% in late pregnancy. This range was taken as a good rule of thumb, although the skilled clinician would also be aware that there was considerable variation between individuals. A paper published by Professor Lo in 1998 reports a range of foetal fractions of 0.39% to 11.9% in early pregnancy and 2.33% to 11.4% in late pregnancy.

276. The discovery of extracellular foetal DNA allowed the detection of foetal genes not possessed by the mother. Examples of genes that were detected were the *SRY* gene on the Y chromosome and the *RHD* gene in Rh negative mothers. In addition, extracellular foetal DNA was used to test for SNPs and recessive and dominant genes that result in a disease phenotype.

Extracellular DNA and the cancer field

277. In the Lo 1997 paper, Professor Lo stated that he had identified the potential that extracellular foetal DNA might exist in maternal plasma on the basis of papers from the cancer field in which cell free DNA was found to contain distinctive mutations from tumours. As a result of this, in the years that followed genetic similarities between cancer and aneuploidy were discovered. Further, there was greater collaboration between the fields. The Circulating Nucleic Acids in Plasma and Serum ('CNAPS') Congress was set up in 1999 to bring together researchers from oncology and prenatal genetic screening to share knowledge and developments in their fields.

Approaches to aneuploidy detection

278. In terms of diagnostic methods on invasively obtained samples, new techniques such as Array Comparative Genome Hybridisation (Array CGH), MLPA and quantitative fluorescent PCR were developed.

279. As noted above, the other area of research was extracellular foetal DNA. Attempts were made to use markers that were present in the foetus but not in the mother. If such a marker could be found, the maternal DNA could be effectively disregarded. In addition to the SNP approach, other methods tried included:

    i) First, the analysis of messenger RNA ("mRNA") from placentally expressed genes that are not expressed by the mother. Quantification of allelic imbalance using SNPs carried by placental RNA indicated the presence of an extra copy of either the maternal or paternal chromosome.

    ii) Second, the analysis of differently methylated sequences. Placental (i.e. foetal) genes can be differently methylated to maternal genes. This allowed foetal DNA to be differentiated from maternal.

Enrichment of foetal fraction

280. Efforts were being made to increase the foetal fraction. These efforts included improvements to the isolation techniques, preferential exclusion of maternal DNA, and attempts to stabilise cell membranes to prevent maternal DNA leaching into the plasma sample. Some of the strategies were based upon the then-held consensus opinion that extracellular foetal DNA was on average <300bp in length and therefore shorter than maternal cell-free DNA. In order to enrich for DNA of this length, size selection methods (such as size-based separation by electrophoresis followed by cutting of bands of the desired size from a gel) were used.

281. These size separation strategies allowed for modest enrichment, perhaps increasing foetal fraction by 50%. This was relative, so a starting foetal fraction of 5% might be enriched to 7.5%. Other methods tried included fixing maternal leukocyte fraction by use of formaldehyde. However, this method was controversial and not generally accepted.

Advances in instrumentation

282. The relevant improvements in molecular biology techniques were:

    a) The availability of new and more robust qPCR platforms;

b) Digital PCR or "dPCR", which first developed in 1999;

c) The development of emulsion droplet PCR;

d) The launch of the first next generation sequencing platform, followed quickly by a range of other technologies.

Digital PCR

283. Digital PCR uses the limiting dilution technique to identify and quantitate rare or low copy sequences. Although the use of the technique had been first reported some years before, it was popularised and coined as "digital PCR" by Vogelstein and Kinzler in 1999.

284. Digital PCR works by performing a limiting dilution according to a Poisson distribution and distributing the sample into many discrete reaction vessels (commonly, wells of a multi-well plate). The Poisson distribution is used to ensure than on average not more than one target sequence is present per vessel. PCR is then performed in each vessel using primers to target a chosen sequence. The quantitative element of dPCR relies upon the assumption that each vessel found to contain an amplicon of interest indicates that one copy of the target sequence was present prior to PCR. For each vessel analysed, the target molecule will be identified as present or absent – i.e. "digital" results are produced. Counting the number of positive results allows quantitation of the number of target sequences in the original sample.

285. The use of a Poisson distribution to ensure that there is not more than one target sequence per well means that many wells will be empty and therefore only a fraction of the wells used will be able to be used in the quantitative analysis. Limiting dilution was also a highly labour intensive technique. Although in theory dPCR would allow the quantitative analysis of a complex mixture, in practice limitations of the throughput and labour intensiveness meant that its use in routine practice was relatively limited until instruments capable of automation became available.

286. One technique that improved the throughput of dPCR was emulsion PCR, which was first published in 2003. In emulsion PCR, droplets are created in a microemulsion, each droplet acting as a reaction chamber and containing on average one template molecule, a paramagnetic bead to which PCR primers are attached and the necessary enzyme and reagents for PCR. After amplification, copies of the template molecules will be attached to the beads and these can be harvested and probed to identify the target amplified. The large number of droplets created in a microemulsion increased the throughput potential of dPCR by several orders of magnitude over manual pipetting into conventional wells. Emulsion PCR would have been common general knowledge by 2006.

Sequencing techniques

287. Sequencing is the name given to the technique of determining the order of nucleobases (A, C, G, and T) in a DNA molecule.

288. Until the development of next generation sequencing, the most widely used method was "Sanger sequencing". Initially it was an entirely manual process, but in the early 1990s, commercial machines were capable of sequence read lengths of ~1,000bp.

289. Next generation sequencing (or 'NGS', also referred to as 'massively parallel sequencing' or 'MPS') is the term used to describe a variety of sequencing platforms, all of which generate very large numbers of reads in parallel.

290. Targeted sequencing provides a greater number of reads in the area of interest (referred to as the depth of coverage) whereas random sequencing offers a greater breadth of coverage, albeit at reduced depth.

291. The NGS platform that first became commercially available was the GS20 from 454 Life Sciences. This used the light-based pyrosequencing technique. The first paper describing it was by Margulies in 2005. The 454 GS20 would have been very well known to molecular biologists and other MPS platforms were in late stage development including the Solexa Genome Analysis System, the Applied Biosystems SOLiD system and the Helicos Genetic Analysis system.

292. The 454 GS20 can do random or targeted sequencing. It is unnecessary to describe the detail of how it operated. It used emulsion PCR, as referred to in Margulies.

293. The GS20 was able to sequence 3.6 million bases an hour in 2006. This represented a 100 fold increase in speed and a 250 fold increase in capacity over Sanger sequencing. In 2005-2006, the read length produced by the 454 GS20 was ~100-130bp in a single direction or around 200-260bp when sequencing was performed in the forward and reverse directions.

Disputed common general knowledge - the 'direction of travel' at the priority date

The positions of Professors Hogge and Avent

294. This was an important dispute between the parties, of relevance to the obviousness attack based on Shimkets. Illumina contended that the Quake Patents constituted a radical departure from a settled way of thinking in the art, which persisted after the publication of Lo 1997 in the field of NIPD. This settled approach involved attempting to distinguish maternal from foetal DNA. One route being pursued was physical separation. Attempts were made to isolate foetal cells found in maternal circulation, or alternatively to extract foetal DNA from maternal DNA. A second route was to distinguish foetal DNA from the maternal background by the use of foetal 'markers' which could be epigenetic, polymorphic or foetal-specific RNA. The Quake Patents adopted a quite different idea, namely that of detecting aneuploidy in a foetus by counting relative occurrences of sequences from potentially aneuploid and diploid chromosomes in maternal plasma, without differentiation between maternal and foetal DNA.

295. Professor Hogge had no doubt about the significance of the Quake and Lo approaches when they were published in 2007, as until then, he did not consider that digital PCR or massively parallel PCR were being contemplated by those working in NIPD. Having referred to publications by Lo et al, and Fan and Quake, in 2007 he said at [25] – [27] of his second report that:

> "25. These papers represented an exciting development in the non-invasive detection of foetal chromosomal aneuploidy, as they presented non-invasive prenatal diagnosis methods which allowed chromosomal aneuploidies to be detected for the first time without isolating foetal cells or discriminating between the maternal and foetal nucleic acid sequences.
>
> 26. I do not recall any discussion of the use of digital PCR or massively parallel sequencing for non-invasive prenatal diagnosis at any of the meetings or conferences that I attended prior to the publication of these papers by Professor Lo and Professor Quake.
>
> 27. Having read about the work of Professor Lo and Professor Quake, my group sought to build upon it by developing robust statistical models for use with digital PCR and massively-parallel sequencing-based methods, as well as applying these techniques to the non-invasive prenatal diagnosis of recessive Mendelian disease in maternal cell-free DNA."

296. Professor Avent presented a different view. In his opinion, the idea of analysing mixed maternal and foetal samples was well known before the priority dates. All that was required was for technology to be developed which provided the necessary quantitative precision.

297. His evidence was that it was already understood in the art that detecting aneuploidy in a foetus by counting relative occurrences of sequences from potentially aneuploid and diploid chromosomes in maternal plasma, without differentiation between maternal and foetal DNA, could and should be done, once the technology became available. According to Premaitha, that was the 'direction of travel'. At [70] of his First Report Professor Avent said:

> "At the Quake priority date there was an appreciation that cffDNA [cell-free foetal DNA] should enable the detection of aneuploidies from a sample of maternal plasma or serum. As aneuploidy is characterised by a difference in the copy number of the aneuploid chromosome then, in theory, this difference could be distinguishable if a sufficiently accurate method could be used. However, there was thought to be a significant hurdle in reducing the theory into practice as the foetal fraction presented in maternal plasma was believed to be very low. That hurdle was, in essence, a problem in counting the changes in copy number of the foetal chromosome with sufficient accuracy, which was beyond the capabilities of qPCR machines available."

His position was that since this was a counting problem, it was obvious that the NGS platforms, with their increased speed and capacity, would provide the solution. He amplified this by reference to discussions which he recalled having in late 2004/early 2005 with a company known as Pyrosequencing AG, referred to at [116] – [117] of his First Report.

Discussion

Contemporaneous reaction of the experts

298. It is useful to assess the views expressed by the experts during their evidence against their contemporaneous reactions to the concept underlying the Quake Patents. Professor Hogge's response, outside the context of this litigation, was consistent with the evidence that he gave. An article which he co-authored, Chu T *et al.,* Statistical considerations for digital approaches to non-invasive foetal genotype. *Bioinformatics*, 2010:26(22), 2863 - 2866 contained the following statement:

> "It has recently been shown that high-throughput whole genome DNA sequencing can be used for the detection of foetal aneuploidy (Chiu et al 2008; Chu et al 2009a; Fan et al 2008). This is an exciting development with great potential because it is a direct method that requires no gene or chromosome specific biomarkers and provides chromosome wide insight into karyotyping"

299. Other publications also expressed excitement following publication of the Quake invention. Professor Avent was co-author of a publication entitled Avent *et al.*, Cell-free foetal DNA in the maternal serum and plasma: current and evolving applications. *Current Opinion in Obstetrics and Gynaecology* 2009, 21:175 – 179 which contained the following:

> **"Shotgun sequencing: a new era in non-invasive prenatal diagnosis?**
>
> A recent paper by the group of Stephen Quake of Stanford University has provided a potentially novel approach for rapid determination of aneuploidy. The approach is to sequence a population of DNA molecules using so-called next-generation DNA sequencers. Using two such machines (a Solexa and a 454), Fan et al clearly demonstrate that populations of chromosome 21 and 18 derived DNAs are quantitatively different from other chromosomes in trisomy 21 and 18 maternal plasma sample respectively."

300. In addition, in Maddocks *et al.*, The SAFE project: towards non-invasive prenatal diagnosis. *Biochemical Society Transactions* 2009 volume 37, part 2, of which Professor Avent was named as a co-author, it is stated at 463:

> "The latest breakthrough in this area has come from the group of Stephen Quake at Stanford University. They have reported non-invasive diagnosis of aneuploidy by shotgun sequencing of foetal DNA from maternal plasma using Solexa-Illumina and 454/Roche sequencers. This sequencing approach is polymorphism independent and therefore diagnostically universally applicable."

301. These references to ‘a new era in non-invasive prenatal diagnosis’ ‘a potentially novel approach’ and ‘the latest breakthrough’ are not consistent with Professor Avent’s evidence on this issue. If the direction of travel was pointing towards the noninvasive diagnosis of aneuploidy by random sequencing of foetal DNA from maternal plasma, it is difficult to see what the excitement was about. Professor Avent’s answers to these papers during cross-examination did not, in my view, explain this inconsistency.

Avenues explored in the literature

302. There is no dispute, and Professor Avent accepted, that the development of a non-invasive diagnosis of Down’s syndrome was amongst the most important aims in the NIPD field and a number of groups were working towards this before the priority date. If there had been a realisation that, with the advent of new generation sequencers, it would be possible to detect aneuploidy in a foetus by counting relative occurrences of sequences from potentially aneuploid and diploid chromosomes in maternal plasma, without differentiation between maternal and foetal DNA, one would have expected this to have been suggested in articles on the subject published before the priority date. This was not evidenced in the literature.

303. Other routes were being pursued to address this problem. Between 1997 and 2007, efforts to isolate foetal cells in useful quantities from maternal blood continued, without success. Work in this area was significant, costly and time-consuming. It included a large-scale NIFTY study in the United States, which was reported in 2002 to have yielded sub-optimal results, and Work Packages 1 and 2 in the SAFE project (described below), which continued from 2004-2009. Extensive work was also conducted on cell-free maternal DNA, where several groups tried to apply specific markers for foetal DNA, using epigenetic markers, foetal specific RNA or paternally inherited SNPs.

304. These approaches were summarised in Old *et al.*, Candidate epigenetic biomarkers for non-invasive prenatal diagnosis of Down syndrome. *Reproductive Biomedicine* 2007 Vol. 15 No. 2 227 - 235. This provides a valuable insight into the thinking in the art close to the priority date. It was published in June 2007, between the Quake and Lo 2/3 priority dates. One of the authors of the paper was Professor Hultén, who was the project coordinator of SAFE.

305. In the introduction, Old explained that the development of NIPD based on a maternal blood sample, rather than the invasive procedures of CVS and amniocentesis had been a long-term goal in reproductive care. The article emphasised the desirability of this goal, stating that:

> “such a scheme would in particular eliminate the risk of iatrogenic foetal loss, which occurs at a small but non-negligible rate among women investigated in this way.”

306. Old summarised the efforts that been made to address this problem in relation to intact foetal cells:

> "It has been known for over a century that foetal cells migrate into the maternal blood stream. Much effort and large resources have been devoted to capturing these for NIPD, either by

> fluorescence in-situ hybridisation of intact foetal cell nuclei or using DNA extracted from intact foetal nuclei… Most research groups, however, have concluded that this approach is too labour intensive and not reliable enough for use in clinical practice."

307. The authors then turned to investigations into extracellular foetal DNA. They explained that since the publication of Lo 1997, when it was first discovered that cell-free DNA of foetal origin could be reliably identified and quantified in maternal plasma, there been a very rapid development in NIPD by this approach:

> "In the first instance this concerned the exploitation of DNA sequences of paternal origin. These were shown to allow foetal genetic sexing (of special relevance in X-linked disease), identification of rhesus-D-positive foetuses (of special importance when the mother is rhesus D negative, and also NIPD of some other genetic conditions."

308. The authors then turned to consider Down's syndrome. They concisely summarised the problem faced by the art:

> "The most common indication for prenatal diagnosis is, however, an increased risk for Down syndrome (DS). NIPD for DS presents another type of challenge, i.e. how best to identify (and quantify the amount of) foetal chromosome-21-derived material in maternal plasma so as to detect the three copies in a DS pregnancy in comparison to the normal two copies."

309. Old then turned to consider the three main approaches to this problem which had been proposed:

> "So far, three main approaches have been proposed. First, it should be possible to search for chromosome-21-specific polymorphic DNA sequences, such as single nucleotide polymorphisms (SNP) to allow NIPD of DS by measurement of allelic ratios in cff DNA (Chow *et al.*, 2007; Dhallan *et al.*, 2007). Second, the recent identification of chromosome 21 foetal specific mRNA in maternal plasma; this mRNA,originating exclusively from foetal cells in the placenta, provides yet another facility to be exploited for NIPD of foetal DS (Lo *et al.*, 2007). Third, it is also clear that the possibility exists for using differences in DNA methylation between maternal and foetal DNA sequences so as to identify and quantify specific sequences in cff DNA (Chan *et al.*, 2006; Tong and Lo, 2006; Tong *et al.*, 2006)."

310. Professor Avent accepted during his cross-examination that in 2007 there were significant technical difficulties with each of the SNP, mRNA and epigenetics approaches. Old considered that the epigenetic markers approach was the most promising, and it reported results using this approach. The concluding summary of Old stated that:

> "The first method [SNPs] depends upon an enrichment method that is currently controversial… The second, mRNA based, method is promising, but in its current embodiment requires suitable allele combinations in parents and foetus… The third, epigenetic approach does not depend upon allele ratios of common polymorphisms in its simplest embodiment. It therefore has the advantage of applicability to a broad population. The epigenetic markers described herein have been obtained with this approach in mind."

The paper concluded on a note of caution:

> "It remains to be seen how many epigenetic biomarkers will be required for NIPD of Down syndrome to achieve comparable accuracy with that of invasive diagnosis by the 'gold standard' of quantitative fluorescence-PCR and/or karyotyping."

311. There was no suggestion in this paper, or in other papers published by 2007, that a polymorphism-independent way of detecting Down's syndrome could be found by looking at cell-free DNA without discriminating between maternal and foetal DNA.

Professor Avent's 'brute force' approach

312. Professor Avent accepted that this idea was not disclosed in the literature, but referred to a 'brute force' approach which he suggested that he and others had discussed before the priority date, in which all the DNA in a maternal sample is analysed without any attempt to isolate or distinguish the foetal DNA. See for example the following passage from his cross-examination:

> "Q. So far as the work on maternal plasma is concerned, of which there is a published trail in the papers in this case, that falls, as we will see, into a number of different categories, as I think you have appreciated in your report, but they all have one thing in common: they seek specific markers for foetal DNA; correct?
>
> A. They do: foetal placentally-derived DNA, epigenetic markers, which we have heard about before, and single nucleotide polymorphisms inherited from the father, but there was a fourth number-crunching approach, the brute force approach, which was not in the literature, granted, but it was not a novel idea. Several of us had already considered this approach before the priority date."

313. I do not accept that the skilled team at the priority date would have been aware of Professor Avent's brute force approach. As he recognised, no publication before Lo 2007 contemplated this approach. In his reports, Professor Avent claimed that the brute force approach was common general knowledge. I do not accept that. If the brute force approach was well known before the publication of Lo 2007, then it would have been explored further, and referred to in the literature. There were a variety of

methods by which it could have been explored; by digital PCR, which was available from 1999; by emulsion PCR, which was available from 2003; by next-generation sequencing, which was available from 2004; or by polony sequencing, which was available from 2005. There was no adequate explanation as to why none of this was reported.

The SAFE reports

314. I do not consider that the SAFE reports, upon which Professor Avent relied, support his position. I have already referred to the Old *et al.* article, co-authored by the project co-ordinator of SAFE, which makes no reference to the brute force approach. In my judgment, the main message from the 2005 and 2006 SAFE reports was that it was essential to distinguish foetal DNA from the maternal background.

315. The 2005 report on Special Non-Invasive Advances in Foetal and Neonatal Evaluation (Project SAFE) covered the period from March 2004 to February 2005 and reported on seven work packages. Under the heading "Achievement in year 1" the Report made clear that it was crucial to identify and extract 'optimal' (as pure as possible) foetal DNA from maternal plasma:

> "Non-invasive prenatal diagnosis (NIPD) is entirely dependent on the efficacy in identification of foetal cells and/or foetal DNA in maternal blood samples. During the initial year of the SAFE project we have therefore focused attention on the integrated evaluation and development of foetal specific biomarkers. …"

It continued as follows:

> "The application of foetal DNA for maternity screening (for increased risk of foetal aneuploidy such as trisomy 21 Down syndrome and/or pregnancy complications such as pre-eclampsia and preterm labour) as well as NIPD *per se* is crucially dependent on the extraction of optimal (as pure as possible) foetal DNA from maternal plasma."

316. Professor Avent cited the following passage from the 2005 SAFE Report in his Second Report, and suggested that this disclosed the intention of SAFE to use MLPA on maternal samples without purification:

> "The MLPA has also been applied to the analysis of single cells, in particular the detection of chromosomal copy number – e.g. trisomy 21. <u>If this technical approach can be adapted for the utilisation of maternal plasma samples, or foetal DNA purified from this source, then there will be widespread introduction of NIPD for trisomy 21</u>." (emphasis added).

317. Illumina submitted that in the context of the document as a whole, the skilled team would understand this sentence as meaning "or to be more precise foetal DNA purified from this source". I accept this submission. This is consistent with the rest of the document. It is confirmed by the further description of Workpackage 3 which

makes clear that the MLPA assay was to be performed on purified foetal DNA isolated from the maternal background:

> "The MLPA assay involves the simultaneous analysis of 8 chromosome 21 loci and control markers dispersed throughout other chromosomes. The single cells were isolated, and subjected to a pre-amplification stage and then MLPA analysis. The figure clearly shows that three copies of chromosome 21 can be defined by the assay- thus could be applied to purified cells isolated in the activities described in WP1, however WP3 activity will include the adaptation of the technique to purified foetal DNA isolated from maternal plasma."

318. I should mention that in re-examination, Professor Avent was shown Annex 1 to the 2005 SAFE report, which refers to an intended commercial kit for "*MLPA applicable for use on maternal plasma samples*". The 2006 SAFE Report made clear that this did not concern aneuploidy testing: it was an RhD testing kit, which was dependent on detecting foetal-specific alleles.

319. The 2006 SAFE Report is consistent with the conclusions that I have reached about the 2005 Report. It made no mention of a brute force approach, nor of an intention of SAFE to use MLPA on maternal samples without purification. On the contrary, it repeated the statement in the 2005 SAFE Report that

> "Non-invasive prenatal diagnosis (NIPD) is entirely dependent on the efficacy in identification of foetal cells and/or foetal DNA in maternal blood samples"

and referred to the evaluation and development of foetal-specific biomarkers. It referred to maternal DNA as a contaminant in cell-free plasma DNA.

320. It also explained that Workpackage 3A related to cell-free DNA, and one of its objectives was purification of foetal DNA. This was said to be because in aneuploidy, it was "*of utmost importance that foetal DNA can be physically separated from maternal DNA*".

321. I have no doubt that Professor Avent genuinely believed that the sentence that he cited from the 2005 Report (which I was told that he wrote) disclosed the intention of SAFE to use MPLA on maternal samples without purification. However, in the context of litigation, it is easy to look back on such individual sentences, many years after they were written, and read more into them than is objectively justifiable. Even if this is how Professor Avent understood this sentence in 2005, I do not consider that this understanding would have been shared by the notional skilled team.

The Pyrosequencing approach

322. I have considered the evidence of Professor Avent concerning an approach to him by Pyrosequencing AG in late 2004/early 2005. At paragraph [117] of his First Report he did not suggest there that the proposed study involved looking at maternal plasma. Rather, he indicated that it was concerned with "*direct sequence analysis of foetal DNA fragments isolated from maternal plasma can be explored using the*

pyrosequencing technique". The reference to isolation is not consistent with a brute force approach.

323. The approach by Pyrosequencing is not documented and there is no suggestion that it was public, much less common general knowledge. Whilst whatever may have been discussed influenced Professor Avent's evidence, the skilled team would not have known about it. The same is true of Professor Avent's reference during cross examination to a SAFE partner who was seeking to look at a next generation sequencing machine in 2007, as to which no details were provided.

The Hultén review

324. I have considered a review by Professor Hultén and others; Hultén *et al.* Rapid and simple prenatal diagnosis of common chromosome disorders: advantages and disadvantages of the molecular methods FISH and QF-PCR. *Reproduction* (2003) 126, 279 – 297. Professor Avent relied on the following passage which, he suggested, proposed the direct analysis of maternal and foetal DNA in the same sample:

> "It is hoped that, in not too distant a future, the same technology may be applied for 'noninvasive' prenatal diagnosis on foetal cells or DNA retrieved from maternal blood samples, leading to a reduced requirement for invasive procedures that carry a risk for associated foetal loss."

325. I do not accept this suggestion. "The same technology" in the cited passage refers to, as the title of the paper suggests, FISH and QF-PCR. FISH cannot be applied to cell-free DNA and the QF-PCR technique discussed in the paper relates to the detection of polymorphic markers, and is not an approach which is independent of polymorphism.

The positions of Dr Erlich and Professor Lovett

326. I have also considered the dispute between Dr Erlich and Professor Lovett in relation to this same issue. Dr Erlich considered the Quake and Lo 2/3 inventions were obvious in the light of the next-generation sequencers, and Professor Lovett disagreed. I prefer Professor Lovett's evidence on this issue. I consider that Dr Erlich's evidence was based on the hypothesis that someone involved in the NIPD field, such as Professor Avent, had approached him prior to the priority date and had explained the 'counting problem' and the 'direction of travel' to him. For the reasons which I have already explained I do not consider that such an approach was obvious.

Conclusion

327. On this issue, I prefer the view of Professors Hogge and Lovett to those of Professor Avent and Dr Erlich.

The Quake 1 Patent

328. The Quake 1 Patent is concerned with the use of quantitative DNA analysis, which can be used, amongst other things, to identify chromosomal trisomies such as Down's syndrome. It claims to enable the identification of the aneuploidy characteristic of,

amongst other things, Down's syndrome from an analysis of cell free DNA in maternal plasma, without the need to isolate or distinguish the foetal DNA.

329. Paragraph [0005] refers to the observation that 3-6% of plasma in the DNA of pregnant women originates from the foetus. It notes that this observation has been used in conjunction with PCR assays for a variety of foetal genetic screens – gender, Rh and thalassaemia. However, it explains the technique remains limited for two primary reasons: first, the PCR assays trade off sensitivity for specificity, making it difficult to identify particular mutations, and second, the most common genetic disorder, Down's syndrome, is a chromosomal trisomy and therefore cannot be detected by conventional PCR in a mixed sample.

330. [0006] of the Quake 1 Patent suggests a solution to the problems that it has identified with conventional PCR by the use of what it terms "digital analysis":

> "It has now been found that these problems can be solved by quantitative examination of large numbers of chromosome samples through the use of highly scalable techniques. This approach is termed here "digital analysis", and involves the separation of the extracted genomic material into discrete units so that the detection of a target sequence (e.g., chromosome 21) may be simply quantified as binary (0,1) or simple multiples, 2, 3, etc. The primary example of a technique that can be used to yield such "digital" results is "digital PCR," which allows efficient amplification from single molecules, followed by subsequent quantitative analysis. Digital PCR, as the term is used here, refers to a quantitative, limited dilution of a nucleic acid sample, such as into multiwell plates, then the amplification of a nucleic acid molecule in a well, which due to the dilution, should be either 0 or 1 molecule."

331. The method is described in more detail in paras [0024]-[0028]. A sample of maternal plasma is taken and the DNA (which will be from both the mother and foetus) is extracted. Two target sequences are chosen. For Down's syndrome detection a sequence on chromosome 21 is chosen, along with a control sequence on a reference chromosome. The DNA is then diluted and distributed into discrete samples so that on average each sample will contain not more than one target sequence. PCR is conducted on each well using primers for both the control sequence and the sequence that may be altered or found in different copy number in the foetus. The PCR is quantitative, using fluorescently labelled PCR primers. This allows the number of wells positive for each sequence to be counted.

332. [0027] indicates that a very large number of reaction samples may be needed and that the results should be statistically significant for the purposes of the analysis. The end of para [0027] refers to a "commonly used" measure for significance when a highly significant result is desired as being a p value of < 0.01. Para [0028] states that results can be obtained with fewer reaction samples, especially where the foetal DNA is present in higher concentrations. [0028] goes on to refer to enrichment of the foetal sample and gives the example of size separation using DNA fragments of <300bp.

333. The examples of Quake use PCR amplification of the fragments of interest. The detection methods disclosed include the use of fluorescent beacons which give off fluorescence when a probe hybridises to a complementary sequence in the sample. However, it is clear that the invention of Quake 1 is not limited to digital PCR. [0031] refers to another aspect of the invention involving direct sequencing:

> "[0031] In one aspect, the present method of differential detection of target sequences may involve direct sequencing of target sequences the genetic material. Single molecule sequencing, as is known, is further described below. The method may also comprise sequencing of amplified derivatives of the target sequences clones or amplicons of the genetic material. That is, a target sequence in a discrete sample is amplified by PCR, i.e. as an amplicon, or cloned into a vector that is grown up and thereby amplified by obtaining multiple copies of the vector insert."

334. An overview of the invention is provided at [0036] - [0040]. [0037] explains that the invention involves the analysis of maternal blood for a genetic condition, in which mixed foetal and maternal DNA in maternal blood is analysed to detect "*a foetal mutation or genetic abnormality from the background of the maternal DNA*". By using digital analysis, a DNA sample containing DNA from both the mother and the foetus is analysed to distinguish a genetic condition present in "*a minor fraction of the DNA*" which is said to represent the foetal DNA.

335. The paragraph explains, by reference to the digital PCR embodiment, that the maternal plasma is divided into multiple reaction samples, each containing on average not more than one target sequence per sample. Each sample is examined for the presence or absence of a target sequence corresponding to the potentially aneuploid chromosome, and the presence or absence of a target sequence corresponding to a reference chromosome. The reference chromosome typically represents one which is highly unlikely to be subject to aneuploidy if the chromosome of interest is aneuploid in the foetus. The numbers are counted. In the case of foetal aneuploidy (for example Down's syndrome), one would expect a small excess of the target sequences (from chromosome 21) over the reference sequence (e.g. from chromosome 12), even though the excess is in the minor fraction of cell-free DNA originating from the foetus. A large number of reactions need to be run, to exclude the effect of random variations.

336. Quake also states that the method can more easily be used by increasing the size of the foetal fraction using a size separation step. A larger foetal fraction will result in a greater discrepancy between the potentially aneuploid and reference chromosomes, and therefore greater statistical reliability. Processes of enrichment by size separation are disclosed at [0043] - [0045].

337. The method of the Quake I Patent is said, generally, to comprise the following steps, which are set out in paragraph [0040]:

  i) obtaining tissue, such as blood plasma, containing foetal DNA from a pregnant subject;

ii) distributing single DNA molecules from the sample into a number of discrete reaction samples;

iii) detecting the presence of the target in the DNA in a large number of reaction samples, preferably using a sequence-specific technique such as highly multiplexed short read sequencing or a PCR reaction; and

iv) quantitative analysis of the detection of the maternal and foetal target sequences.

338. Premaitha contended that the disclosure of Quake 1 is limited to a disclosure of targeted sequencing and does not include random sequencing. Amongst other things, it relied on [0093] of Quake:

> "[0093] It should be appreciated that methods involving PCR or other amplification are not the only way to detect or enumerate the molecules in a given discrete reaction sample. It is possible to use single molecule flow cytometry to count single molecules that have been labeled with a sequence-specific fluorescent probe. It is also possible to sequence the target sequence in the reaction sample directly, either after amplification or at the single molecule level." (emphasis added)"

339. Illumina disputed this, and relied on the following passages at [0096] and [0097]:

> "[0096] A methodology useful in the present invention platform is based on massively parallel sequencing of millions of fragments using attachment of randomly fragmented genomic DNA to a planar, optically transparent surface and solid phase amplification to create a high density sequencing flow cell with millions of clusters, each containing ~1,000 copies of template per sq. cm. These templates are sequenced using four-color DNA sequencing-by-synthesis technology..".

> "Sequencing may be combined with amplification-based methods in a microfluidic chip having reaction chambers for both PCR and microscopic template-based sequencing. Only about 30 bp of random sequence information are needed to identify a sequence as belonging to a specific human chromosome." (emphasis added)

This issue is relevant to infringement and I shall consider it in that context.

340. Quake explains at [0102] that where the foetal fraction in the maternal plasma is 3%, the presence of a trisomy in the potentially aneuploid chromosome will be reflected in an excess of reaction samples positive for the target sequence corresponding to the potentially aneuploid chromosome over reaction samples positive for target sequence corresponding to the reference chromosome in the ratio of 2.03:2. Illumina submitted that, in principle, this is a difference which is detectable with statistical reliability

provided that enough reactions are carried out. I shall consider this in the context of sufficiency.

341. The Example of Quake 1 is said by Illumina to demonstrate how statistically reliable detection of Down's syndrome can be achieved. This is described at [0131] to [0142] and involves digital PCR-based detection of aneuploidy. Aneuploidy was detected in samples containing a mixture of DNA from a normal human cell line and DNA from a Down's syndrome cell line, as an experimental simulation of maternal blood samples in which the percentage of foetal DNA had been enriched to at least 30%.

342. Quake 1 discloses that the statistical significance of these results could be further improved by increasing the number of wells analysed to enable more robust statistical analysis. Quake states at [0142] that:

> "the statistical reliability of the present method can be dramatically improved simply by increasing the number of wells tested. Since about 240 genome equivalents is required per panel, and about 4,700 genome equivalents are found in a 20 ml sample, it is possible, given the present description, to simply run additional analyses to increase statistical significance."

343. Premaitha disputed the statistical reliability of this Example. It pointed out that all samples used were artificial "spiked" samples. No sample representing the likely fraction of foetal DNA in a maternal sample (3% to 6%) was used. I shall consider this issue further in the context of insufficiency.

The Claims of the Quake 1 Patent

344. It is sufficient to set out claim 1 of Quake 1, which includes a conditional amendment proposed by Illumina to overcome an insufficiency objection:

> "A method of detection of foetal aneuploidy in a mixture of maternal and foetal genetic material, in a sample of maternal tissue, characterized by:
>
> (a) distributing the genetic material into reaction samples, <u>wherein each sample contains on average not more than about one target sequence per sample,</u> wherein DNA to be analyzed will be either present or absent in a reaction sample, due to random variations between reaction samples;
>
> (b) measuring the presence of different target sequences in the reaction samples by digital analysis to obtain binary results providing differential detection of the target sequences in a mixture of maternal and foetal genetic material, wherein said target sequences comprise sequences from two chromosomes, one of which is possibly aneuploid and one of which is presumed diploid;

> (c) analyzing the binary results from step (b) by counting the frequency of positive responses from target sequences followed by (d) statistical analysis of the results of step (c) whereby the frequency of positive responses from target sequences provides data sufficient to distinguish euploid from aneuploid target sequences, wherein the measuring step comprises direct sequencing of the maternal and foetal genetic material."

The Quake 2 Patent

345. The specification of Quake 2 is materially the same as Quake 1. There are some differences in the claims, which are relevant to infringement. Claim 1 is as follows:

> "A method for detecting a genetic abnormality that involves a quantitative difference between maternal and fetal genetic sequences by differential detection of target sequences in a mixture of maternal and fetal genetic material, comprising the steps of:
>
> a) distributing the genetic material into discrete samples, each sample containing on average not more than one target sequence per sample, wherein the discrete samples are in reaction samples where the target sequences can be analyzed;
>
> b) measuring the presence of different target sequences in the discrete samples, wherein the measuring comprises direct sequencing of the genetic material or sequencing of amplified derivatives of the target sequences in clones or amplicons of the genetic material; and,
>
> c) analyzing a number of the discrete samples, wherein the number of discrete samples analyzed and the results from the discrete samples provide data sufficient to obtain results distinguishing said different target sequences,
>
> wherein one of the different target sequences is diploid in the maternal genetic material and aneuploid in the fetal genetic material and another of the different target sequences is diploid in both the maternal and the fetal genetic material, thereby detecting a genetic abnormality that involves a quantitative difference between maternal and fetal genetic sequences."

Shimkets

The disclosure of Shimkets

346. Shimkets is a United States patent application published in October 2005. Its inventors were employed by the manufacturers of the 454 sequencer. It proposes the use of the 454 sequencer to karyotype a genome of a test cell, a technique which it terms "sequence based karyotyping."

347. At [0003] – [0004] Shimkets discusses traditional karyotyping methods and their limitations. [0003] of Shimkets states that:

> "Current methods for analysis of cellular genetic content include comparative genomic hybridization (CGH) (3), representational difference analysis (4), spectral karyotyping/M-FISH (5,6), microarrays (7-10), and traditional cytogenetics. Such techniques have aided in the identification of genetic aberrations in human malignancies and other diseases (11-14). However, methods employing metaphase chromosomes have a limited mapping resolution (about 20 Mb) (15) and therefore cannot be used to detect smaller alterations. Recent implementations of comparative genomic hybridization to microarrays containing genomic or transcript DNA sequence provide improved resolution, but are currently limited by the number of sequences that can be assessed (16) or by the difficulty of detecting certain alterations (9). There is a continuing need in the art for methods of analyzing and comparing genomics."

348. Paragraph [0004] states that:

> "Because chromosomes are visualized on an optical microscope, the ability to resolve detailed mutations (involving only a small part of a chromosome) is limited. While more detailed karyotyping techniques, such as FISH (fluorescent in situ hybridization) are available, they rely on specific probes and it is not economically or technically feasible to perform FISH on the entire chromosome set (i.e., the complete genome)."

349. Paragraph [0005] of Shimkets discusses the use of a technique which it describes as "digital karyotyping":

> "In recent work, a method was provided for karyotyping a genome of a test eukaryotic cell by generating a population of sequence tags after restriction endonuclease digestion from defined portions of the genome of a test cell (17). This method is not optimal because a small number of areas of the genome are expected to have a lower density of restriction endonuclease cleavage sites and could be incompletely evaluated. The authors estimate these areas to encompass 5% of a genome. Furthermore, the resolution of the method is dependent on the restriction enzyme used and the method cannot reliably detect very small regions of the genome on the order of several thousand base pairs or less."

350. The invention of Shimkets is a sequence-based karyotyping method, which is summarised in paragraphs [0007] to [0016]. Paragraph [0007] explains:

> "The current invention provides for a method of karyotyping a genome of a test cell (e.g., eukaryotic or prokaryotic) by generating a pool of fragments of genomic DNA by a random fragmentation method, determining the DNA sequence of at least 20 base pairs of each fragment, mapping the fragments to the genomic scaffold of the organism, and comparing the distribution of the fragments relative to a reference genome or relative to the distribution expected by chance. The number of a plurality of sequences mapping within a given window in the population is compared to the number of said plurality of sequences expected to have been sampled within that window or to the number determined to be present in a karyotypically normal genome of the species of the cell. A difference in the number of the plurality of sequences within the window present in the population from the number calculated to be present in the genome of the cell indicates a karyotypic abnormality."

351. Shimkets contemplates that this method of karyotyping may be used on a wide range of cell types. Paragraph [0010] states that:

> "Preferably, the test cell and the reference cell is from the same species. The cell is a eukaryotic cell or a prokaryotic cell. The eukaryotic cell a mammalian cell. The mammal is, e.g., a human, non-human primate, mouse, rat, dog, cat, horse, or cow. The cell is a cancer cell, an embryonic cell, or a foetal cell. The cell is isolated from amniotic fluid or is derived from in vitro fertilization. Optionally, the cell is from a subject with a hereditary disorder."

352. Paragraph [0011] of Shimkets explains that "*[t]he plurality of DNA sequences obtained are mapped to a genomic scaffold to create a distribution of mapped sequences to a region of the genome*". Paragraph [0012] further explains that:

> "By mapping to a genomic scaffold is meant that the sequences are aligned along each chromosome. The test cell distribution (i.e. chromosome map density) is defined as the number of mapped sequences (i.e., fragments) by the number of possible map locations present in a given chromosome. The number of possible map locations is defined by the size of the observation window and the length of the chromosome. No particular length is implied by the terms observation window. For example, the observation window is 25 Mb, 10 Mb, 4 Mb, 2 Mb, 500 kb, 250 kb, 60 kb, 30 kb, or 10 kb or less in length."

353. Paragraph [0049] describes the types of chromosomal aberrations which may be detected using the karyotyping method disclosed by Shimkets. These are said to include aneuploidy, polyploidy, inversion, translocation, deletion, and duplication. It is also stated that:

> "Furthermore, chromosome abnormality includes any sort of genetic abnormality including those that are not normally

> visible on a traditional karyotype using optical microscopes, traditional staining, of FISH. One advantage of the present invention is that chromosomal abnormality previously undetectable by optical methods (e.g., abnormalities involving 4 Mb, 600 kb, 200 kb, 40 kb or smaller) can be detected."

354. Paragraph [0060] explains that:

> "The method of the invention can be used to determine changes in copy number for portions of the genome on a genomic scale. Such changes include gain or loss of whole chromosomes or chromosome arms, interstitial amplifications or deletions, as well as insertions of foreign DNA. Rearrangements, such as translocations and inversions, can be detected by the method of the invention, e.g., where large fragments are generated and the ends sequenced, or where the scaffold-predicted ends are a different distance apart than the size of the fragment sampled."

355. Paragraph [0061] explains the advantages that the method disclosed by Shimkets provides:

> "The data shown herein demonstrate that the method of the invention, called Sequence-Based Karyotyping, can accurately identify regions whose copy number is abnormal, even in complex genomes such as the human genome. Advantageously, the method permits the identification of specific amplifications and deletions that had not been previously described by comparative genomic hybridization (CGH) or other methods in any human cancer. The approach is particularly applicable to the analysis of human cancers, wherein identification of homozygous deletions and amplifications has historically revealed genes important in tumor initiation and progression. The method of the invention can be used with a variety of other applications. For example, the approach could be used to identify previously undiscovered alterations in hereditary disorders. A potentially large number of such diseases are thought to be due to deletions or duplications too small to be detected by conventional approaches. These may be detected with Sequence-Based Karyotyping, even in the absence of any linkage or other positional information."

356. Paragraph [0062] explains that the sequence-based karyotyping method of Shimkets may be used for the diagnosis of disease, or a propensity to develop diseases such as chronic myeloproliferative disease, myelodysplastic syndromes, acute non-lymphocytic leukaemias, B-cell acute lymphocytic leukaemias, T-cell acute lymphocytic leukaemias, non-Hodgkin lymphomas, or chronic lymphoproliferative diseases by detecting one or more chromosomal abnormalities associated with each disease. Paragraphs [0065] to [0244] explain the methodology by which sequence-based karyotyping can be carried out. Paragraphs [0245] to [0625] of Shimkets set

out 23 Examples, each of which is a detailed description of a step in an example of a sequence-based karyotyping method.

Issues in relation to the disclosure of Shimkets

357. Premaitha accepted that the embodiment described from [0065] onwards is directed towards karyotyping of a test cell, but submitted that the general description is not so limited. Amongst the paragraphs relied upon by Premaitha, all of which I have considered, it emphasised the summary of the invention in [0007]; the use of the method disclosed in Shimkets to detect aneuploidy, for example at [0014], [0049], [0063] and [0083]; and the reference to both cell and tissue in [0060]. It said that [0082] discloses that the samples may be obtained from amniotic fluid or CVS, both of which could be contaminated with maternal tissue or affected by placental mosaicism. It referred to [0090] which discussed the advantages of the Shimkets method and in particular its higher resolution than previously known methods. It pointed out that its application to the counting of mRNA and methylated DNA fragments is suggested at [0093] and [0094], which were both being used in the context of cell-free foetal DNA in maternal plasma samples at the priority date.

358. It relied upon [0095] which states that:

> "Complex sample sequencing in accordance with the invention can be used for detection of pathogens in blood, water, air, soil, food, and for the identification of all organisms in a sample without any prior knowledge. In accordance with this method, populations of organisms can be identified by preparing a mixed DNA and cDNA sample, sequencing random fragments from the DNA and RNA in the sample and mapping sequences to a hierarchical database of all known sequences… According to one embodiment, a sample (e.g. blood, water, air, food, or soil) can be used to generate 1 million sequence reads …. "

Premaitha pointed out that this describes the application of the method to the detection of pathogens in complex samples including cell-free samples of blood. The reference to complex sample sequencing of fragments of genetic material in a mixture of "*for example, microorganisms from blood*" is also mentioned at [0244]. Premaitha accepted that although these passages did not contemplate the use of the method to detect aneuploidy in a mixed sample, they nonetheless showed that the method does not require a cellular sample in order to work.

359. In my view, Premaitha's analysis does not take full account of the limitations of the Shimkets disclosure in relation to detection of aneuploidy. Illumina submitted, and I accept, that in the context of foetal diagnosis, Shimkets examines a *pure* sample of foetal cells *isolated* from the amniotic fluid or by CVS, and asks whether there is a greater frequency of reads associated with the chromosome in question in that cell than was the case with a reference (non-trisomic) cell ([0082] - [0083]). This is an automated way of carrying out traditional karyotyping in which the excess of chromosome 21 was identified by looking at a foetal cell obtained from amniocentesis or CVS under the microscope, and comparing it with what would be expected in a normal cell. It required the prior isolation of a foetal cell by an invasive technique;

and the use of separately acquired reference information using the same configuration and experimental process but on a different cell.

360. [0095] and [0244] refer to the identification of different pathogens in a sample of blood, water, air, soil and food. This is the only disclosure of a mixed sample test and is a qualitative assessment made by looking for markers unique to those pathogens. It finds a DNA sequence unique to the pathogen that allows the pathogen to be separately identified out of the background DNA.

Obviousness in the light of Shimkets – the parties' submissions in outline

361. Premaitha did not dispute that the difference between Shimkets and the claims of Quake and Lo 2/3 is that the analysis is performed on foetal DNA obtained invasively rather than on DNA obtained from a maternal plasma sample. However, it submitted, amongst other things, that:

i) It was clear on the evidence that the skilled team would have wanted to try Shimkets on maternal plasma samples at the earliest priority date with the requisite expectation of success.

ii) The evidence showed that it was entirely routine to apply new technologies carried out on amniotic/CVS samples to cell free foetal DNA at the priority date. The skilled team would want to use Shimkets in this way and the biostatistician would confirm that it would be expected to work. Both the idea and the implementation of the idea (with access to an NGS machine) in the Quake and Lo 2 Patents are therefore obvious over Shimkets.

iii) All of the expert evidence, when properly analysed, led to a conclusion of obviousness.

iv) In the case of Shimkets, there was a clear answer to the question 'if it was so obvious, why did no-one do it before?' (a question which was of limited value, since it could apply to many cases where a patent was technically obvious). There was no evidence (and it appears inherently unlikely) that anyone in the relevant field saw the Shimkets patent application at any time prior to the publication of the Lo 2007 paper.

v) Two independent groups (Lo and Quake) came up with the same plans of using first digital PCR then massively parallel sequencing to seek to detect aneuploidy from a maternal plasma sample at the same time. They were only doing what would inevitably have been done with access to the relevant technology.

362. Illumina submitted, amongst other things, that:

i) Shimkets exemplified, but did not solve, the problem that the art had been grappling with for decades. Shimkets disclosed a method of karyotyping a genome of a 'test cell' – the teaching and claims of Shimkets are exclusively focused on the use of cells.

ii) Shimkets teaches that foetal aneuploidy may be detected by isolating foetal cells from amniotic fluid or by CVS, and does not even attempt to apply non-invasive techniques.

iii) The only use of 'mixed samples' described by Shimkets is the detection/identification of pathogens in e.g. soil samples. This is not a karyotyping method and has no relevance to the Quake Patents.

iv) The invention of the Quake Patents is not simply the application of massively parallel sequencing on a maternal plasma sample – it is the use of a polymorphism-independent method which does not involve distinguishing the maternal and foetal DNA, something which went in the opposite direction to the direction of travel at the priority date.

v) If the skilled person had applied the Shimkets karyotyping method to a maternal plasma sample, he would have used purified foetal DNA, in line with the direction of travel – there is nothing in Shimkets to suggest the adoption of the 'brute force approach', in which the foetal DNA is not in some way isolated or distinguished from the maternal DNA.

vi) Shimkets proposes that his system be used to identify RNA markers, SNPs and methylation sites, giving the skilled person multiple avenues of research without ever straying outside the areas presented on the face of the document. None of these avenues takes the skilled person towards the polymorphism independent method of the Quake Patents.

Discussion

The two groups

363. I will begin by considering Premaitha's submission that because two independent groups (Lo and Quake) came up with the same plans of using first digital PCR, and then massively parallel sequencing, to seek to detect aneuploidy from a maternal plasma sample at the same time, this was an indication of obviousness; in that they were only doing what would inevitably have been done with access to the relevant technology.

364. This submission might have some force if it was said that the invention was obvious in the light of common general knowledge, or alternatively that both groups were working from the same prior art as a starting point. Even then, it might not be an indication of obviousness; the two groups might have had a similar approach because they were both inventive. In the present case Premaitha has always disclaimed any reliance upon obviousness in the light of common general knowledge. Furthermore, it was keen to emphasise that there was no evidence that anyone in the relevant field saw Shimkets at any time prior to the publication of the Lo 2007 paper. I accept that there was no evidence that either the Quake or Lo 2 groups had seen Shimkets, and it was most unlikely that they were working from it. In those circumstances, neither of them could have been influenced by the only prior art relied upon.

The expert evidence

365. The principal point made by Premaitha, as to the combined effect of the expert evidence, has considerably more substance, and requires careful analysis. Premaitha began by addressing the evidence of the clinicians. It pointed out that Professor Hogge did not give any evidence about Shimkets, and since the clinician is the leader of the team, Premaitha claimed that there was a lacuna in Illumina's evidence. I accept that the skilled clinician would read Shimkets, and that Professor Hogge did not discuss it in his reports. However, Shimkets is a document concerned with a general method of NGS testing with many different potential applications, which is addressed to and would be understood by the skilled geneticist, and therefore the evidence of Professor Lovett and Dr Erlich is of primary relevance.

366. Premaitha submitted that Professor Hogge's cross-examination showed that the skilled clinician would be interested in applying Shimkets to maternal plasma samples at the earliest priority date. I believe that this submission goes too far. Professor Hogge was not asked about Shimkets during his cross-examination, and from the rest of his evidence, there was no suggestion that he would have agreed that the Patent was obvious in the light of Shimkets; on the contrary.

367. A key point in Premaitha's argument is the submission that Professor Hogge agreed that the general view in 2006 was that techniques first developed for use on cells or pure foetal DNA should be tried on cell-free foetal DNA in maternal plasma; and that it would be logical to try techniques first used on amniotic fluid and chorionic villi samples as a non-invasive method. The two passages of cross-examination relied upon are as follows:

> "And this reflected the general view in 2006 that techniques developed first for use on cells or pure foetal DNA should be tried on cell-free foetal DNA?"
>
> "That is correct."

(T5/426/2-5)

and

> "They carried out the technique on amniotic fluid and chorionic villi samples and then the idea was to go on and try it as a non-invasive method, and that would be logical?"
>
> "That would be very logical."

(T5/428/12-15)

On this basis, it was argued that the skilled clinician would give Shimkets to the skilled geneticist, with instructions to carry out the technique on cell free foetal DNA.

368. Premaitha also relied upon Professor Avent's view that it would have been immediately obvious to apply the method disclosed in Shimkets to maternal plasma and would have approached the skilled geneticist and biostatistician to determine the feasibility of the approach. He would have asked the skilled geneticist whether it could be applied to maternal plasma in the same way that it would have been asked of

any technique which had been applied to foetal cells whether that technique could be applied to maternal plasma.

369. Premaitha denied the suggestion that Professor Avent had viewed Shimkets with hindsight and submitted that his position was entirely justified in the light of the evidence he had given about the direction of travel in the field, backed up by the contemporaneous documentation such as the SAFE report and the Hulten review. He stated that no one in the SAFE network (including himself) knew about Shimkets, but had they known about it they would have followed the same approach that had been proposed in respect of MLPA and pyrosequencing and transferred the technique to maternal plasma samples.

370. Professor Lovett was cross examined about Shimkets, and clearly did not agree with the suggestion that the Quake and Lo 2/3 Patents were obvious in the light of its disclosure. However, Premaitha contended that his evidence was flawed. Professor Lovett was asked to assume that the skilled clinician would want the skilled geneticist to carry out Shimkets on cell free foetal DNA in maternal plasma. He made clear that he did not accept the assumption. Premaitha referred to the following passage of cross examination, and contended that it was inconsistent with the evidence of Professor Hogge, and with general evidence given by Professor Lovett, which, according to Premaitha, provided the foundation for this assumption:

> "Q. On the assumption that the general approach of the skilled clinician in 2006 was to try techniques developed first for use on cells or pure foetal DNA to cell-free foetal DNA, you could have carried out the technique in Shimkets on cell-free foetal DNA for the skilled clinician at that time?
>
> A. I do not agree with the assumption, right at the start. I do not know why anybody would make that leap, especially when it is technology-based rather than concept-based, but if you did it and you had a lucky foetal fraction, then you might see some changes by that sequence.

371. Premaitha then relied upon the evidence of Dr Erlich who had suggested in his reports that the skilled molecular biologist would consider the method in Shimkets to be promising in relation to the detection of aneuploidy and it would be obvious to apply it to maternal plasma. His opinion was that the skilled team would be confident that a next-generation sequencing method such as that described by Shimkets would be able to detect foetal aneuploidy, and that, having consulted the skilled biostatistician, the molecular biologist would consider that the technique would have a good chance of being able to detect foetal aneuploidy in a maternal sample.

372. Finally, Premaitha submitted, and I agree, that there was no disagreement between the biostatisticians. Professor Marchini performed the necessary power calculations for the application of NGS to detect aneuploidy from maternal plasma which had not been challenged by Professor Holmes. They demonstrated that Shimkets worked. Otherwise, the Quake and Lo 2/3 Patents would be insufficient.

373. It was contended that all the expert evidence should lead the court to a finding of obviousness. Attractively this argument was put, I do not accept it. The cross

examination of Professor Hogge, which I have cited above, did not refer to Shimkets at all. He was not asked whether he considered that the skilled clinician would have referred Shimkets to the skilled geneticist. When Professor Lovett was asked about Shimkets, he was quite clear that it did not render the invention obvious, and supported his view with detailed reasons. The evidence of Professor Avent and Dr Erlich was based upon a series of propositions, for example as to the direction of travel in the art of the priority date, which I have not accepted.

Conclusion

374. I have reached the conclusion that the Quake Patents are not obvious in the light of Shimkets, for the following reasons. First, Shimkets is not concerned with NIPD. Its approach is to test a foetal cell obtained using an invasive technique such as amniocentesis or CVS. Applying the *Pozzoli* approach, this is a profound difference to the claimed inventions of the Quake Patents. Considering the common general knowledge, I have referred to the three settled approaches that were applied at the priority date in NIPD. Shimkets would not prompt the skilled team to depart from any of these approaches. Shimkets disclosed the analysis of isolated foetal cells and the use of separately acquired information from a normal reference cell. It did not contemplate mixed samples other than in a pathogen detection system, and even in that context used a qualitative assessment made by looking for unique markers.

375. The Quake approach renders it unnecessary to extract a foetal cell, or to isolate or identify foetal DNA. There is no requirement to use reference information. The invention uses digital analysis on a mixture of foetal and maternal DNA, from plasma or serum, and considers the ratio of sequence reads or detections of individual target sequences from two chromosomes, both present in the mixture being tested. In my judgment, Shimkets would confirm the need to apply one of the settled approaches which was common general knowledge at the priority date in order to obtain a pure cell upon which Shimkets based his analysis, and would not suggest the Quake approach.

376. Secondly, in my view, Premaitha's experts approached Shimkets from an incorrect starting point. When considering Shimkets, Professor Avent assumed that the skilled person would come to the document with the approach set out in [70] – [74] of his first report. That characterised the problem in the art as merely one of counting, to which the development of new technology, such as the 454 GS20, obviously provided a solution. He claimed that his 'brute force' approach was part of the common general knowledge. I have not accepted any of these propositions. Dr Erlich's evidence proceeded on the basis that he was working in a skilled team with a clinician who took Professor Avent's approach. I regard this approach as hindsight.

377. Finally, even if the clinician had referred Shimkets to the geneticist, I was not satisfied that the geneticist would have arrived at the Quake invention. Professor Lovett was strongly of the view that the invention was not obvious, and provided detailed reasons, for example at [208] – [219] of his Second Report, which I found to be logical and coherent. Dr Erlich, whose frank and honest evidence did him great credit, referred during his cross examination to a proposal that he had made to Roche in 2008 or 2009, after the priority date. It appears that this concerned the use of sequencing machines for quantifying an allelic imbalance, which fell outside the claims of the Quake Patents.

378. This involved identifying a polymorphic allele in the chromosome of interest. In order to establish allelic imbalance caused by foetal chromosomal aneuploidy, the mother must be heterozygous for the allele in question. This is different from the Quake concept. The approach that Dr Erlich said he would have taken, if asked by the skilled clinician how to look for aneuploidy in cell-free maternal samples at the priority date, was the idea that he discussed with Roche. He explained that he

> "would have used the SNP allele approach that I suggested to Roche many years ago, and also that I outlined in my report. So, use the 454 system to count allelic sequence reads, look at the ratio derived from maternal plasma and then try to make an inference about the trisomy".

On that basis, even someone as inventive as Dr Erlich would not have arrived at the Quake inventions.

Insufficiency

379. Many of the insufficiency objections against Quake were advanced by Premaitha as a squeeze on obviousness. They were designed to prevent Illumina from contending that difficulties in implementing the molecular biological techniques in the prior art, including Shimkets, would mean that the skilled team would not expect that those techniques would work to detect aneuploidy, and therefore that they were not obvious. However, I have accepted Professor Marchini's power calculations, which demonstrated that the 454 sequencer used in Shimkets would be sensitive enough to detect aneuploidy. On that basis, those insufficiency objections which were advanced as a squeeze are no longer pursued by Premaitha.

380. However, Premaitha advanced a classical insufficiency objection in relation to digital PCR, which was accepted by the European Patent Office and resulted in a limitation to the claims which is advanced as a conditional amendment by Illumina in these proceedings. The parties devoted considerable amounts of evidence and written argument to the issue, which I will endeavour to address briefly, as it makes no difference to the ultimate outcome of the case. I do not consider it necessary to address every argument advanced by the parties.

381. Dr Erlich explained that in 2006 digital PCR did not have the sensitivity to detect aneuploidy in maternal plasma. Professor Marchini calculated that about 130,000 wells would be needed for a 5% foetal fraction and 5% false positive and negative rates. Dr Erlich estimated that using 384 well plates, two lab technicians using 10 thermal cyclers running two PCR experiments per day would take 17 days to analyse a single sample, at a cost of approx. US$510,000. Professor Lovett accepted this would not have been commercially viable, but he suggested that there were alternative technologies that could be used, which allowed higher throughput than 384 well plates.

382. I prefer the evidence of Dr Erlich to that of Professor Lovett on this issue. It appeared from a number of papers subsequent to the priority date, which were put to Professor Lovett in cross-examination, that the techniques that he proposed did not solve the problem, and it has only been in the last few years that significant progress has been made with dPCR for this purpose. In particular:

i) A paper by Fan and Quake published in 2008 explained that although in principle it should be possible to use digital PCR to create a universal polymorphism independent test for foetal aneuploidy by using maternal plasma, because of the technical challenges relating to the low fraction of foetal DNA, such a test has not been practically realised. Fan *et al.*, Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood (2008), *PNAS* 105(42), 66-16271.

ii) A paper by Zimmermann published in 2008 identified the "current barrier" to the use of digital PCR for prenatal diagnosis of foetal aneuploidy as being that the foetal fraction was too low. Zimmerman *et al.*, Digital PCR: a powerful new tool for noninvasive prenatal diagnosis. *Prenat Diagn 28*¸ 1087-1093.

iii) A paper from Professor Hogge's group published in 2010 Chu T *et al.*, Statistical considerations for digital approaches to non-invasive fetal genotyping. *Bioinformatics*, 2010:26(22), 2863-2866, concluded that

> "Despite the obvious promise of the digital PCR method, we have concern that it may be limited by its inability to allow parallel amplification of multiple target loci. This is largely due to the fact that foetal genome equivalents are scarce in maternal plasma, limiting the potential for running multiple assays."

iv) A paper by Nicolaides *et al.* published in 2012 explained that the level of sensitivity that was desirable was far beyond the then current commercial technology. Evans *et al.*, Digital PCR for noninvasive detection of aneuploidy: power analysis equations for feasibility. *Fetal Diagn Ther 31*, 244-247.

v) A paper by El Khattabi published in 2016 explained that that digital PCR had been hampered by the large number of PCR reactions needed to meet statistical requirements, preventing clinical application. The paper described a technique called octoplex droplet digital PCR, which had achieved progress with digital PCR for this purpose. But this was 10 years after the Quake priority date.

383. In the light of these publications, I accept that although in principle it was possible in 2006 to detect aneuploidy in maternal plasma using digital PCR, this technique did not have sufficient sensitivity for a practical application at the priority date, without undue burden. The Opposition Division referred to much of this literature in concluding that claim 1 as granted was insufficient. I believe that they were right to do so.

384. I do not consider that the experimental Example in Quake provides a practical solution to this problem. The experiment was not performed on maternal plasma samples, but rather on samples of genomic DNA extracted from a normal human cell line that had been "spiked" with various levels of DNA from a trisomy 21 cell line (100%, 60%, 50%, 40%, 30% and 0% Down's DNA). The conclusion to be drawn from the expert evidence is that it shows borderline evidence at an artificially high foetal fraction of 30%, using spiked samples of genomic DNA.

385. I conclude that claim 1 of Quake as granted is insufficient insofar as it extends to digital PCR. However, Quake teaches that the invention can alternatively be carried out by massively parallel sequencing techniques. Dr Erlich accepted in his first report that the method of Quake was feasible and achievable without undue burden using massively parallel sequencing techniques which were part of the common general knowledge of the skilled team at the priority date. I shall allow Illumina to make the same amendments that were accepted by the Opposition Division, which limit claim 1 to the use of direct sequencing and claim 10 to massively parallel sequencing.

Added matter

386. The only added matter point which was pursued by the end of the trial relates to the average amount of DNA in each reaction sample in the claimed method. The disclosure of the Quake Application is that the genetic material is distributed into reaction samples such that each reaction sample contains on average not more than about one target sequence per sample. This is an express limitation in the claims of the Quake application and appears as feature (b) in claim 1. There is no such limitation in the claims of the granted Quake patent, which only require that once the genetic material is distributed into the reaction samples, the DNA to be analysed will either be present or absent in a reaction sample.

387. The Opposition Division at [3.3.3.4] of its decision concluded that this constituted added subject matter. The patentee added a limitation that "*each sample contains on average not more than about one target sequence per sample*". The same amendment is offered, conditionally, in these proceedings.

388. Pre-grant amendment of claims, where the amendment widens the monopoly by deletion of integers, do not add subject matter where the matter sought to be omitted was not an essential feature of the invention in the application as filed. However, this must be clear to the skilled reader. Aldous J (as he then was) said in *Southco v Dzus Fastener Europe Ltd* [1990] RPC 587, as summarised in the headnote, that:

> "Section 76 did not prevent the granted patent claiming a different combination from that in the application if the amended claim had in it the essential elements required by both the application and the specification of the patent to achieve the objects of the invention. The section prevented disclosing either by deletion or addition any inventive concept which was not disclosed before, but did not prevent him from claiming the same invention in a different way"

389. Illumina submitted that if there are several target sequences on average in each sample, it will become more difficult (when using digital PCR) to detect the precise number of such sequences, even though in principle the Patent (and the application) teaches that multiple numbers of a sequence can be detected by increased fluorescence. It suggested that the Application made clear that the feature was not essential to the invention. It relied upon page 31 lines 24-25, which was part of the 'specific applications' in the disclosure and contained a protocol for preparation for trisomy with frequency analysis. The application referred to '*genome equivalents*' as '*the entire genomic content of a single normal cell (46 chromosomes)*'. Illumina submitted that since there are two copies of a given target chromosome in each

genome equivalent, there are at least two targets per '*genome equivalent*'. Thus, any time the Quake patent refers to performing digital PCR with anything above a 0.5 genome equivalent of DNA per well, it is contemplating having, on average, more than one target per well.

390. I do not accept Illumina's submission. There is a summary of the invention in the Application from page 5 line 28 – page 8 line 22. This indicates, in my judgment, that the disputed feature is an essential element of the invention and the skilled team would read the rest of the disclosure with that general teaching in mind. I do not consider that it would be clear or apparent to the skilled team that this feature was inessential.

391. I conclude that claim 1 of Quake 1 as granted is invalid on the basis of added subject matter. However, I propose to allow the conditional amendment proposed by Illumina.

Issues of infringement of the Quake 1 Patent

Integer (a)-limiting dilution

392. Premaitha submitted that a key part of digital PCR is the process of limiting dilution. This ensures that on average there is not more than one target sequence per well. This dilution is critical to the method because it allows the subsequent counting of positive wells as it can be assumed that if the well is positive for a target sequence, there was only one target sequence present. There is therefore no need to quantitate the amplitude of the positive signal. Similarly, if sequencing is being used as the measuring step, the skilled person would be aware that it was crucial that only a single DNA sequence was present in each sequencing reaction (albeit that multiple copies of it could be present to increase the signal). The skilled person would know that if there were more than one sequence present, the well would be uninformative. Premaitha contended that the skilled person would understand that integer (a) of the claim was directed to such a limiting dilution step.

393. Considering claim 1 as granted, I accept that the claim *includes* methods in which a limiting dilution step is used, for example in digital PCR, but I do not accept that integer (a) of claim 1 *requires* limiting dilution. The claim specifies that the DNA to be analysed will be either present or absent in a reaction sample, due to random variations between reaction samples. There is no limitation which restricts the claim in the manner contended for by Premaitha.

394. In digital PCR, samples are diluted, for example to about half a genome per well. As there are two copies of each autosomal chromosome, this dilution means that those wells which contain target sequences can be assumed to have one instance of the target sequence per well. However, this is not the case in massively parallel sequencing, in which each reaction contains only one DNA fragment or sequence, and not half a genome. Massively parallel sequencing is expressly disclosed at [0096] of the Quake Patent, and was the subject of claim 16 as granted. Claim 1 as granted covers massively parallel sequencing which does not require a dilution step. Premaitha's argument is even more difficult in respect of claim 10 as proposed to be amended, which is limited to massively parallel sequencing.

395. Applying this construction to the issue of infringement, the IONA test detects whether the DNA to be analysed is either present or absent in a reaction sample, due to random variations between reaction samples. The wells on the chip are, randomly, either empty or full. Premaitha argued that this was due to the loading process, but whatever the cause, the result satisfies the claim. Furthermore, not all DNA sequences are used in subsequent steps. Those wells that map to the Y chromosome and those wells which contain DNA that is unmappable are excluded from the analysis, as Dr Erlich explained at [249] of his First Report. Occupied wells containing target DNA (used in subsequent analysis) and occupied wells containing non-target DNA or unmappable DNA, vary randomly, due to the random nature of the distribution of ISPs, which also vary randomly. In my judgment, the IONA test satisfies this feature of the claim.

Integer (a) as proposed to be amended – 'wherein each sample contains on average not more than about one target sequence per sample'

396. Premaitha submitted that the ISPs that are added to the wells on the Ion PI chip will on average have more than about one target sequence. It made two points:

i) After the emulsion PCR step, about 70% of the ISPs have no DNA, 20% are monoclonal (i.e. have multiple copies of a single sequence) and 10% are polyclonal (i.e. have multiple copies of more than one different sequence). The ISPs containing no DNA are separated from those containing DNA and only the latter are added to the wells of the Ion PI chip. Thus, on average, only 2/3rds of the ISPs added have one target sequence and 1/3rd have more than one.

ii) Even taking into account that only 80% of the wells on the Ion PI chip may contain an ISP and assuming that the polyclonal ISPs only contain two different sequences, Mr Hinchcliffe QC prepared a calculation to show the average number of DNA fragments per ISP was 1.07 on average. This calculation was put to the Claimant's expert, Professor Holmes. Premaitha said that this was based upon assumptions which were the most favourable for Illumina, and the number would probably be a little higher.

397. I do not accept Premaitha's submission. According to the PPD at [33], a reaction sample containing a polyclonal ISP cannot be analysed as it will not yield usable results. Feature (a) of claim 1 refers to reaction samples which contain 'DNA to be analysed'. Polyclonal ISPs do not contain data to be analysed, as they cannot be analysed. Therefore, the polyclonal ISPs should not be taken into account when calculating the average number of target sequences per reaction sample. Once polyclonal ISPs are excluded, each sample in the IONA test contains on average considerably less than about one target sequence per sample. A calculation submitted on behalf of Illumina shows that the average is 0.73.

398. Even if I am wrong about this, the calculation put to Professor Holmes of an average of 1.07 fragments per well is "on average not more than about one target sequence per sample" as 1.07 is "not more than about 1". Premaitha submitted that given the importance for the Quake process of ensuring that a positive well represented one target sequence only so that they can be counted, the skilled reader would not

understand that there was such flexibility in the meaning of the words of the claim. I disagree, as this appears to give no effect to the word 'about' in the claim.

399. Furthermore, I do not accept that the calculation was based on the most favourable assumptions to Illumina's case. For example, the calculation assumes that every well which does not contain an ISP has been successfully removed. If, in practice, this aim has not been achieved (see PPD at [40]), then the result of the calculation would decrease. The calculation of the figure to two decimal places has a spurious precision, as the calculation was performed using only the relatively limited information in the PPD to work from.

Target sequences (integer (b))

400. Premaitha argued that the references to "target sequences" in claim 1 make clear that insofar as the claims cover sequencing, they are limited to targeted sequencing, which requires an area of interest to be selected, amplified and then sequenced. In random sequencing, no sequence is selected and targeted.

401. Random and targeted sequencing are both processes of massively parallel, next generation sequencing. Dr Erlich explained at [225] – [234] of his First Report that the difference between them is manifested in how the sequencing libraries are prepared prior to sequencing. In random, or 'shotgun' sequencing, the sample DNA is broken up into fragments and adapter sequences are attached to each of the fragments of DNA so that PCR amplification of the whole genome library can occur and the library fragments can later be attached to a bead or site for clonal amplification and sequencing. In the case of targeted sequencing, specific sequences are pre-isolated before sequencing. Dr Erlich's evidence, which I accept, was that both methods of sequencing were common general knowledge at the priority date.

402. I do not believe that there was any technical reason why the Quake patentees would have wished to limit the claims to exclude random sequencing. Both random and targeted sequencing could have been used at the priority date, without undue burden, to put the invention into effect. Nonetheless, it is of course necessary to consider the specification to see if, on a normal interpretation, the invention has been so limited.

403. There was much debate about [0096] – [0097] of the Quake Patent. Illumina claimed that paragraph [0096] expressly discloses random sequencing. [0096] states that:

> "A methodology useful in the present invention platform is based on massively parallel sequencing of millions of fragments using attachment of randomly fragmented genomic DNA to a planar, optically transparent surface… These templates are sequenced using four-color DNA sequencing-by-synthesis technology. See, products offered by Illumina, Inc., San Diego California… "

404. Whilst Dr Erlich disagreed with Professor Lovett as to whether [0097] disclosed random sequencing, there appeared to be no such disagreement about [0096]. Dr Erlich was cross-examined about the passage which I have cited and was clear that it was talking about random shotgun sequencing:

> "Q. That is talking about random fragmentation; correct?
>
> A. Yes.
>
> Q. And that the randomly fragmented DNA is attached to the surface to create a sequencing flow cell?
>
> A. Yes, that is the kind of text I was referring to, where there is some text that looks as if it is lifted from an Illumina brochure and inserted into the text, but it seems to me that is referring to an Illumina technology.
>
> Q. Which was random shotgun sequencing?
>
> A. Yes."

405. During his re-examination, it was suggested to Dr Erlich, and he agreed, that DNA could be fragmented to make a library and could thereafter be sequenced either randomly or in a targeted way. However, the cited passage in [0096] does not refer to random fragmentation to make a library, but rather to attachment of sequences to the transparent surface in the sequencer. Following re-examination, Mr Purvis asked to cross-examine further about [0096], which I allowed. This made clear that the passage was not referring to library creation:

> "Q. You would agree the natural reading, so far as the skilled person is concerned, of this sentence is that it is describing a shotgun sequencing method, because it is talking about attaching a randomly fragmented DNA to a planar optically transparent surface. There is no reference at all to any intermediate step of library creation or anything else.
>
> A. No, I agree with that, but I just wanted to point out that it does not exclude a certain kind of targeted library."

406. I conclude that the specification expressly discloses random sequencing. Premaitha submitted that purposive construction does not require the words of a patent claim to be construed to encompass everything mentioned in the specification. However, given that the Quake Patent discloses random sequencing as "*a methodology useful in the present invention*" this is, at least, a strong indication that there was no intention to exclude it.

407. Applying a normal interpretation of the phrase '*target sequences'* in the claim, I do not consider that this excludes random sequencing. The claim cannot be limited to targeted sequencing as it is common ground that it includes digital PCR. Integer (a) of claim 1 refers to '*distributing the genetic material into reaction samples, wherein the DNA to be analysed will be either present or absent in a reaction sample'*; integer (b) refers to '*measuring the presence of different target sequences in the reaction sampl*e'; and integer (c) refers to '*counting the frequency of positive responses from target sequences*'. Accordingly, the '*DNA to be analysed'* is sequenced to enable '*target sequences*' to be detected. The target sequence is the sequence that the

method is designed to detect, and is the subject of the detection process. That is the way in which the term is used in the specification. For example, [0025] states that:

> "The presence or absence of different target sequences in the discrete samples is detected; and the results are analysed whereby the number of results from the discrete sample provide data sufficient to obtain results distinguishing different target sequences"

408. Premaitha relied on a declaration of Dr Stacey Gabriel of the Broad Institute at Harvard and MIT, served in the EPO by the proprietor of Lo 2/3 (the Chinese University of Hong Kong), which it suggested, and I accept, is consistent with its construction. In her declaration, Dr Gabriel discussed the teaching of the Quake PCT Application and concluded that it "*does not teach or suggest the use of random sequencing or subsequent alignment of random sequence reads to a reference genome*".

409. However, this declaration was filed by the proprietors of Lo 2/3 in an Opposition where the Quake PCT Application was relied upon as prior art. It was an attempt to distinguish Lo 2/3 from the Quake PCT application. I did not find it of assistance in interpreting the claims of the Quake Patent.

Integers (b) and (c) – additional issues

410. Even if, as I have found, the claims are not limited to targeted sequencing, Premaitha nonetheless contended that the IONA test does not fall within integers (b) or (c) of claim 1 for the following reasons:

    i) Because of the random nature of the sequencing performed in the IONA test, no sequences are targeted. Rather, all the DNA in the sample is randomly sequenced.

    ii) Insofar as the IONA test identifies a sequence as originating from chromosome 21 or originating from any other autosome or the X chromosome, those reads are not binary. The first stage of the IONA test produces the sequence. The software then attempts to align this to the reference genome. The outcome of this exercise will be one of three options: a unique map to one of the 22 autosomes or the X chromosome; a multiple mapping; or no mapping. These are not binary results.

    iii) For each aligned read, the system then increments the count of the chromosome to which it maps. There are 23 possible outcomes. Each sequence can be added to the count of any of chromosomes 1-22 or the X chromosome. A process that results in 23 possible outcomes does not produce "binary results".

    iv) The IONA test uses the chromosome counts after GC correction and other processing, which is after the reads have been weighted based on the region from which they originate. Therefore, each aligned sequence can contribute differently to the total count and that contribution need not be 1. This is not a binary count, but an analogue one.

v) The claim requires the target sequences to comprise sequences from two chromosomes, one which is presumed aneuploid, and a second that is presumed diploid. However, in the IONA test, although the number of reads aligning to the potentially aneuploid chromosome are counted, there is no second chromosome that is presumed diploid that is used as a reference. Rather the number of reads aligning to all the autosomes (which will include the presumed aneuploid chromosome) are counted.

i) Target sequence in the IONA test

411. In order to assess Premaitha's non-infringement case, it is necessary to set out certain aspects of the operation of IONA. The IONA test aligns the detected sequence reads with the human genome to identify the corresponding section from a chromosome to which each sequence read maps; ([PPD [48]). The IONA system holds in its memory the entire sequences of each chromosome (except, in the modified versions of IONA, the Y chromosome). There are 23 in total. Illumina submitted that the "*targets*" include 3 chromosomes which, for any given analysis, one is possibly aneuploid (13, 18, or 21) and the remaining 21 are presumed diploid.

412. The IONA test calculates the frequency of positive responses (sequence reads) from the possibly aneuploid target sequence (e.g. chromosome 21) being tested for, as well as the frequency of positive responses from the reference target sequences, in carrying out the equation that results in the "*chromosome count ratio*". Those results are statistically analysed to establish whether the ratio of frequency of positive responses given by the chromosome count ratio is sufficient to distinguish an aneuploid (as opposed to a euploid) sequence.

413. I have interpreted "*the target sequence*" in claim 1 of Quake 1 as the sequence that the method is designed to detect, i.e. which is the subject of the detection process. The target sequences detected in the IONA test include one chromosome that is possibly aneuploid and the remaining chromosomes that are presumed diploid. In my judgment, the IONA test falls within this feature of the claim

ii) – iv) Binary Results

414. The IONA system allocates to each sequence read a chromosome in order to create a table of raw aligned sequence count values setting out the number of sequence reads detected for each chromosome. Illumina submitted that these are "*binary results*" because the process separates the number of reaction samples belonging to the possibly aneuploid chromosome being tested for from those belonging to one of the other autosomes, in order to produce the figures for the equation used to give the "*chromosome count ratio*"; (PPD [93]). I accept this submission. For each chromosome which is considered in the process, the answer is a yes or a no for any given read. It is correct that reads may be assigned to multiple chromosomes, but the allocation step for each such chromosome is binary.

415. Professor Marchini explained, and it was not disputed, that a GC correction is applied so that each read is given a weighting factor when the data is analysed. However, Professor Holmes said, and I accept, that the mapping of the sequence reads to the chromosomes is the *'binary result providing differential detection'*. The sequence either maps to the target chromosome or it does not, giving binary results. These

binary results are subsequently analysed by reference to the GC weighting appropriate to each chromosome portion. Step (c) of claim 1 refers to analysing the binary results from step (b). Professor Holmes explained during his cross examination, and I accept, that step (c) may include mathematical transformations such as GC correction, which may be required to adjust for instrument-specific bias. In the IONA test, the binary results from step (b) are analysed by GC correction in step (c). In my judgment, the IONA test falls within this feature of the claim.

v) Number of target sequences

416. Step (b) of claim 1 of Quake requires that the target sequences '*comprise sequences from two chromosomes*.' Therefore, the method includes sequences from at least two chromosomes, but it may not be limited to such sequences, and may comprise sequences from other chromosomes. In the IONA test, target sequences are detected which comprise sequences from one chromosome which is possibly aneuploid and one which is presumed diploid. The claim is not limited to counting *only* one presumed diploid chromosome to act as a '*reference*'.

417. Illumina submitted that if the claim was so limited, then it would be an immaterial variant to count more than one reference, or to use all autosomes as a reference. As I have decided that the IONA test falls within the normal interpretation of the language of the claim, it is unnecessary to consider equivalents. However, in the absence of clear evidence directed to this issue, I would not have accepted Illumina's submission.

Issues of infringement of the Quake 2 Patent

418. Relying upon the same arguments that it advanced in relation to Quake 1 Premaitha submitted that:

i) The skilled team would understand claim 1 of Quake 2 (as granted and as proposed to be amended) only to cover targeted sequencing and not random sequencing.

ii) Claim 1 of Quake 2 requires a limiting dilution step.

iii) Claim 1 of Quake 2 also requires two target sequences, one of which is presumed aneuploid and the other diploid. This feature is not present in the IONA test. IONA compares the number of reads mapping to a potentially aneuploid chromosome to all the reads mapping to all the autosomes (including the potentially aneuploid chromosome).

419. I reject these submissions, for the same reasons that I rejected them in respect of Quake 1.

Title issues relating to Quake

Quake and the Quake Divisional

420. Premaitha accepted that the Second Claimant, the Board and Trustees of the Leland Stanford Junior University ("Stanford") is the proprietor of the Quake Patents. The Fourth Claimant ("Verinata") claims to have been granted an exclusive licence by Stanford under clause 3.1(A) and 3.2 of the Second Amended and Restated Co-

Exclusive Agreement ("the Co-Exclusive Agreement"). However, Premaitha challenged the purported exclusive licence on two grounds:

i) Premaitha contended that the licence granted to Verinata, although purporting to be exclusive, is not an exclusive licence within the definition of s130 of the Act because the licence does not exclude the patentee, Stanford.
ii) Alternatively, Premaitha contended that if Verinata does have an exclusive licence, the IONA test does not fall within the licensed field, on the basis that Digital PCR and similar nucleic acid amplification and detection procedures are not licensed to Verinata under the Co-Exclusive Agreement.

Is the licence granted to Verinata exclusive?

421. The following provisions of the Co-Exclusive Agreement are relevant to this issue:

i) Article 3.1(A): *'Subject to the terms and conditions of this Agreement, Stanford grants Verinata a license under the Licensed Patents in the Verinata Exclusive Field to make, have made, use, import, offer to sell and sell Licensed Products in the Licensed Territory.'*
ii) Article 3.2(A):*'The license granted under Section 3.1(A) is Exclusive, including the right to sublicense under Article 4, in the Verinata Exclusive Field during the period beginning on the Second Restatement Effective Date…'*
iii) Article 2.6: "*"Exclusive" means that, subject to Articles 3 and 5, Stanford will not grant further licenses under the Licensed Patents in the Verinata Exclusive Field in the Licensed Territory*";
iv) Article 3.4: "*…Stanford retains the right, on behalf of itself and all other non-profit academic research institutions, to practice the Licensed Patent for any non-profit purpose, including sponsored research and collaborations. …*"

422. Premaitha argued that, although the word "Exclusive" is used in article 3.1(A), the Co-Exclusive Agreement's definition of an "Exclusive" licence does not fulfil the requirements of s130(1)(b) of the 1977 Act. Article 2.6 of the Co-Exclusive Agreement merely defines "Exclusive" as meaning that Stanford will not grant *further* licences in respect of the Quake patents in the Verinata Exclusive Field. This does not exclude Stanford, which retains the full unfettered right to practice the invention for itself in any field and for any reason.

423. I do not accept this argument. It is necessary to read the Agreement as a whole, rather than a single clause in isolation. Clause 2.6 is expressly made subject to clauses 3 and 5. Clause 3.4 defines the extent of the rights retained by Stanford. It does not retain the full unfettered right to practice the invention for itself in any field and for any reason, but only for non-profit purposes. If Premaitha's interpretation of Article 2.6 was correct, then the retention of rights in Clause 3.4 by Stanford to itself, in respect of non-profit purposes, would be redundant. It would already have the right to practice the invention for any purpose.

424. Premaitha pointed out that Article 3.4 reserves to Stanford, not only for itself, but also additionally for all other non-profit academic research institutions, the right to practise the invention in each of the Quake patents for any non-profit purpose. Verinata acknowledged in Article 3.4 that the Howard Hughes Medical Institution has been

granted a licence to the Licensed Patents (including the Quake application) under the Co-Exclusive Agreement.

425. As discussed in relation to the title issue concerning Lo 1, the definition of 'exclusive licence' in section 130(7) extends to a licence which confers on the licensee *'and persons authorised by him'* (to the exclusion of all *other* persons) any right in respect of the invention. Article 3.4 retains to Stanford, as a party to the agreement, the right to authorise others to practise the Quake inventions. It is an exclusive licence within the meaning of section 130(7).

426. In addition, Stanford's right to authorise other persons is limited to "all other non-profit academic research institutions, to practice the Licensed Patent for any non-profit purpose, including sponsored research and collaborations". It does not extend to authorisation of any third party for commercial purposes. The licence an exclusive licence of the right to exploit for commercial purposes, and, according to section 130(7) an exclusive licence may be granted in respect of any right.

Does the IONA test fall outside the licensed field?

427. The following provisions of the Co-Exclusive Agreement are relevant to this issue:

i) Article 2.20 which defines the Verinata Exclusive Field as meaning "*Genetic Analysis by Nucleic Acid Sequencing for research and diagnostic applications*";

ii) Article 2.8 which defines Genetic Analysis as meaning "*the use of nucleic acid sequence information, whether resulting from Nucleic Acid Sequencing or Digital Nucleic Acid Amplification, as applicable, to identify genetic conditions, disorders or characteristics of a patient or foetus…*";

iii) Article 2.18 which defines Nucleic Acid Sequencing as:

"All methods for determining the order of nucleotides in a nucleic acid molecule, which methods are capable of determining the nucleotide sequence of nucleic acid and having an unknown sequence and greater than fifteen base pairs in length, including, without limitation, Sanger sequencing, sequencing by hybridization, sequencing by synthesis, single molecule sequencing and sequencing by ligation. Nucleic Acid Sequencing does not include digital PCR or similar nucleic acid amplification and detection procedures comprising steps in which a sample potentially containing target nucleic acids is diluted or distributed into reaction samples containing zero, one or more target nucleic acids such that, if a reaction sample contains a target nucleic acid, a signal is produced by the reaction conditions within the reaction sample, and the reaction samples producing a signal are counted as positive and/or the reaction samples that do not produce a signal are counted as negative";

v) Article 3.1(B) which grants a licence to Verinata "*in the Co-Exclusive Field*";

vi) Article 2.4 which defines "*Co-Exclusive Field*" as meaning "*research and diagnostic applications other than (i) Genetic Analysis by Nucleic Acid Sequencing or (ii) Genetic Analysis by Digital Nucleic Acid Amplification*".

428. Premaitha advanced a somewhat convoluted argument to explain why the IONA test falls outside the Licensed Field. It said that the IONA test is alleged to infringe the claims of Quake, which are directed to digital PCR, albeit digital PCR that uses direct sequencing in the measuring step. The definition of "Verinata Exclusive Field" excludes (by operation of the definition of the term "Nucleic Acid Sequencing") digital PCR and "similar nucleic acid amplification and detection procedures", which are then defined in functional terms that map directly on to the claims of the Quake patents. As such, Premaitha argued that digital PCR and similar nucleic acid amplification and detection procedures are not licensed to Verinata. Rather, such techniques are licensed to Fluidigm (see clause 2.7 of the Co-Exclusive Agreement).

429. Premaitha submitted that if the IONA process infringes the claims of the Quake patents, which are directed to digital PCR, it is because performing digital analysis by sequencing is a similar technique to digital PCR. As such, the IONA process test falls outside the scope of the Verinata Exclusive.

430. I do not accept these submissions. The definition of Nucleic Acid Sequencing is a broad one. Clause 2.18 states that, subject to its express exclusion of digital PCR or similar nucleic acid amplification and detection procedures comprising defined steps: "*"Nucleic Acid Sequencing" means all methods for determining the order of nucleotides in a nucleic acid molecule, which methods are capable of determining the nucleotide sequence of a nucleic acid having an unknown sequence…"*

431. The definition distinguishes between sequencing and digital PCR. The Quake 1 Patent covers both digital PCR and sequencing. The Patent is within the definition (and hence within the Verinata Exclusive Field) insofar as it covers sequencing, but not insofar as it covers digital PCR. The Quake 2 Patent is limited to sequencing, so it is wholly within the Exclusive Field. The IONA test uses sequencing not digital PCR. It therefore falls within rights exclusively licensed to Verinata.

PART C – JUDGMENT IN RELATION TO THE LO 2 AND LO 3 PATENTS

Issues in dispute

432. The issues which remained in dispute at the conclusion of the trial are:

    i) Obviousness in the light of Shimkets.

    ii) Lack of priority; if this challenge is successful, Premaitha is entitled to rely upon "Digital PCR for the molecular detection of foetal chromosomal aneuploidy" by Lo *et al.* August 2007 *PNAS*, Vol 104, No. 32, 13116-13121 ("Lo 2007"). Illumina accepts, for the purposes of these proceedings only, that if the Lo 2 and 3 Patents are not entitled to priority then all of their claims are invalid in light of Lo 2007.

    iii) Infringement by the IONA test and non-infringement by the two proposed alternative methods.

    iv) Further issues as to whether the Claimants have title to bring these proceedings.

Additional common general knowledge in 2007

433. Between the Quake and Lo 2/3 priority dates, the availability of MPS platforms increased. New platforms that became available were the Illumina (Solexa) Genome Analyzer and Applied Biosystems SOLiD system. In addition, the Fluidigm Biomark digital PCR platform was a microfluidic device that improved the throughput of dPCR, and this was common general knowledge. It has 12 panels each with 765 reaction chambers, allowing 9,180 reactions to be performed on each run.

The Lo 2 Patent

434. Lo 2 is entitled "*Diagnosing foetal chromosomal aneuploidy using genomic sequencing*". At [0004], Lo 2 explains that the prenatal detection of foetal chromosomal aneuploidies using cell-free foetal DNA in maternal plasma has presented a considerable challenge because of the high background of maternal nucleic acids and the difficulty in deriving dosage information of genes or chromosomes within the foetal genome. Lo 2 describes several approaches that have been taken to overcome this challenge, and their limitations to foetuses which are heterozygous for the targeted polymorphism. At [0008] - [0010], Lo 2 refers to limitations of the digital PCR approach because of the small number of data points and statistical fluctuations. It sets out the object of the invention at ([0011]):

> "It is therefore desirable that noninvasive tests have high sensitivity and specificity to minimize false negatives and false positives, respectively. However, foetal DNA is present in low absolute concentration and represent a minor portion of all DNA sequences in maternal plasma and serum. It is therefore also desirable to have methods that allow the noninvasive detection of foetal chromosomal aneuploidy by maximizing the amount of genetic information that could be inferred from the limited amount of foetal nucleic acids which exist as a minor population in a biological sample containing maternal background nucleic acids."

435. There is a brief summary of the invention at [0012] - [0017]. It provides methods for determining whether a nucleic acid sequence imbalance (e.g. chromosome imbalance) exists within a biological sample obtained from a pregnant female. This involves detecting an imbalance in sequences obtained from the potentially aneuploid chromosome compared to those from one or more euploid reference chromosomes. A pre-determined number of sequences are obtained by performing random sequencing on the DNA sample. Each sequence is aligned to the human genome by a computer system. The number of sequences aligned to a potentially aneuploid chromosome is obtained, as are the number of sequences aligned to one or more second, or reference, chromosomes. A parameter is determined from these amounts, the parameter representing the relative amount between the first and second amounts. This parameter is then compared to a cut-off and based upon this comparison, a classification of whether a foetal chromosomal aneuploidy exists in the first chromosome is determined.

436. [0047] - [0087] provide a detailed description of the method of the invention. [0053] states that "*In one embodiment the random sequencing is done using massively*

parallel sequencing." Examples of suitable platforms are said to include, amongst others, the 454 platform, the Illumina Solexa platform, and the SOLiD system. [0056] explains that the second chromosome(s) can be either a single chromosome or all the other chromosomes beside the first one.

437. [0059] explains that a parameter is determined which represents the relative amount between the amounts of the first chromosome and the second chromosome(s). It discloses that:

> "[0059] … The parameter may be, for example, a simple ratio of the first amount to the second amount, or the first amount to the second amount plus the first amount. In one aspect, each amount could be an argument to a function or separate functions, where a ratio may be then taken of these separate functions. One skilled in the art will appreciate the number of different suitable parameters."

438. [0061] - [0062] provide suitable ways for determining appropriate cut-off values, to which the parameter is compared. Reference is made to statistical methods such as Bayesian-type analysis, sequential probability ratio testing (SPRT) and the use of confidence intervals. One example given is where the parameter is the fractional representation of the clinically relevant chromosome, which is compared to a reference range established in pregnancies involving normal foetuses. Such a reference range may be adjusted with respect to the foetal fraction determined using Y-chromosome specific markers, foetal-specific epigenetic markers or analysis of SNPs.

439. [0063] states that:

> "Based on the comparison, a classification of whether a foetal chromosomal aneuploidy exists for the first chromosome is determined. In one embodiment, the classification is a definitive yes or no. In another embodiment, a classification may be unclassifiable or uncertain. In yet another embodiment, the classification may be a score that is to be interpreted at a later date, for example, by a doctor."

440. Figure 2 and [0077] - [0079] describe a flow chart for performing prenatal diagnosis of a foetal chromosomal aneuploidy according to one embodiment of the invention. In step 220, the number N of sequences to be analysed is calculated for a desired accuracy, for example based on the foetal fraction such that N would increase when the foetal fraction is low and vice versa. N may be a fixed number or a relative number. In another embodiment, the number of sequences to be analysed is that which is known to be adequate for accurate diagnosis – for example N could be made sufficient even for samples with foetal DNA concentrations at the lower end of the normal range.

441. Paragraph [0088] onwards is an example of the described method performed on samples for eight pregnant women in their first or second trimesters, four of whom were carrying a normal (euploid) foetus and four of whom were carrying a foetus with trisomy 21. In each case, the percentage of sequences that mapped to chromosome 21

is depicted in Figure 3A. Figure 4A compares the percentage of sequences that aligned to individual chromosomes in a trisomy 21 pregnancy and in a normal pregnancy. The difference in representation of each chromosome is shown in Figure 4B – chromosome 21 sequences are over-represented by 11% in the plasma of the woman carrying a trisomy 21 foetus ([0097]).

442. The correlation between over-representation of chromosome 21 sequences and foetal fraction (in trisomy 21 male foetuses) is reported in Figure 5 and [0099]. It is disclosed that the degree of over-representation of chromosome 21 sequences in maternal plasma is related to the fractional concentration of foetal DNA in the maternal plasma sample. Therefore, cut-off values in respect of the degree of chromosome 21 sequence over-representation relevant to the fractional foetal DNA concentrations could be determined to identify pregnancies involving trisomy 21 foetuses. Foetal fraction can be determined either by analysing the representation of Y chromosome sequences in male foetuses ([0099]) or through quantification of polymorphic differences between the mother and the foetus ([0102]).

443. Claim 1 of Lo 2 as proposed to be amended unconditionally is as follows:

> "A method for performing prenatal diagnosis of a foetal chromosomal aneuploidy in a biological sample obtained from a female subject pregnant with a foetus, wherein the biological sample <u>is maternal plasma or serum and wherein the sample</u> includes cell-free nucleic acid molecules from the female subject and the foetus, the method comprising:
>
> performing a random sequencing on at least a portion of a plurality of the nucleic acid molecules contained in the biological sample to obtain a pre-determined number of sequences, wherein the sequences represent a fraction of the human genome;
>
> aligning, with a computer system, each sequence to a human genome;
>
> determining a first amount of sequences identified as being aligned to a first chromosome;
>
> determining a second amount of sequences identified as being aligned to one or more second chromosomes;
>
> determining a parameter from the first amount and the second amount; wherein the parameter represents a relative amount between the first and second amounts; and
>
> comparing the parameter to one or more cut-off values, to determine a classification of whether a foetal chromosomal aneuploidy exists for the first chromosome."

The Lo 3 Patent

444. Lo 3 has a specification that is identical to the Lo 2 Patent for all material purposes. However, the claims are somewhat different, and I shall consider relevant differences in the context of infringement. Claim 1 of Lo 3 is as follows:

> "A method for performing prenatal diagnosis of a foetal chromosomal aneuploidy in a biological sample obtained from a pregnant female subject, wherein the biological sample is maternal plasma and includes nucleic acid molecules, the method comprising:
>
> receiving the biological sample;
>
> randomly sequencing at least a portion of a plurality of the nucleic acid molecules contained in the biological sample, wherein the sequenced portion represents a fraction of the human genome;
>
> based on the sequencing:
>
> determining a first amount of a first chromosome from sequences identified as originating from the first chromosome;
>
> determining a second amount of one or more second chromosomes from sequences identified as originating from one of the second chromosomes;
>
> determining a parameter from the first amount and the second amount;
>
> comparing the parameter to one or more cut-off values; and
>
> based on the comparison, determining a classification of whether a foetal chromosomal aneuploidy exists for the first chromosome."

Proceedings in the EPO

445. Lo 2 was the subject of opposition proceedings at the EPO in which Premaitha intervened. Lo 2 was upheld by the Opposition Division on the basis of an auxiliary request that corresponds to the amendments which are sought unconditionally in these proceedings. These address certain added matter objections advanced by Premaitha, and the amendments are not opposed. The Board of Appeal upheld the decision of the Opposition Division. Their written decision is not yet available. The Opposition Division held that Lo 2 was not entitled to claim priority from the Priority Document; and the Board of Appeal reached the same conclusion. In the EPO, that conclusion did not result in a finding of invalidity. Premaitha relies on Lo 2007 as intervening prior art for inventive step. For the purposes of these proceedings only, Illumina does not seek to defend any of the claims of Lo 2 or Lo 3 if they are not entitled to priority.

Obviousness in the light of Shimkets

446. Premaitha contended that Lo 2 and Lo 3 were invalid over Shimkets for the same reasons as advanced in respect of Quake 1 and Quake 2, and for the purposes of its obviousness attack, did not seek to distinguish between them. For the same reasons that I rejected the obviousness attack in respect of Quake 1 and 2, I reject it in respect of Lo 2 and 3.

Lo 2 and 3 – entitlement to priority

447. It is unnecessary to set out extensive extracts from the Lo 2 Priority Document as it is primarily concerned with digital PCR and it is common ground that most of its disclosure is irrelevant to the challenge to priority advanced by Premaitha.

448. Premaitha submitted that Lo 2 was not entitled to its claimed priority date for three reasons:

i) there was no disclosure in the priority document of random sequencing by a method which did not involve an emulsion PCR step;

ii) there was no disclosure in the priority document of obtaining a predetermined number of sequences; and

iii) there was no disclosure in the priority document of obtaining the sequences representing a fraction of the human genome.

In respect of Lo 3, which does not require obtaining a predetermined number of sequences, Premaitha relied on points (i) and (iii) above.

Passages in the Priority Document relied upon by Illumina

449. Illumina relied on [0132] and [0192] of the Priority Document in answer to these objections. These paragraphs disclose:

> "[0132] Additionally, there are now a number of alternative approaches to the manual setup of digital real-time PCR analysis as used in the current study for conducting digital PCR. These alternative approaches include microfluidics digital PCR chips (Warren, L et al. 2006 *Proc Natl Acad Sci USA* 103, 17807 - 17812; Ottesen EA et al. 2006 *Science* 314, 1464-1467) emulsion PCR (Dressman D et al. 2003 *Proc Natl Acad Sci USA* 100, 8817 - 8822), and massively parallel genomic sequencing (Margulies M et al 2005 *Nature* 437, 376 - 380), etc. With the use of these methods, digital RNA SNP and digital RCD could be performed rapidly on a large number of sample, thus enhancing the clinical feasibility of the methods proposed here for non-invasive prenatal diagnosis."
>
> …
>
> "[0192] The variant of digital PCR is the performance of massively parallel genomic sequencing using emulsion PCR in a sequencing machine such as the Roche GS20 system (http://www.454.com/about-454/partners.asp) the Applied

> Biosystems 'supported oligo ligation detection' (SOLiD) and the Illumina Solexa sequencing technology. The general principle of this strategy is that if one is to do random sequencing of DNA fragments that are present in the plasma of a pregnant woman, then one would obtain genomic sequences which would originally have to come from either the foetus or the mother. A proportion of such sequences would be from the chromosome involved in an aneuploidy such as chromosome 21 in this illustrative example… ”

The decision of the Opposition Division

450. As to random sequencing, the Opposition Division rejected the patentee's argument and said at [3.8] that:

> "The opposition division finds that in the cited paragraphs "random sequencing" is not used in a general context applicable to all embodiments of the invention, but in sections relating to specific embodiments, namely "digital (real-time) PCR" and "massively parallel genomic sequencing" (see paragraphs [0132] and [0192] of the priority document. The expression "the general principle of this strategy" in paragraph [0192] can only be understood in relation to "the variant of digital PCR [which] is the performance of massively parallel genomic sequencing using emulsion PCR" and would not be read by the skilled person to apply to the broad concept as in present claim 1."

451. As to a fraction of the human genome, the Opposition Division rejected the patentee's argument and said at [3.9] that:

> "The opposition division also considers the expression "fraction of the human genome" to lack priority because even if one would consider that the sequencing methods of [0192] inevitably yielded "a fraction of the human genome" the disclosure of [0192] would still remain limited to a specific embodiment of the invention, namely "Massive parallel genomic sequencing using emulsion PCR" (see heading of para. [0192])… ”

The same objections to priority were argued in the Board of Appeal, which upheld the decision of the Opposition Division and found that the Lo 2 Patent was not entitled to its claimed priority date. The Board's reasons for this decision are not yet available.

(i) Random sequencing

<u>The submissions of the parties in outline</u>

452. As to [0132], Premaitha submitted in relation to random sequencing that:

i) The Priority Document is only concerned with Digital RNA-SNP and Digital RCD. Digital RNA-SNP seeks to distinguish foetal from maternal DNA, whereas Digital RCD does not. It is clear from the last sentence of [0132] that there is no disclosure of methods going beyond these techniques, and the alternatives referred to are limited to use within the confines of the methods disclosed.

ii) There is no disclosure of how to apply these techniques to the Digital RNA-SNP and Digital RCD methods. The skilled person would have to use common general knowledge to do this and this does not amount to a clear and unambiguous disclosure.

iii) The MPS method disclosed in Margulies (the publication referred to in [0132]) is emulsion based. [0132] takes the case for priority no further than [0192] which appears under the heading "Massively Parallel Genomic Sequencing Using Emulsion PCR".

453. Illumina responded that:

i) The claims of Lo 2/3 are directed to digital RCD using random sequencing. This is precisely what is taught as one of the alternatives in [0132] of the priority document.

ii) There is, and can be, no suggestion, that the skilled person would have been unable to apply massively parallel genomic sequencing to the digital RCD method using his common general knowledge.

iii) The skilled person would not understand the massively parallel sequencing method disclosed in [0132] to be limited to the specific method used by Margulies, which was emulsion based. Margulies would be understood to be an example of the method of massively parallel sequencing generally, and there was nothing in the paragraph that would lead the skilled person to conclude that the use of massively parallel sequencing was confined to the 454 GS20, discussed in Margulies.

Discussion

454. I shall apply the legal principles which I have set out above. In particular, the skilled person must be able to derive the subject matter of the claim directly and unambiguously, using common general knowledge, from the Priority Document as a whole; however, the analysis is not formulaic and the question is whether the priority document given to the skilled person essentially the same information as forms the subject the Lo 2/3 claims and enabled him to work the invention in accordance with those claims; and when testing for priority, one must guard against simply asking whether the features called for by the claim are present in the priority document. The test has more substance, and is less formal than that.

455. Margulies describes the use of the 454 GS20 Sequencer for the purpose of sequencing a small bacterial genome. There is no doubt that this sequencer uses emulsion PCR. This was common general knowledge at the priority date, and was expressly disclosed in Margulies. The key question is whether Margulies is cited as an example of a

platform suitable for use in the invention of the Priority Document, or whether the disclosure is confined to the use of that platform, or that platform together with other platforms which used emulsion PCR.

456. One factor which could suggest that the disclosure of the priority document is confined in this way is paragraph [0192]. [0192] appears in a section entitled "Massively Parallel Genomic Sequencing Using Emulsion PCR", and is the only other discussion of massively parallel sequencing in the document. So, it might be thought that the Priority Document, consistently, limits its disclosure to this specific method.

457. I do not believe that this is the case. In contrast to [0192], [0132] appears as part of a general disclosure of alternatives to digital PCR for use in the clinical applications discussed in the Priority Document, including the detection of foetal chromosomal aneuploidy. It appears in a section beginning at [0129] entitled "*Increasing %, Multiple Markers, and PCR Alternatives*". [0129] – [0131] are concerned with methods to increase the foetal fraction. [0132] is concerned with alternative approaches to the manual setup of digital real-time PCR analysis, which are said to enable the performance of digital RNA-SNP and digital RCD rapidly on a large number of samples, thus enhancing the clinical feasibility of the proposed methods for NIPD. The alternative approaches are not confined to a specific embodiment, but apply generally to the invention in the Priority Document.

458. [0132] lists a number of non-exclusive alternatives, namely microfluidics digital PCR chips; emulsion PCR; and massively parallel genomic sequencing. In each case, it provides a literature reference, and in one case, more than one reference. I do not consider that the skilled person would read any of those alternatives as confined to the specifics of the publication cited in that paragraph. Rather, each publication or publications would be viewed as examples of the alternative techniques which have been identified. This interpretation is supported by two further matters.

459. First, the document must be read as a whole, and [0192] refers to a number of alternative platforms to the 454 GS20 sequencer. Margulies is only concerned with the 454 GS20. This must be by way of example, as there are further example platforms expressly disclosed in the Priority Document. Of course, it could be said that they are all examples of sequencers which use emulsion PCR, although even this is not, in fact, correct (see below). But the reference to other platforms is not consistent with the argument that the disclosure is confined to Margulies.

460. Secondly, it was common general knowledge that other platforms were available which were suitable for massively parallel sequencing. Illumina submitted, and Premaitha accepted, that the Illumina Solexa system used "*bridging PCR*" amplification, not emulsion PCR. This sequencer is expressly referred to in [0192]. Although it was agreed that the Illumina Solexa system was common general knowledge, there was a dispute about whether it was also well known at the priority date that it used bridging PCR amplification.

461. Premaitha contended that this was not common general knowledge. However, Dr Erlich's evidence did not support this contention. At paragraphs [434] – [441] of his first report, Dr Erlich considered additional common general knowledge between the Quake and the Lo 2/3 priority dates. He explained that awareness and availability of

the various next generation sequencing platforms continued to increase. He contrasted the method used by the Illumina Solexa Sequencer with the 454 method. His view was that the Illumina method, which was not emulsion PCR, was common general knowledge at the Lo 2/3 priority date. This was not challenged by Illumina, as it was a part of its case that the NGS platforms were well known at the priority dates, and that if obvious, the inventions would have been made before.

462. I accept Dr Erlich's evidence on this issue and I find that it was common general knowledge that the Illumina Solexa did not use emulsion PCR. No technical reason was suggested by Premaitha as to why the patentee would have chosen to confine himself to platforms which used emulsion PCR in the Priority Document, and I do not consider that this is the effect of its disclosure. The skilled person would read [0132] in the light of the common general knowledge and would not consider that the reference to massively parallel sequencing was intended to exclude non-emulsion PCR methods.

463. I should make it clear that if the only disclosure in the Priority Document of massively parallel sequencing was at [0192] then I would have agreed with Premaitha that the Lo 2/3 Patents were not entitled to their claimed priority date. Paragraph [0192] appears in a section entitled "Massively Parallel Genomic Sequencing Using Emulsion PCR", and it immediately follows that title. Even though it refers to the Illumina Solexa Sequencer, the disclosure, on its own, is not sufficiently clear. This paragraph is not a general disclosure but one which is confined to emulsion PCR. However, that is not the case if the document is read as a whole, for the reasons which I have considered above.

464. As to the other arguments, I accept Illumina's submissions. In particular, Dr Erlich explained that digital RCD detects an over-representation of signal from the target sequence on the potentially aneuploidy chromosome. Detection of over-representation enables a conclusion to be reached as to the presence of aneuploidy or otherwise in the chromosomes of interest. The claims of Lo 2/3 are directed to digital RCD using random sequencing. This is taught as one of the alternatives in [0132] of the Priority Document. It is true that there is no disclosure of how to apply massively parallel genomic sequencing to the digital RCD method. However, the skilled person would have no difficulty in implementing the method, using common general knowledge.

(ii) A fraction of the human genome

465. Illumina submitted that it was common general knowledge at the priority date that random sequencing necessarily resulted in a fraction of the gene being sequenced. This was because the new generation sequencers had a throughput that was well under a genome's worth. This was supported by the evidence of Dr Erlich at [242], [244], [438] and [441] of his first report and by the evidence of Professor Lovett at [165] of his second report. Thus, it was said that the priority document implicitly disclosed the use of random sequencing to obtain sequences representing a fraction of the human genome – no other conclusion would make sense.

466. However, Premaitha pointed out that Margulies (only) discloses the sequencing of a whole genome (and does not disclose sequencing of a fraction of the genome). Therefore, the use of a random sequencing method at the priority date does not necessarily result in a fraction of the genome being sequenced. It is correct that

Margulies sequenced a complete genome. However, this was a small bacterial genome whereas the Priority Document is concerned with the human genome. Dr Erlich explained at [267] of his first report that the bacterial genome sequenced in Margulies was 580 kbp, whereas the human diploid genome is about 10,000 times larger. The 454 GS20 sequencer would need to have been run for a vast number of hours to sequence the whole human genome, and the disclosure of the Priority Document would not be read as contemplating this.

467. The purpose for which massively parallel sequencing is disclosed in the two documents is quite different. Margulies set out to sequence the entire genome of a bacterial genome. Paragraph [0132] of the Priority Document discloses the use of massively parallel genome sequencing to sequence human DNA in order to detect foetal aneuploidy. The detection of human foetal aneuploidy does not require sequencing of the entire genome, and this would be plain to the skilled person - it would be pointless. Therefore, I reject this attack on entitlement to priority.

(iii) a predetermined number of sequences

468. This issue applies to Lo 2 only as it is not a requirement of the claims of Lo 3. Premaitha contended that there was no disclosure in the priority document of obtaining a predetermined number of sequences and it drew attention to the decision of the Opposition Division which denied priority for this reason as well (although it is not clear that this was independent of its conclusions on MPS using emulsion PCR).

469. Illumina submitted that "pre-determined" in claim 1 of Lo 2 means a minimum number of sequences to give the test statistical significance. It said that this concept is plainly disclosed in the Priority Document. It is implicit in the teaching to use random sequencing for the detection of foetal chromosomal aneuploidies and it is self-evident that one will use a sufficient number of sequences for that purpose. The concept was also said to be explicitly disclosed in the Priority Document, which sets out the way of performing statistical calculations to determine the power/throughput required to allow the detection of foetal chromosomal aneuploidy to the desired level of confidence. It relied upon:

i) paragraph [0129] and Figure 12 which describe the number of reactions needed to classify samples as euploid or trisomic at different foetal fractions; and

ii) [0146]-[0150] where the Priority Document explains how to perform the calculation and work out the number of samples for any foetal fraction and any other assumptions, especially [0150] where the requisite number of reaction wells is established (predetermined).

470. I accept Illumina's submissions on this issue. The skilled person would know that, in order to use massively parallel sequencing for the detection of foetal chromosomal aneuploidies, it would be necessary to use a sufficient number of samples for this purpose. 'Predetermined', in the context of the claims, means the minimum number of sequences to give the test statistical significance. This must be done, in order to make the result reliable, and the skilled person would be aware of this, as a matter of common general knowledge.

Conclusion

471. This has been a difficult issue to resolve. Although I have reached the same overall conclusion as to the validity of the Lo 2 Patent, as proposed to be amended, as the Board of Appeal, I have differed from the Board in respect of entitlement to priority. I conclude that Lo 2 and Lo 3 are entitled to their claimed priority date.

Title issues in relation to Lo 2

472. Illumina claimed that its rights as exclusive licensee under Lo 2 are recorded in the Pooled Patents Agreement and derive from the amended CUHK 2008 Licence and Novation Agreements. Lo 2 is listed in Annex IV to the Pooled Patents Agreement as a 'Sequenom In-Licensed Patent', defined as *'all Patents in-licensed by Sequenom or its Affiliates immediately prior to the Effective Date under, and as set forth in, the CUHK Licenses (2008/2011)'.*

473. The 'Sequenom In-Licensed Patents' are owned by the Chinese University of Hong Kong and were licensed to Sequenom under the CUHK Licences (2008/2011). The CUHK Licences (2008/2011) were amended and Sequenom assigned and novated these licences to Illumina.

474. Premaitha's argument focused upon clause 2.4 of the CHUK licence which states that:

> "2.4 University reserves the right to:
> 2.4.1 use and develop any of the Inventions and the Prospective Patent solely for academic research and publication purposes at all times provided that University provides a copy of any manuscript to Licensee, at the time of submission, for any publications submitted to a journal indexed by the Institute of Scientific Information; and to extend the academic research and publication rights, set forth above, to other collaborating academic organisations in whatever countries.
> 2.4.2 forthwith upon the request of the Hong Kong SAR Government (the "Government") unconditionally grant to the Government an irrevocable, non-exclusive, perpetual world-wide, freely transferable, sub-licensable and royalty free license to use the Invention in such manner and for such purposes as may be decided by the Government. Such request will be made by the Government when in the opinion of the Government:
> (a) the public mission of the Commissioner for Innovation and Technology of the Government or any person authorized to act on his behalf needs to be fulfilled; or
> (b) it is in the public interest to do so."

475. Premaitha argued that since CUHK had reserved rights to use and develop Lo 2 and Lo 3 for academic research and publication at all times, the licence was not exclusive to Illumina. My conclusion on this issue is the same as in relation to the Quake Patents. The reservation does not extend to authorisation of any third party for commercial purposes. The licence an exclusive licence of the right to exploit for commercial purposes and, according to section 130(7) an exclusive licence may be in respect of any right.

476. Premaitha also relied on the reservation by CUHK of the right to grant to the Hong Kong Government a non-exclusive licence. However, the right to grant a licence to the Hong Kong Government is conditional and contingent on a request being made,

which has not happened. The licence to Illumina remains exclusive since no other party has a licence nor is CUHK contractually able to grant a licence to any other party.

Lo 2 – issues of infringement

477. Premaitha argued that the IONA test:

i) is not a method of performing a prenatal diagnosis;

ii) does not align each sequence to a reference genome;

iii) does not satisfy the parameter/cut-off requirements of claim 1 of Lo 2.

i) A method of performing a prenatal diagnosis

Construction

478. Premaitha submitted that the IONA test is not a method of performing a prenatal *diagnosis*. It is a method of performing a prenatal *screening*, which falls outside the claims. It argued that a screen is typically less definitive than a diagnostic test, in that a screen involves an assessment of risk that a condition exists, whereas a diagnosis should provide a definitive determination that it does.

479. Illumina submitted that the terms 'diagnostic test' and 'screening' are not sharply defined and depend on context. This is also the case in relation to 'a method of diagnosis'. In the context of the description and claims, it was used in a broad sense to include tests which did not provide a definitive determination.

480. Premaitha relied upon the NHS definition of screening, which states that:

> "Screening is the process of identifying healthy people who may be at increased risk of disease or condition.
>
> The screening provider then offers information, further tests and treatment. This is to reduce associated risks or complications."

Discussion

481. Professor Hogge agreed that the NHS definition of screening was correct and also applied in the United States. He agreed that in a screen it is desirable primarily to minimise false negatives, as false positives can be catered for at a later stage and that (in most cases) diagnosis is confirmatory. He considered that the gold standard to confirm trisomy in 2006 was microscopic karyotyping. He accepted that if a screen was going to be used for the entire population then it would be necessary to follow it with a confirmatory test, at least in low risk patients.

482. Professor Avent's evidence was that the guidance in the UK is that a non-invasive prenatal test is a screening test on the basis of which a decision should not be taken without an invasive test. He explained that such tests are diagnoses of the placenta which are not necessarily a reflection of the foetal genotype. The outcome of tests are

complicated by conditions such as confined placental mosaicism which occurs in 1-2% of pregnancies and leads to inaccurate results. There must be procedures in place to ensure that a test is not incorrectly scored as a positive.

483. I accept that the distinction between a screen and a diagnostic test contended for by Premaitha is commonly made, and was commonly made at the priority date. However, I do not accept that this is the only way in which those terms could be used, nor that the distinction between them referred to by Premaitha is a rigid one; it is context dependent. Prof. Hogge explained that whether a test result is used diagnostically depends entirely on the context, with a considerable degree of overlap between the two. He gave two examples:

   i) CVS, which is definitely diagnostic, was known to give false negatives and false positives at rates of less than 1%. A positive result in CVS is often followed by a confirmatory amniocentesis before a medical intervention is taken.

   ii) Ultrasound was originally intended to be used as a precursor to amniocentesis, but in practice it was found that ultrasound was treated as sufficiently definitive by many patients as a basis for clinical decisions. The same test can therefore be characterised as a screening and a diagnostic test, depending on the context.

484. Professor Avent maintained his position during cross examination that a test which did not produce definitive results, and which might lead to a further confirmatory test, would always be described as a screening test, and not a diagnostic test. However, I prefer the evidence of Professor Hogge on this issue, for the reasons that he gave. I do not accept that these terms were mutually exclusive, nor that they were used with the precision that Professor Avent suggested.

485. Since the terms are context dependent, it is necessary to see how the term ‘diagnostic test’ is used in the specification. Both sides relied upon [0003] of the Lo 2/3 specification which discloses that:

> “Conventional prenatal diagnostic methods of a foetal chromosomal aneuploidy, e.g., trisomy 21, involve the sampling of foetal materials by invasive procedures such as amniocentesis or chorionic villus sampling, which pose a finite risk of foetal loss. Noninvasive procedures, such as screening by ultrasonography and biochemical markers, have been used to risk-stratify pregnant women prior to definitive invasive diagnostic procedures. However, these screening methods typically measure epiphenomena that are associated with the chromosomal aneuploidy, e.g., trisomy 21, instead of the core chromosomal abnormality, and thus have suboptimal diagnostic accuracy and other disadvantages, such as being highly influenced by gestational age.”

486. Premaitha argued that this passage draws a distinction between screening and diagnosis. It refers to conventional prenatal diagnostic measures such as amniocentesis and CVS, and contrasts them with noninvasive methods such as

screening by ultrasonography and biochemical markers. However, a positive result in CVS is often followed by a confirmatory amniocentesis before a medical intervention is taken. On Premaitha's case, this would indicate that it should properly be characterised as a screening test, but the Patents regards it as a diagnostic test. I do not consider that the patentee is using these terms in paragraph [0003] with the precision suggested by Premaitha.

487. Furthermore, [0112] of the specification states that the sequencing of about 0.6% of the human genome "*may represent the minimal amount of sequencing required for diagnosis with at least 95% accuracy in detecting foetal chromosomal aneuploidy for any pregnancy*." On Premaitha's construction, this should be classified as a screening test, as it is, potentially, only 95% accurate and a further confirmatory test would be required. Yet the Patent uses the word 'diagnosis' in this context.

488. Stepping back from this close analysis of the text, if Premaitha's construction were correct, then the inventions of Lo 2/3 would be concerned with, and confined to, a test which, of itself, enabled a decision to be made as to whether to terminate a pregnancy. There is nothing in the specification which indicates that this is the case, and I do not believe that this is how the skilled person would understand the inventions of the Lo 2/3 Patents. At [191] of his First Report, Professor Avent stated that "*the Lo II patent describes the use of an NGS methodology to screen maternal plasma or serum or the extracellular foetal DNA to indicate aneuploidy.*" Although his report then suggests that the patent distinguishes between diagnostic and screening tests, I see no technical reason why the patentee would have wished to limit his invention in this way. The skilled person would consider that a further confirmatory test might well be required before termination, following a positive result in the test disclosed and claimed in the Lo 2/3 Patents.

The IONA tests

489. Premaitha contended that the IONA test only provides an assessment of the risk of foetal aneuploidy, as opposed to a definitive determination, and merely informs the decision as to whether to undertake further testing, for example by amniocentesis. Accordingly, it argued that the IONA test is not a method for performing prenatal diagnosis of foetal aneuploidy. Professor Avent characterised it as a "*highly accurate screening technique*". This issue depends on the correct interpretation of this term, as used in the patents. Since I have rejected Premaitha's construction of the term "*method for performing prenatal diagnosis*" in the claims of the Lo 2/3 Patents, I do not accept its non-infringement argument.

490. The IONA test determines the risk of a foetus being aneuploid for chromosomes 13, 18 and 21, expressed as the 'IONA Test Risk Score'. Annex 2 of the PPD reports the risk of trisomy 21 reported as "greater than 95%". I do not accept that a test with this degree of accuracy falls outside the scope of the claims of the Lo 2/3 Patents. This degree of accuracy is expressly disclosed as falling within the scope of the inventions in [0112].

491. This conclusion is consistent with Premaitha's own description of its test. A print out from the Wayback machine of a previous version of Premaitha's website (XX-A/3) as it stood on 18 January 2015 was put to Prof Avent. This describes the IONA test as the "*first non-invasive in vitro diagnostic product for prenatal screening*" and "*a*

complete diagnostic system that is simple and standardised". The website has now been changed to exclude reference to the word "*diagnostic*". Professor Avent considered that this language was used because of the requirements concerning CE marking of a medical device in the EU. IONA is approved under Directive 98/79/EC, which regulates in vitro diagnostic devices. It was submitted that this was a description required for regulatory purposes in respect of a test which would not be considered diagnostic by the skilled team. I do not consider that this meets the point. In my judgment, this is further confirmation that the word "*diagnostic*" is context-dependent, and, in appropriate circumstances, is apt to describe the IONA test.

ii) Aligning each sequence to a reference genome

492. Premaitha submitted that in the IONA test, not all the sequences obtained are aligned to the human genome. It argued that in all versions of the IONA test, only those monoclonally amplified sequences which are 8 or more base pairs long are aligned to a reference genome. Any sequences which are polyclonally amplified or less than 8 bp are discarded. Similarly, in the modified versions of the IONA test, sequences originating from the Y chromosome are not aligned because the Y chromosome has been removed from the reference genome. Therefore, the IONA test does not align *each* sequence obtained to a human genome.

493. This argument has no application to Lo 3. I do not accept that it is correct in relation to Lo 2. As to polyclonal ISPs, they do not produce usable sequence reads. Therefore, they cannot be mapped to the genome. Claim 1 of Lo 2 refers to "*performing a random sequencing*". This does not require a random sequencing of unmappable sequences. There is therefore no requirement in the claims of Lo 2 to align such unmappable sequences to a human genome.

494. Fragments of fewer than 8 base pairs raise a similar issue. The skilled person would know that such fragments would not provide relevant information since it would not be possible to map such a fragment to a single place in the genome. The skilled person would not understand the Lo 2 Patent to require mapping of every tiny fragment, for no useful purpose.

495. As to removal of the Y chromosome in the modified version of the IONA test, this means that sequences which would otherwise align no longer do so. In my judgment, this makes no difference to the issue of infringement. A reference human genome includes a genome without a Y chromosome. The claim does not require the alignment of sequences in circumstances where this is impossible, because they do not correspond with any part of the reference genome. In my judgment, the IONA test falls within the 'aligning step' of claim 1 of the Lo 2 Patent.

Parameter/cut-off

496. This is an issue of considerable complexity in relation to Lo 2, claim 1 of which requires (a) that a parameter is determined from the amount of sequences aligning to a first chromosome (which is the potentially aneuploid chromosome) and the amount aligning to a second chromosome(s), which is the reference chromosome(s); and (b) that the parameter also "represents a relative amount between the first and second amounts". However, requirement (b) is not a feature of claim 1 of the Lo 3 Patent, and the argument is considerably simpler.

Lo 2

497. Premaitha submitted that in the IONA test, the only value that is compared to a cut-off to determine whether an aneuploidy exists is P_{post}, the posterior probability. If this is greater than or equal to 1 in 150 (0.67%), the pregnancy is classified as "high risk". The principal issue between the parties was whether P_{post} is a parameter that represents a relative amount between the potentially aneuploid chromosome and a reference chromosome(s). I have not found it possible to decide this issue without discussion of information which is confidential to Premaitha. This is set out in Confidential Appendix 2. I have concluded that P_{post} in the IONA system is a parameter that represents a relative amount between the potentially aneuploid chromosome and a reference chromosome(s), which is compared with a cut-off value, within the meaning of claim 1 of the Lo 2 Patent.

Lo 3

498. Premaitha acknowledged that the parameter referred to in claim 1 is not required to represent a relative amount between the first and second amounts. It is only required to be determined "from the first amount and the second amount". Nonetheless, it submitted that there is nothing in Lo 3 to suggest that this includes determining a parameter from the first and second amounts and another factor e.g. a risk factor based upon maternal age. It contended that P_{post} is not a parameter within the meaning of the claim of Lo 3.

499. I do not accept this argument, for the reasons which I have set out in relation to Lo 2. The issue in relation to Lo 2 raised a difficult point, but only because of the requirement in its claims that the parameter was to represent a relative amount between the first and second amounts. Consideration of an additional risk factor does not avoid infringement. Claim 1 of Lo 3 does not contain this requirement, and the IONA test falls within its scope.

The IONA Test – Alternative Proposed Process

500. Premaitha seeks a declaration of non-infringement in respect of all of the Patents for its Alternative Proposed Process, where some steps of the process are conducted in Taiwan. In summary, the DNA preparation and sequencing is (to be) conducted in the UK but the multiplexed raw i.e. unmapped sequence data resulting from those steps, along with patient and sample data, is then sent to a data analysis site in Taiwan where the remainder of the steps are carried out. A PDF format test report is then returned to the UK. Specifically, the Alternative Proposed Process comprises the following steps:

i) receiving a blood sample from a patient in the UK;

ii) carrying out the preparatory steps and the sequencing processes in the UK;

iii) sending the raw data comprising the results of the sequencing reads electronically to Taiwan;

iv) performing the analysis of the data in Taiwan, including the R_x calculation, sex determination and foetal fraction estimation;

v) generating a report in Taiwan;

vi) sending the report back to the UK;

vii) receiving and unpacking the report in the UK and formatting it for printing, storage and sharing with the patient.

501. Illumina contended that the Alternative Proposed Process would infringe pursuant to sections 60(1)(b) or 60(1)(c) of the Patents Act 1977. Alternatively, it relied upon section 60(2) and, in relation to certain claims of Lo 2 and Lo 3, section 60(1)(a).

Section 60(1)(b)

502. Section 60(1)(b) provides that a person infringes a patent;

> "where the invention is a process, he uses the process or he offers it for use in the United Kingdom when he knows, or it is obvious to a reasonable person in the circumstances, that its use there without the consent of the proprietor would be an infringement of the patent."

Submissions of the parties

503. Premaitha submitted that the steps of detection and analysis, crucial to the inventive concepts of each of the Patents, take place outside the United Kingdom in the Alternative Proposed Process. It submitted that Illumina's allegations of infringement are dependent on the data analysis steps of the IONA test. In the Alternative Proposed Process those steps are not carried out in the UK and therefore the process of the claims is not used in the UK.

504. Illumina contended that the laboratories located in the UK, which are using the inventions, are indifferent as to where the sequencing information is processed; the processes managed by human operators outside the UK are non-specialised tasks; and the steps undertaken in Taiwan that are relevant to infringement are all undertaken by a computer. It submitted that a finding of non-infringement would render claims of this kind impossible to assert as a practical matter.

505. The parties referred to certain cases, primarily concerned with section 60(2). Illumina relied upon the judgment of the Court of Appeal in *Menashe v William Hill* [2003] RPC 31 at [32] *per* Aldous LJ.

> "The claimed invention requires there to be a host computer. In the age that we live in, it does not matter where the host computer is situated. It could be in the United Kingdom, on a satellite, or even on the border between two countries. Its location is not important to the user of the invention nor to the claimed gaming system. In that respect there is a real difference between the claimed gaming system and an ordinary machine. For my part I believe that it would be wrong to apply the old ideas of location to inventions of the kind under consideration in this case. A person who is situated in the United Kingdom

> who obtains in the United Kingdom a CD and then uses his terminal to address a host computer is not bothered where the host computer is located. It is of no relevance to him, the user, nor the patentee as to whether or not it is situated in the United Kingdom."

506. Premaitha contrasted the facts of *Menashe* with the facts of *RIM v Motorola* [2010] EWHC 118 (Pat). In *Menashe*, the case concerned a gambling system comprising a player station and a host computer. Although the punter's computer (the player station) was in the UK, the host computer was not. However, the Court of Appeal held that this did not matter. The system as a whole was used by the punter and that use took place in the UK, even if part of the system was outside of the UK. In *RIM v Motorola,* the claim was to a messaging gateway system. The claimed system included the user's wireless devices and a messaging gateway. RIM's servers (the messaging gateway) were in Canada, but emails were sent by and to users in the UK. Arnold J considered *Menashe* at 155 – 156:

> "As Aldous LJ said at [33]:
>
> "If the host computer is situated in Antigua and the terminal computer is in the United Kingdom, it is pertinent to ask who uses the claimed gaming system. The answer must be the punter. Where does he use it? There can be no doubt that he uses his terminal in the United Kingdom and it is not a misuse of language to say that he uses the host computer in the United Kingdom. It is the input to and output of the host computer that is important to the punter and in a real sense the punter uses the host computer in the United Kingdom even though it is situated in Antigua and operates in Antigua. In those circumstances it is not straining the word 'use' to conclude that the United Kingdom punter will use the claimed gaming system in the United Kingdom, even if the host computer is situated in, say, Antigua. Thus the supply of the CD in the United Kingdom to the United Kingdom punter will be intended to put the invention into effect in the United Kingdom."
>
> 156. I agree with RIM that asking and answering Aldous LJ's questions in this case leads to a different answer. Who uses the method of operating a messaging gateway system that has the claimed features? The answer is RIM. Where do they operate it? The answer is in Canada."

Discussion

507. In my judgment, the crucial question is where, in substance, is the Alternative Proposed Process to be used? The answer is the United Kingdom. In substance, the 'method of detecting a nucleic acid of foetal origin in a sample' (Lo 1), the 'method of detection of foetal aneuploidy' (Quake) and the 'method for performing prenatal diagnosis' (Lo 2/3) would be performed by laboratories in the UK. The blood test would be taken in the UK, the sequencing machine would be operated in the UK and the information so obtained would be transmitted to Taiwan for a pre-determined set

of automated computer processes to be applied to it. The output of the computer processing would be sent back to the United Kingdom for use in the United Kingdom.

508. As Aldous LJ said in *Menashe*, it does not matter where the computer is situated. The process is operated, in substance in the UK. I accept Illumina's submission that any other result would make it far too easy to avoid infringement of patents of this nature, given the ease of digital transmission and the ability to off-shore computer processing.

Other allegations of infringement

509. Illumina's best case of infringement is under section 60(1)(b), which I accept. A finding of non-infringement under other sub-sections of the Act would not assist Premaitha. I do not consider that it is necessary to determine the alternative allegations under sections 60(1)(a), 60(1)(c), or 60(2) to resolve the dispute between the parties.

The Additional Alternative Proposed Process

510. I consider this issue in Confidential Appendix 3. For the reasons set out in the Appendix, I have concluded that the Additional Alternative Proposed Process would not infringe the Lo 1 Patent, but would infringe the Quake Patents and the Lo 2/3 Patents. I shall grant a declaration of non-infringement in respect of the Lo 1 Patent only.

Overall conclusions

511. In relation to Lo 1:

i) Lo 1 is not obvious in the light of Kazakov.

ii) Of the claims alleged to be independently valid, claims 1, 2, 5 and 7 of Lo 1, as proposed to be amended, are not entitled to the claimed priority date. Claim 8 is entitled to the claimed priority date. It is accepted by Illumina that claims which are not entitled to priority are invalid.

iii) The claims of Lo 1 do not relate to a discovery as such.

iv) The Harmony prenatal test (polymorphic assay) does not infringe any valid claim of Lo 1.

v) The Harmony prenatal test (non-polymorphic assay) infringes claim 8 of Lo 1 insofar as it is used for sex determination.

vi) The IONA test infringes claim 8 of Lo 1 insofar as it is used for sex determination.

vii) Premaitha is not entitled to a declaration of non-infringement of Lo 1 in respect of its Alternative Proposed Process.

viii) Premaitha is entitled to a declaration of non-infringement of Lo 1 in respect of its Additional Alternative Proposed Process.

ix) Illumina is not an exclusive licensee under Lo 1.

512. In relation to the Quake Patents:

i) The Quake Patents are not obvious in the light of Shimkets.

ii) Claim 1 of Quake 1 as granted is insufficient, but as proposed to be amended is sufficient. Otherwise, the insufficiency objections are dismissed.

iii) Claim 1 of Quake 1 as granted is invalid for added subject matter, but as proposed to be amended is valid.

iv) The IONA test infringes the Quake Patents.

v) Premaitha is not entitled to a declaration of non-infringement of the Quake Patents in respect of either the Alternative Proposed Process or the Additional Alternative Proposed Process.

vi) Verinata is an exclusive licensee of the Quake Patents and the IONA test falls within the licensed field.

513. In relation to the Lo 2 and Lo 3 Patents:

i) The Lo 2 and Lo 3 Patents are not obvious in the light of Shimkets.

ii) The Lo 2 and Lo 3 Patents are entitled to their claimed priority date.

iii) The Lo 2 and Lo 3 Patents are infringed by the IONA test.

iv) Premaitha is not entitled to a declaration of non-infringement of the Lo 2 and Lo 3 Patents in respect of either the Alternative Proposed Process or the Additional Alternative Proposed Process.

v) Illumina is an exclusive licensee for commercial purposes of the Lo 2 and Lo 3 Patents.