HIGH COURT OF AUSTRALIA

Yvonne D'arcy

Vs.

Myriad Genetics Inc & Anor

[2015] HCA 35

(French CJ, Kiefel, Bell, Gageler, Keane, Nettle and Gordon JJ.)

7.10. 2015

ORDER

French CJ, Kiefel, Bell And Keane JJ.

Introduction

1. A human gene which codes for the production of a protein called BRCA1 may bear variations from the norm, characterised as mutations or polymorphisms, which are associated with susceptibility to breast and ovarian cancers . Like all genes, it is a functional unit of the deoxyribonucleic acid ("DNA") molecule found in the nucleus of the human cell. By a biochemical process within the cell involving ribonucleic acid ("RNA"), a gene gives rise to the production of the protein molecule or "polypeptide", which is defined by, or is an "expression" of, the sequence of components of the gene known as nucleotides. That sequence comprises "the genetic code" . The BRCA1 gene is one of approximately 25,000 genes in the human DNA molecule, which consists of about 3.2 billion linked nucleotides. The isolation of any of a class of molecules bearing a sequence of nucleotides coding for a BRCA1 polypeptide is said by the first respondent, Myriad Genetics Inc ("Myriad"), to give rise to a patentable invention if the sequence carries certain mutations or polymorphisms indicative of susceptibility to cancer. The mutations and polymorphisms are set out in tables attached to the patent based on information derived from the DNA of human subjects.

2. The validity of the invention claimed in Myriad's patent was challenged by the appellant, Ms D'Arcy, in revocation proceedings, on the ground that it was not a patentable invention within the meaning of the Patents Act 1990 (Cth) ("the Act"). That challenge was dismissed by a Judge of the Federal Court , as was an appeal from that decision to the Full Court of the Federal Court . Ms D'Arcy appeals to this Court by special leave from the decision of the

Full Court . The second respondent, Genetic Technologies Ltd, holds the exclusive licence in Australia for the patent from Myriad.

3. The patent in suit contains 30 claims. The validity of the first three claims is in issue in this appeal . They are for:

> "1. An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19[ ].
>
> 2. An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a mutant BRCA1 polypeptide, said DNA containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations set forth in Tables 12, 12A and 14.
>
> 3.An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a polymorphic BRCA1 polypeptide, said DNA containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more polymorphisms set forth in Tables 18 and 19[ ]."
>
> Each of those claims relates to "an isolated nucleic acid". That term is defined in the complete specification as including DNA, RNA or a mixed polymer and as "one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, eg, ribosomes, polymerases, many other human genome sequences and proteins." It embraces a nucleic acid sequence or protein removed from its naturally occurring environment and includes recombinant or cloned DNA isolates and chemically synthesised analogs or analogs biologically synthesised by heterologous systems . It seems to have been assumed by all parties that a nucleotide sequence derived from a nucleic acid originating in a human cell may itself appropriately be designated as a "nucleic acid". That assumption can be treated as taxonomical, and accepted for the purposes of this appeal."

4. This appeal is concerned with the application of the centuries old terminology, reflected in the requirement of the Act, that to be patentable an invention as claimed must be a "manner of manufacture" within the meaning of s 6 of the Statute of Monopolies . The "archaic language" of the section declared all monopolies to be void save for:

> "Letters Patents and Grants of Privilege for ... the sole working or making of any manner of new Manufactures within this Realm, to the true and first Inventor and Inventors of such Manufactures, which others at the time of making such Letters Patents and Grants shall not use, so as also they be not contrary to the Law, nor mischievous to the State, by raising prices of Commodities at home, or hurt of Trade, or generally inconvenient ..."

5. This Court in National Research Development Corporation v Commissioner of Patents ("NRDC") held that the terminology of "manner of manufacture" taken from s 6 of the Statute of Monopolies was to be treated as a concept for case-by-case development . It thereby mandated a common law methodology for its application. It did not confine that methodology to the use of any verbal formula in lieu of "manner of manufacture". Nor, in the case of a new class of claim, did the decision of the Court in NRDC preclude consideration of policy factors informed by the purpose of the Act and considerations of coherence in the law.

6. Claims 1 to 3 are formally expressed as product claims. The class of products claimed is derived from naturally occurring sequences of nucleotides in the bodies of individual human beings. An essential integer requires that the isolated nucleic acid must code for all or part of a mutant or polymorphic BRCA1 polypeptide. It must therefore reproduce a relevant sequence of nucleotides existing in the body of the human being from which it is derived. The sequence so reproduced is isolated from structural and discrete components which would enliven its functionality in the human cell. Despite the formulation of the claimed invention as a class of product, its substance is information embodied in arrangements of nucleotides. The information is not "made" by human action. It is discerned. That feature of the claims raises a question about how they fit within the concept of a "manner of manufacture". As appears from s 6 of the Statute of Monopolies, an invention is something which involves "making". It must reside in something. It may be a product. It may be a process. It may be an outcome which can be characterised, in the language of NRDC, as an "artificially created state of affairs". Whatever it is, it must be something brought about by human action . The requirement, in each claim, that the sequence in the isolate bear specified mutations or polymorphisms raises the same problem in a particular way. Satisfaction of that integer depends upon a characteristic of the human being from whom the nucleic acid is isolated, a characteristic which is not shared by all human beings. It has nothing to do with the person who isolates the nucleic acid bearing the mutant sequence.

7. The proposition that a broad statutory concept applies to a new class of case on the boundaries of existing judicial development of that concept requires consideration of the limits of judicial law-making inherent in common law methodology. Where an affirmative

application of the concept is likely to result in the creation of important rights as against the world, to involve far-reaching questions of public policy and to affect the balance of important conflicting interests, the question must be asked whether that application is best left for legislative determination. The patentability of nucleotide sequences derived from human DNA is in that category. The inherent patentability of the invention as claimed would powerfully imply patentability of any claim for an isolated nucleic acid coding for a specified polypeptide.

8. Claims 1 to 3 include the products of applying any process, known or unknown, to the cells of a human being which extracts or replicates from them nucleotides which code for mutant or polymorphic BRCA1 in the sequences specified in the Patent, whether or not the isolate contains other components and sequences. The size of the class of the products as defined is large. No upper limit was suggested in argument. The boundaries of the class are not defined by a limiting range of chemical formulae. There is a real risk that the chilling effect of the claims, on the use of any isolation process in relation to the BRCA1 gene, would lead to the creation of an exorbitant and unwarranted de facto monopoly on all methods of isolating nucleic acids containing the sequences coding for the BRCA1 protein. The infringement of the formal monopoly would not be ascertainable until the mutations and polymorphisms were detected. Such a result would be at odds with the purposes of the patent system. As Cornish, Llewelyn and Aplin observed generally in the 8th edition of their well-known work on intellectual property :

> "A patent over a single gene may prove to set up a barrier against its use in a quite distinct genetic procedure for a different medical condition which is worked out only subsequently."
>
> They further observed, in the context of the Patents Act 1977 (UK) but relevantly to the present case :
>
> "The question of what activity by an unauthorised person actually amounts to infringement of these claims is a problematic one, raising the issue when does that person 'make the patented product' in the sense of PA 1977 s 60."

9. Those features of the invention as claimed in Claims 1 to 3, and its substance as an invention relating to sequence information, lead to the conclusion that its patentability would not serve the purposes of the concept of "manner of manufacture" in s 18(1)(a) of the Act or of the Act itself. It should not be brought, by analogy or otherwise, within that concept. The contested claims do not meet the requirement of s 18(1)(a).

10. Essentially, for the preceding reasons, further explained in the following sequence of topics, the appeal should be allowed:

> “(i) The statutory framework.
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> (ii) A manner of manufacture — relevant principles.
>
> (iii) Legislative history.
>
> (iv) The primer — setting out the relevant science.
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> (v) DNA and RNA in the human cell.
>
> (vi) Genes.
>
> (vii) Genes expressing proteins.
>
> (viii) Isolation of nucleic acids.
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> (ix) Isolated nucleic acids.
>
> (x) The uses of isolated nucleic acids.
>
> (xi) The patent specification.
>
> (xii) Isolated nucleic acid — composite or extract?
>
> (xiii) The primary judge's decision.
>
> (xiv) The decision of the Full Court.
>
> (xv) Conclusions.
>
> The statutory framework “

11. Section 18(1) sets out "the essential characteristics of a 'patentable invention' for the purposes of the Act." Section 18(1)(a) provides:

> "Subject to subsection (2), a patentable invention is an invention that, so far as claimed in any claim:
>
> (a) is a manner of manufacture within the meaning of section 6 of the Statute of Monopolies" The other requirements of s 18(1) of novelty , inventive step , usefulness and no secret user before the priority date are not raised in this appeal. Nor is s

18(2), which precludes the patentability of "[h]uman beings, and the biological processes for their generation".

12. The term "patentable invention" is defined in the Dictionary in Sched 1 to the Act as "an invention of the kind mentioned in section 18." The term "invention" is defined as :

> "any manner of new manufacture the subject of letters patent and grant of privilege within section 6 of the Statute of Monopolies, and includes an alleged invention.
>
> It is not clear, and was not debated in this appeal, how the expression "manner of manufacture" differs from the expression "manner of new manufacture" . The definition of "invention" has been used in Commonwealth patent statutes since federation . It allows for exclusion from the class of "invention", and therefore from the class of "patentable invention", anything which is not, on the face of the specification, a proper subject of letters patent according to traditional principles . That anterior exclusion may be based upon an admission, on the face of the specification, which makes clear that the invention claimed is not novel or does not involve an inventive step . This appeal, however, collapses the anterior and subsequent questions — "Is there an invention?" and "Is there a patentable invention?" — into one inquiry. That inquiry requires a definition of the allegedly patentable invention. That definition depends upon the construction of the impugned claims read in the light of the specification as a whole and the relevant prior art . The prior art in this case was reflected in expert evidence at trial and set out in the scientific primer agreed between the parties and summarised later in these reasons."

13. The conditions of patentability in s 18(1) must be satisfied by the invention "so far as claimed in any claim". That term directs attention to the formal requirement of s 40(2)(b) that a complete application for a standard patent must "end with a claim or claims defining the invention". The word "invention" in that context does not import the definition in the Dictionary, but means "the embodiment which is described, and around which the claims are drawn" .

14. Historically, the claim, as definer of the inventor's property, emerged in the late 19th century . The statutory requirement to set out at the end of a complete specification a "distinct statement of the invention claimed" first appeared in s 5(5) of the Patents, Designs, and Trade Marks Act 1883 (UK). It was reflected in successive Commonwealth patent statutes from the time of federation . The function of the claim was described by Lord Russell of Killowen in 1938 as "to define clearly and with precision the monopoly claimed,

so that others may know the exact boundaries of the area within which they will be trespassers." Its limiting role was emphasised :

> "It and it alone [defines] the monopoly; and the patentee is under a statutory obligation to state in the claims clearly and distinctly what is the invention which he desires to protect."

Lord Russell's observations have stood the test of time in the United Kingdom as "[t]he best-known statement of the status of the claims in UK law" . They also describe the function of the claim mandated by s 40(2)(b) of the Act. As succinctly, but accurately, stated in a recent Australian text that function is "to define what it is that the patentee has exclusive right to, during the term of the patent." The breadth of the class of invention claimed in this case, using the generic term "isolated nucleic acid", makes definition of the boundaries of the monopoly which is sought elusive.

15., The rights of the patentee are conferred by s 13(1) of the Act, which provides:

> "Subject to this Act, a patent gives the patentee the exclusive rights, during the term of the patent, to exploit the invention and to authorise another person to exploit the invention."The term "exploit" in relation to an invention includes :
>
> "(a) where the invention is a product—make, hire, sell or otherwise dispose of the product, offer to make, sell, hire or otherwise dispose of it, use or import it, or keep it for the purpose of doing any of those things; or
>
> (b) where the invention is a method or process—use the method or process or do any act mentioned in paragraph (a) in respect of a product resulting from such use."

16. The definition of "exploit" distinguishes between an invention which is a product and an invention which is a method or process which may or may not yield a product. In Northern Territory v Collins , Gummow ACJ and Kirby J linked that distinction to the way in which, over time, the expression "manner of manufacture" had been construed to include the practice and means of "making", as well as its product, which would include an economically useful outcome effected by an inventive method . The idea of something which can be "made" by human intervention is central and long standing — "'[m]anufacture' connotes ... the making of something." It is an important element of the exclusive right to exploit a patented product.

17. The proceedings for the revocation of the Myriad patent Claims 1 to 3, which have led to this appeal, were instituted under s 138 of the Act. The relevant ground for revocation is that set out in s 138(3)(b):

> "that the invention is not a patentable invention". The answer to the question of patentability raised by that ground depends upon the principles governing the criterion prescribed by s 18(1)(a), considered in the next section of these reasons. A manner of manufacture — relevant principles"

18. The legislative history of the requirement for patentability imposed by s 18(1)(a) of the Act has been set out in previous decisions of this Court . The question posed by the application of s 18(1)(a) may be framed as in NRDC :

> "Is this a proper subject of letters patent according to the principles which have been developed for the application of s 6 of the Statute of Monopolies?"

That question is to be answered according to a common law methodology under the rubric of "manner of manufacture" as developed through the cases, but consistently with "a widening conception of the notion [which] has been a characteristic of the growth of patent law." That widening conception is a necessary feature of the development of patent law in the 20th and 21st centuries as scientific discoveries inspire new technologies which may fall on or outside the boundaries of patentability set by the case law which predated their emergence.

19. The Court in NRDC upheld the validity of a patent for the use of previously unknown properties of a known chemical to effect a new purpose. The Court generalised what had come to be treated, erroneously, as a "rule", that for a method or process to be a "manner of manufacture" it should result in the production, improvement, restoration or preservation of a "vendible product" . By treating the word "product" as covering every end produced and the word "vendible" as pointing to the requirement of utility in practical affairs, the vendible product "rule" could be accepted as wide enough to convey the broad idea which a long line of authority on the subject had been shown to be comprehended by the Statute . The Court said of the method patent in suit before it :

> "The effect produced by the appellant's method exhibits the two essential qualities upon which 'product' and 'vendible' seem designed to insist. It is a 'product' because it consists in an artificially created state of affairs, discernible by observing over a period the growth of weeds and crops respectively on sown land on which the method has been put into practice. And the significance of the product is economic ..."

20. The terminology of an "artificially created state of affairs of economic significance" is to be understood in the context in which it was used in NRDC. It was not intended as a formula exhaustive of the concept of manner of manufacture. The Court made that point emphatically :

> "To attempt to place upon the idea the fetters of an exact verbal formula could never have been sound."

Hayne J made it in Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd :

> "Nothing said in the Court's reasons for decision in that case can be taken as an exact verbal formula which alone captures the breadth of the ideas to which effect must be given."

In similar vein, Crennan and Kiefel JJ, with whom Gageler J agreed, said that :

> "In Australian law, the starting point is the recognition in the NRDC Case that any attempt to define the word 'manufacture' or the expression 'manner of manufacture', as they occur in s 6 of the Statute of Monopolies, is bound to fail." (footnote omitted)
>
> It is true that in Anaesthetic Supplies Pty Ltd v Rescare Ltd Lockhart J in the Full Federal Court, in a passage endorsed by Crennan and Kiefel JJ in Apotex , said :"
>
> "If a process which does not produce a new substance but nevertheless results in 'a new and useful effect' so that the new result is 'an artificially created state of affairs' providing economic utility, it may be considered a 'manner of new manufacture' within s 6 of the Statute of Monopolies." (citations omitted) Importantly, however, his Honour used the word "may". Neither Lockhart J nor Crennan and Kiefel JJ should be read as holding that satisfaction of that formula would mandate a finding of inherent patentability. That is not to say that it will not suffice for a large class of cases in which there are no countervailing considerations."

21. In CCOM Pty Ltd v Jiejing Pty Ltd , the Full Court of the Federal Court said the NRDC case "requires a mode or manner of achieving an end result which is an artificially created state of affairs of utility in the field of economic endeavour." As Professor Monotti wrote in an article in the Federal Law Review in 2006, the passage from the judgment in NRDC characterising the process claimed before the Court as a product consisting in an "artificially created state of affairs" merely explained "the qualities of the invention before the court." The Court could hardly have intended the phrase to be seen as a definition of manner of manufacture because it had already denounced the idea of an exact formula . The

formulation in CCOM, like the so-called vendible product "rule", should be taken as a guide rather than as a rigid formula .

22. Counsel for Myriad posited "the test" in NRDC for patentability of a product as — "is it an artificially created state of affairs of economic utility?". Myriad's approach was accepted by the primary judge who derived from NRDC the proposition that :

> "a product that consists of an artificially created state of affairs which has economic significance will constitute a 'manner of manufacture'." (emphasis added) In similar vein, the Full Court said of NRDC that : "The Court held that it is sufficient for a product to result in 'an artificially created state of affairs', leading to 'an economically useful result'." That proposition underpinned the conclusion by the Full Court in the second last paragraph of its judgment that:
>
> The isolated nucleic acid, including cDNA, has resulted in an artificially created state of affairs for economic benefit. The claimed product is properly the subject of letters patent. The claim is to an invention within the meaning of s 18(1) of the Act." Myriad's proposition and the approach of the primary judge and the Full Court, with respect, rested upon an unduly narrow characterisation of the effect of the decision in NRDC. It rested upon the premise that the claims were for a product well within existing conceptions of a "manner of manufacture".

23. This Court in NRDC did not prescribe a well-defined pathway for the development of the concept of "manner of manufacture" in its application to unimagined technologies with unimagined characteristics and implications. Rather, it authorised a case-by-case methodology. Consistently with that approach, and without resort to the "generally inconvenient" proviso in s 6 of the Statute of Monopolies, there may be cases in which the court will decide that the implications of patentability of a new class of invention are such that the invention as claimed should not be treated as patentable by judicial decision.

24. The Full Court disclaimed any consideration of "whether, for policy or moral or social reasons, patents for gene sequences should be excluded from patentability." The question for its determination, however, was not whether a claimed invention, prima facie patentable, should be denied patentability by judicial fiat. The question was whether the claimed invention lay within the established concept of a manner of manufacture and, if not, whether it should nevertheless be included in the class of patentable inventions as defined in s 18(1)(a) of the Act. Purposive and consequentialist considerations which, no doubt, could be classed as "policy" reasons may play a part in answering the second limb of that question. As

Professor Monotti percipiently remarked in her article in the Federal Law Review, which, of course, predated Apotex :

> "Although it was important to expand patentable subject matter and remove artificial fetters on patentable subject matter at the time of NRDC, there is no consensus that we should continue to expand the scope of patentable subject matter into all fields of endeavour so as to remove the remaining fetters on patentable subject matter. The continuing debates on whether methods of medical treatment, business systems and genes should be patentable subject matter demonstrate that there is no universal acceptance of an approach that would accept that anything under the sun invented by man is patentable."
>
> "The proposition that patents should extend to "anything under the sun that is made by man" was a statement of legislative intention attributed to Congress by the Supreme Court of the United States in Diamond v Chakrabarty in relation to 35 USC §101 which provides:Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

25. NRDC was decided in 1959. The Act in 1990 re-enacted, in s 18(1)(a), the definition of "invention" in the Patents Act 1952 (Cth) , to which NRDC was directed. That re-enactment bore with it the judicial methodology for its application and the constraints attaching to that methodology. The proper function of the judicial branch was considered in an analogous, but not identical, context in two successive decisions of the Supreme Court of the United States in 1978 and 1980. In Parker v Flook , the Court said that the judiciary "must proceed cautiously when ... asked to extend patent rights into areas wholly unforeseen by Congress." In Chakrabarty, Burger CJ, writing for the majority, and finding for patentability of a manufactured micro-organism as "any new and useful ... manufacture, or composition of matter" under 35 USC §101, said :

> "It is, of course, correct that Congress, not the courts, must define the limits of patentability; but it is equally true that once Congress has spoken it is 'the province and duty of the judicial department to say what the law is.'"
>
> The majority rejected the proposition that the claim before them was a matter of high policy for resolution within the legislative process, saying that the contentions to that effect should be pressed on the political branches of government and not on the courts . Brennan J, who was joined in dissent by White, Marshall and Powell JJ, put the other side of the argument :"

"It is the role of Congress, not this Court, to broaden or narrow the reach of the patent laws. This is especially true where, as here, the composition sought to be patented uniquely implicates matters of public concern."

The debate about institutional competency in Chakrabarty was resolved by the majority on the basis that the statutory authority conferred on the courts by Congress under 35 USC §101 required an approach to patentability unconstrained by policy considerations. In Australia, the Parliament has left it to the courts to carry out a case-by-case development of a broad statutory concept according to the common law method in a representative democracy.

26. The term "manner of manufacture", and the concept it embodies, was and is no more pregnant with rules and applications awaiting discovery, than is the common law. Its statutory origin in 1624 is embedded in historically contingent concepts of patent and invention. It has been described as an act of economic policy the objectives of which were the "encouragement of industry, employment and growth, rather than justice to the 'inventor' for his intellectual percipience." It has also been characterised, persuasively, as a "political compromise" . That characteristic and the relative inaccessibility, nearly four centuries after its enactment, of contemporary understandings of patent and invention no doubt played a part in its application as a general common law concept, rather than as a well-defined statutory category. The modest and constrained role of courts in the common law tradition was spoken of in Breen v Williams by Gaudron and McHugh JJ. Their Honours, nevertheless, acknowledged the necessity, from time to time, to reformulate existing legal rules and principles to take account of changing social conditions. Their Honours said :

"But such steps can be taken only when it can be seen that the 'new' rule or principle that has been created has been derived logically or analogically from other legal principles, rules and institutions."

The question whether a propounded application of a general concept amounts to an extension of that concept is often debatable. In some cases, the distinction between a new application and an extension is likely to be a distinction without a practical difference.

27 Myriad submitted that the Court ought to treat the impugned claims as claims for a chemical compound. It argued that there was "no jurisprudential basis or normative principle upon which claims to isolated nucleic acids should be treated differently from any other product claims." The Court should look to their subject matter and determine the question of patentability according to the principles in NRDC which had been affirmed in Apotex. That submission sought to locate the claims well within the established understanding of "manner of manufacture" in a way that would make normative

considerations, which might inform the development of that concept, irrelevant. Properly construed, however, the claims are not within the established boundaries and wider considerations than Myriad's characterisation of them as an "artificially created state of affairs of economic utility" come into play.

28 A number of factors may be relevant in determining whether the exclusive rights created by the grant of letters patent should be held by judicial decision, applying s 18(1)(a) of the Act, to be capable of extension to a particular class of claim. According to existing principle derived from the NRDC decision, the first two factors are necessary to characterisation of an invention claimed as a manner of manufacture:

1. Whether the invention as claimed is for a product made, or a process producing an outcome as a result of human action.

2. Whether the invention as claimed has economic utility.

When the invention falls within the existing concept of manner of manufacture, as it has been developed through cases, they will also ordinarily be sufficient. When a new class of claim involves a significant new application or extension of the concept of "manner of manufacture", other factors including factors connected directly or indirectly to the purpose of the Act may assume importance. They include:

3. Whether patentability would be consistent with the purposes of the Act and, in particular:

> 3.1. whether the invention as claimed, if patentable under s 18(1)(a), could give rise to a large new field of monopoly protection with potentially negative effects on innovation;
>
> 3.2. whether the invention as claimed, if patentable under s 18(1)(a), could, because of the content of the claims, have a chilling effect on activities beyond those formally the subject of the exclusive rights granted to the patentee;
>
> 3.3.whether to accord patentability to the invention as claimed would involve the court in assessing important and conflicting public and private interests and purposes."

4. Whether to accord patentability to the invention as claimed would enhance or detract from the coherence of the law relating to inherent patentability.

5. Relevantly to Australia's place in the international community of nations:

5.1. Australia's obligations under international law;

5.2. the patent laws of other countries.

6. Whether to accord patentability to the class of invention as claimed would involve law-making of a kind which should be done by the legislature. Factors 3, 4 and 6 are of primary importance. Those primary factors are not mutually exclusive. It may be that one or more of them would inform the "generally inconvenient" limitation in s 6 of the Statute of Monopolies. It is not necessary to consider that question given that no reliance was placed upon that proviso. They are nevertheless also relevant to the ongoing development of the concept of "manner of manufacture".

29. Factors 1 and 2 have been discussed in the light of NRDC. The purpose of Australian patent legislation has been discussed in general terms in decisions of this Court. At a functional level, it can be defined narrowly by what the Act does — it confers upon a patentee, in return for disclosure of his or her invention, a limited monopoly at the expiration of which an invention is available to the public at large . That function may be expressed as an objective but it serves the larger purpose of encouraging innovation by means which do not stifle it. The inventive step which emerged as an independent requirement from the general limiting criterion of want of subject matter "reflected the balance of policy considerations in patent law of encouraging and rewarding inventors without impeding advances and improvements by skilled, non-inventive persons." It follows that the purpose of the Act would not be served by according patentability to a class of claims which by their very nature lack well-defined boundaries or have negative or chilling effects on innovation. There may also be flow-on consequences for the balance that the Act seeks to strike and the coherence of the law as developed by judicial decision in giving effect to the purposes of the law. If there be a significant risk of such a consequence, the existence of that risk will weigh against inherent patentability.

30. Coherence and the limits of the judicial function were both relevant in the determination in Apotex that methods of medical treatment can be inherently patentable. Having regard to the established patentability of pharmaceutical products, the exclusion of treatments using such products was anomalous and had no stable logical or normative basis . Their inclusion was consistent with the existing application of the law and served to enhance its coherence.

31. The decision to accord or refuse patentability to a particular class of claims may have implications for Australia's obligations under international law. The existence of such obligations can affect the construction of statutes where, as in the case of "manner of manufacture", constructional choices implicit in its development are available .

32. There was no submission that Australia would breach its international legal obligations by failing to accord patentability to inventions of the kind claimed in this case. Article 27(1) of the Agreement on Trade-Related Aspects of Intellectual Property Rights ("the TRIPS Agreement") requires, subject to pars (2) and (3), that patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. There is provision for "ordre public or morality" exclusions in Art 27(2) and specific exclusions are authorised in Art 27(3). They relate to methods of treatment for humans or animals, and to plants and animals other than micro-organisms.

33. It was not argued that the claims in this case fall within an "ordre public or morality" exclusion or otherwise under the express exclusions of Art 27(3). Article 27(1) requires that patents be available for any invention "in all fields of technology" and that patent protection not discriminate against specific areas of technology. There is, of course, an anterior question about the scope of the concept of "invention" under the TRIPS Agreement. The materials and submissions before the Court offered no basis for inferring that Australia has an international obligation to recognise as inventions the subject matter of the impugned claims.

34. The relevant law of other countries may appropriately be taken into account where an application of the Act would enhance or detract from the harmonisation of Australia's patent law with other jurisdictions. There was no real debate about the implications for harmonisation arising out of a decision one way or another about the patentability of isolated nucleic acids. The legislative frameworks in the jurisdictions of regional trading partners — China, Japan, Korea, Singapore and India — establish criteria for the patentability of inventions which do not specifically address the patentability of isolated nucleic acids . The reported practice of the Patent Offices in most of those jurisdictions is to grant patents for isolated nucleic acids, particularly if the claim demonstrates that they are not mere discoveries . In Europe, under Arts 52 and 57 of the European Patent Convention, an isolated nucleic acid is capable of being a patentable subject matter provided that its industrial application is disclosed . The application of that requirement was recently discussed by the Supreme Court of the United Kingdom in Human Genome Sciences Inc v Eli Lilly & Co on the clear premise that such claims are patentable. The Supreme Court of the United States in Association for Molecular Pathology v Myriad Genetics Inc , discussed later in these reasons, recently held that a claim for an isolated DNA coding for a BRCA1 polypeptide was not patentable as it fell within a "law of nature" exception.

35. Lord Neuberger in Human Genome Sciences made an observation about harmonisation which recognised contemporary realities :

"There have been moves over the past fifty years (and more) to harmonise patent law across jurisdictions (the EPC and TRIPS ... being two important examples), and it is a laudable aim to seek to ensure that all aspects of the law of patents are identical throughout the world. However, the achievement of such an aim is plainly not currently practicable, and, although they have a great deal in common, there are significant and fairly fundamental differences (over and above the different words used in Arts 52 and 57 of the EPC and s 101 of 35 USC) between US patent law and the EPC (two notorious examples being the first to file rule in Europe, and file wrapper estoppel in the US)."

His Lordship further observed :

"Accordingly, particularly when it comes to a nice question such as the precise delineation of boundaries between patentability and unpatentability on the ground of industrial application, it would be unsurprising if the law was not identical under the two jurisdictions." The latter observation may be applied to nice questions of patentability between jurisdictions generally and, a fortiori, where new questions of patentability are to be determined judicially on a case-by-case basis. Legislative history"

36. Myriad submitted that what it called "the legislative history" did not support any implied "exclusion" of isolated DNA or RNA sequences from patentability. It relied upon the following events:

"The rejection in the Senate of an amendment to the Patents Bill 1990, which would have excluded genes from patentability, whether derived from cells or chemically synthesised .

The rejection by the Legal and Constitutional Affairs Legislation Committee of the Senate of a Private Members' Bill, the Patent Amendment (Human Genes and Biological Materials) Bill 2010 .

Myriad also referred to the Report of the Australian Law Reform Commission on gene patenting, published in 2004 ("the ALRC Report"), and its conclusion that "the ALRC considers that a new approach to the patentability of genetic materials is not warranted at this stage in the development of the patent system" . Myriad's submissions on legislative history rested upon the premise, derived from debates on the failed amendments and the recommendation in the ALRC Report, that this case is

about exclusion from patentability of an otherwise patentable invention. In its written submissions, Myriad said that:

> "Parliament has expressly declined to enact any such exclusion on more than one occasion. This making of a conscious decision not to act sets this area apart from mere silence by the legislature, which might be characterised as the legislature leaving the field to the Courts for resolution." (emphasis in original)

37. This Court is not concerned in this appeal with "gene patenting" generally, but with whether the invention as claimed in Claims 1 to 3 falls within established applications of the concept of manner of manufacture. If it does not, then the question is one of inclusion not exclusion. The legislative history cannot be read as impliedly mandating the patentability of claims for inventions relating to isolated nucleic acids coding for particular polypeptides. The legislative history does not assist the Court in answering the question posed in this appeal.

38. Against that general background, the relevant science, the patent specification and the impugned claims can be considered.

The primer — setting out the relevant science

39. The parties agreed on a primer of scientific matters setting out aspects of the structure and functions of DNA, the nucleotides which make it up, and the gene sequences which they form that determine the production of the various proteins which generate bodily tissues and fluids. The primer described how DNA replicates in the human cell and the way in which a sequence of nucleotides can be derived from a naturally occurring sequence and reproduced artificially as a distinct molecule outside the cell. Based upon the expert evidence at trial, the primer may be taken as embodying the scientific background, presumably comprising common general knowledge, or at least relevant prior art, against which the complete specification, including the claims, is to be read.

DNA and RNA in the human cell

40. The human body is a multi-cellular organism. Its cells reproduce by binary division. Their contents are the cytoplasm and the nucleus, which are all contained in an outside membrane. The bulk of the cytoplasm consists of water, salts and organic molecules. It also contains discrete functional components, including ribosomes, which are important to protein and energy production. The nucleus is confined within the cell by a nuclear envelope or membrane. The nuclear envelope is porous such that certain molecules may pass between it and the cytoplasm.

41. The nucleus contains DNA and RNA. The DNA molecule comprises arrangements of hydrogen, oxygen, carbon, nitrogen and phosphorus atoms. Those arrangements, called "nucleotides", are linked end-to-end. The sequence of the nucleotides incorporates a "genetic code" that defines the growth, development, maintenance and reproduction of the human body. Each nucleotide comprises a group of atoms including nitrogen, called a nitrogenous base, coupled with a phosphate group and a sugar group. There are four kinds of nitrogenous bases in DNA: adenine, guanine, cytosine and thymine designated A, G, C and T respectively. Those letters may be regarded as the alphabet of the genetic code.

42. The sugar and phosphate group components of each nucleotide make up the backbone of the DNA chain. Each nitrogenous base is covalently bonded to the sugar group. Covalent bonding is an electrostatic attraction which binds atoms together when they share unpaired electrons.

43. Covalent bonds run from the fifth carbon atom of the sugar group of one nucleotide to the third carbon atom of the phosphate group of the adjacent nucleotide. One end of each DNA chain has a free fifth carbon on the sugar group. The other end has a free third carbon on the phosphate group. DNA chains are accorded, by convention, a directionality from the 5' end to the 3' end.

44. DNA is almost always found in the cell nucleus as two polynucleotide chains intertwined to form a double helix. The two chains or strands are oriented in opposite directions. One, which runs from 5' to 3', is known as the "sense" or "coding" strand. The other, running from 3' to 5', is known as the "anti-sense" or "non-coding" strand. The sugar and phosphate groups form the outside of the double helix, while the nitrogenous bases are arranged on the inside in pairs perpendicular to the axis of the double helix so that the base G bonds with the base C and the base A bonds with the base T. The bonds are hydrogen bonds .

45. DNA molecules within the cell nucleus are wrapped around spooling proteins called histones to form complexes known as nucleosomes. The nucleosomes are stacked on top of each other to form chromatin fibres organised into chromosomes.

46. RNA mediates the transmission of the information contained in the genetic code for the purposes of the production of proteins. It has some similarity to DNA. It has the nitrogenous bases A, G and C, but its fourth base is uracil ("U") instead of thymine. It is single stranded and shorter than DNA. Its nitrogenous bases are exposed. Two important kinds of RNA are messenger RNA ("mRNA") and pre messenger RNA ("pre-mRNA").

Genes

47. A gene is a functional unit of the DNA molecule which provides a chemical blueprint or code used by other parts of the human cell to produce a particular protein. A gene is said to be "expressed" when it results in the synthesis of a protein within the cell. The sequences of the bases in DNA comprising genes are called "exons". They may include "non-coding" or "untranslated" regulatory regions. Those regulatory regions occur at the 5' and 3' ends of the gene. Other parts of the DNA chain which do not code for proteins and do not form part of the untranslated region of a gene are called "introns". Introns comprise about 25 per cent of the human genome. The term "genome" refers to the entirety of the DNA sequence within an organism. The human genome consists of about 25,000 genes arranged onto chromosomes and comprises approximately 3.2 billion nucleotides. Absent mutation all nuclear cells in an individual human body contain the same genomic sequences in their DNA.

48. Proteins are sequences of amino acids linked together by what are called peptide bonds on a phosphate backbone. They are referred to as "polypeptides". Each protein has its own unique amino acid sequence. There are 20 different amino acids known in nature. Some proteins act as enzymes, others generate movement, others form structures and others regulate cell division. When the DNA which encodes those regulatory proteins is mutated or damaged, uncontrolled cell division, characteristic of cancer, can occur.

49. The so-called "genetic code" consists of groups of three nucleotides, called "codons" or "triplets", each coding for an amino acid. There are a number of different DNA or RNA sequences that can code for the same protein. The sequences of codons that represent specific amino acid sequences ultimately will determine the particular protein to be synthesised in the cell.

Genes expressing proteins

50. Gene expression, by which a cell produces protein, begins within the nucleus of the cell with the "transcription" process. A portion of the DNA nucleotide sequence of a gene is copied onto an RNA nucleotide sequence. A single strand of the DNA double helix synthesises a complementary strand of nascent mRNA, known as pre-mRNA. Pre-mRNA contains both the exonic and intronic sequences of the genes transcribed from the DNA. The nucleotide sequence of the strand of pre-mRNA transcribed from the DNA template strand will correspond to the non-template (the "sense" or "coding") DNA strand.

51. During transcription, the 5' end of the transcribed sequence in the pre mRNA is modified by the addition of a "cap" to protect the molecule from enzymatic degradation and to assist in transport of the mature mRNA molecule from the nucleus to the cytoplasm. The 3' end of the

sequence is also modified by addition of a string of adenosine bases, known as the "poly-A tail". The introns are then removed and the exons joined together by an enzyme complex called a "spliceosome". The result is an mRNA molecule comprising a complementary sequence of the exons found in the DNA strand from which they were transcribed.

52. The mRNA molecule moves through the nuclear envelope into the cytoplasm. Its nucleotide sequence is used as a template in a process of "translation" resulting in the manufacture of the polypeptide chains comprising the relevant protein. That manufacture takes place in the ribosomes located in the cytoplasm. The RNA sequence is scanned in groups of codons which each define a specific amino acid. Depending upon which strand of DNA is read and the start site for its transcription and translation, different mRNAs and different proteins can result from the same stretch of DNA. It is also possible that a single stretch of DNA may be transcribed in two different directions, resulting in two different proteins with different amino acid sequences. The notion of one gene per protein is now understood to be simplistic.

53. The production of a protein or RNA from a gene is tightly regulated by other genes and DNA sequences and regulatory proteins, including histones. Together they are colloquially described as "the committee". The committee regulates whether a polypeptide is expressed in a cell, when, in what form and in what quantity. Those associated molecules are essential for the operation of DNA inside the cell. The BRCA1 gene in DNA, which is relevant to the patent in suit, can be transcribed and translated into a number of different mRNA sequences and proteins. Inside the cell, the genome beyond the BRCA1 gene controls the expression of proteins.

Isolation of nucleic acids

54. An isolated nucleic acid bearing a DNA sequence is a sequence of nucleotides derived from a DNA molecule that has been removed from its normal cellular environment. The means by which that can be done may be summarized as follows:

> "•DNA is obtained from cells removed from a sample of tissue or blood extracted from an individual. The tissue sample is broken into clumps of cells or individual cells using enzymes or chemicals suitable for that purpose.
>
> • Contents of the nucleus, including DNA and RNA, can be released into a free-floating liquid suspension by bursting the cell membrane or nuclear membrane using ultrasonic pressure waves or simple grinding.

• Proteins associated with the DNA, including histones, can then be degraded by the addition of enzymes known as proteases. They destroy the nucleosomes but do not eliminate all of the protein associated with the DNA.

• The addition of a high salt solution precipitates the degraded proteins which are then separated from the DNA using a well-known chemical procedure that takes advantage of the fact that the proteins are soluble in phenol, while DNA and RNA are not.

• The remaining liquid suspension is subject to centrifugation which places DNA and RNA in the interface between phenol and chloroform. The RNA can then be broken down by enzymes, leaving only the purified DNA which can be precipitated into a solid state."

The isolation of the nucleic acid by extraction and purification from a cell involves:

"(a) breaking the hydrogen bonds between nitrogen bases; and

(b) breaking some of the covalent bonds in the sugar phosphate backbone."

55. There is also a way in which a "synthetic human DNA" can be created with the use of mRNA as a template. The product is called "complementary DNA" ("cDNA"). The technique is called "reverse transcription" as it involves the use of an enzyme, "reverse transcriptase", not naturally found in humans. The result of reverse transcription is the creation of an RNA cDNA hybrid molecule which can be converted to a double stranded DNA molecule by more than one means. Although mRNA is less stable than DNA it can, like DNA, be isolated from the natural environment of the cell. The hybrid molecule, being more stable, is better suited than the mRNA molecule for use in molecular biology applications.

Isolated nucleic acids

56. An isolated nucleic acid, lacking histones and regulatory proteins, is not part of the complex three-dimensional structure of which DNA in the cell nucleus is part. That structure is an essential element in the transcription process. Without it the genome would not fit within the cell nucleus.

57. The BRCA1 gene comprises about 100,000 bases within the 3.2 billion base pair genome. It is exposed to the actions of the whole of the genome controlling a complex and interdependent network of DNA sequences, proteins and mRNA. The isolated nucleic acid referred to in Claims 1 to 3 of the Patent is separated from those influences. It is not exposed to any of the regulatory mechanisms which affect the way in which nucleic acid within the

cell produces protein. The isolated nucleic acid, removed from its cellular environment, cannot produce a polypeptide. It is inert, although capable of being artificially manipulated to produce a protein.

58. In order to effect transcription of isolated DNA it is necessary to add primers, chemical buffers, RNA polymerases and nucleotides. Even so the isolated DNA can only be transcribed into a single mRNA transcript. In a nucleus as part of the genome, the BRCA1 gene can be transcribed into a number of different isoforms. Some intronic mutations in BRCA1 influence breast cancer by their effects on RNA splicing.

The uses of isolated nucleic acids

59. Isolated nucleic acid has properties useful in experimental circumstances which are not possessed by nucleic acid in the native state. Once isolated and purified, the nucleic acid sequence can be determined using a number of different laboratory techniques. The sequence of nucleotides of DNA, or any part of it, cannot be determined in situ in the cell.

60. The isolated nucleic acid can be used in a number of ways as a probe to determine whether particular genes are being expressed in tissues. It can be cloned into vectors such as plasmids, which can be used to infect bacterial host cells and to take advantage of their transcriptional and translational machinery to produce "recombinant protein". It can also be artificially mutated or otherwise manipulated to produce novel genetic sequences and potentially recombinant proteins. Isolated nucleic acid can also be used in gene therapy, typically by incorporating it into a viral vector and introducing it into the cells of a patient with a defective copy of the gene in the patient's nucleic acid sequence. Isolated nucleic acid has application in genetic testing, where the sequence of the isolated sample is compared to a normal reference sequence. The reference sequence may be one of many developed by professional bodies or government agencies in the United States or Europe. The purpose of genetic testing is to determine what variations, if any, are present in a specific region of DNA and their clinical significance. This points up the matter which is the subject of a concession by Myriad namely that the utility of what is here claimed lies in the sequence.

61. In BRCA1 genetic testing, the patient's DNA is extracted and the relevant site sequence is determined . That is compared with the sequence for normal BRCA1, thus enabling the identification of mutations or polymorphisms in the patient's DNA. Absent such a genetic test it would not be possible to know whether an individual or family carries normal or mutated BRCA1. DNA in the natural state cannot be used to identify sequence variations in defined genes for genetic testing purposes.

The patent specification

62. The "Field Of The Invention" is defined, under that heading, as relating to "methods and materials used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer, in particular, breast and ovarian cancer."

63. The "background of the invention" refers to "[i]ntense efforts to isolate the BRCA1 gene [which] have proceeded since it was first mapped in 1990". The problem to which the invention as claimed was at least in part directed is stated:

> "Identification of a breast cancer susceptibility locus would permit the early detection of susceptible individuals and greatly increase our ability to understand the initial steps which lead to cancer. As susceptibility loci are often altered during tumor progression, cloning these genes could also be important in the development of better diagnostic and prognostic products, as well as better cancer therapies."

The "Summary Of The Invention" Repeats In Substance The First Paragraph Of The Section Headed "Field Of The Invention".

64. The first paragraph of the "DETAILED DESCRIPTION OF THE INVENTION" repeats in substance the first paragraph of the "FIELD OF THE INVENTION". Relevantly to the three impugned claims, the next paragraph states:

> "The present invention provides an isolated polynucleotide comprising all, or a portion of the BRCA1 locus or of a mutated BRCA1 locus, preferably at least eight bases and not more than about 100 kb in length. Such polynucleotides may be antisense polynucleotides. The present invention also provides a recombinant construct comprising such an isolated polynucleotide, for example, a recombinant construct suitable for expression in a transformed host cell."

65. The range of lengths of the mutant BRCA1 locus does not define the range of lengths of the isolated nucleic acids claimed in the invention. That is made clear from the further statement in the specification that the DNA sequences usually comprise at least about five codons, with 15 nucleotides, more usually at least about 7-15 codons and, most preferably, at least about 35 codons. One or more introns may also be present. This number of nucleotides is said to be usually about the minimal length required for a successful probe that would hybridise specifically with a BRCA1-encoding sequence.

66. There are a number of definitions. The definition of "isolated nucleic acid" has already been discussed. Others appearing in the specification include "encode" and "BRCA1 nucleic acids":

> "'Encode'. A polynucleotide is said to 'encode' a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for and/or the polypeptide or a fragment thereof. The anti-sense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom."
>
> "'BRCA1 Locus', 'BRCA1 Gene', 'BRCA1 Nucleic Acids' or 'BRCA1 Polynucleotide' each refer to polynucleotides, all of which are in the BRCA1 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancers ..."
>
> Those terms, applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA1 polypeptide fragment, homolog or variant, including protein fusions or deletions. It is then said:
>
> "The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA1 encoding gene or one having substantial homology with a natural BRCA1 encoding gene or a portion thereof. The coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO:1, with the amino acid sequence shown in SEQ ID NO:2."
>
> The specification goes on:
>
> "The polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art."
>
> There is no limitation, express or implied, in the claims or derived from the specification, upon the class of processes which may yield the claimed products."

67. The claims, as counsel for Myriad accepted, cover "a very wide number" of chemical compounds. As described in the specification, the invention includes isolated polynucleotides ranging in length from 8 bases to 100,000 bases. Myriad's submission that Claims 1 to 3 relate to chemical compounds raises a question about their chemical formulae. The formula for any member of the class would depend upon the number of bases in the isolate and whether, in addition to the BRCA1 sequence, it contained introns or other

non-coding regions. It would also depend upon which of the specified mutations or polymorphisms appear in the isolate. No upper limit on the number of isolated nucleic acids in the classes covered by the impugned claims was identified.

68. The specification explains that a combination of sequences obtained from cDNA clones, hybrid selection sequences and amplified PCR products allowed construction of a composite full length sequence for BRCA1 cDNA designated SEQ ID No:1. That sequence description, as shown in the specification, sets out nucleotides and codons which are numbered sequentially. The amino acid encoded by each codon is shown. The bases comprising the sequence are A, T, C and G, which are found in DNA. The corresponding RNA sequences can be inferred by substituting U for T where T appears in SEQ ID No:1. It contains only exons and the regulatory non-coding sequences mentioned earlier.

69. Tables also set out in the specification identify mutations and polymorphisms by reference to SEQ ID No:1. Predisposing mutations found in the BRCA1 genes of various patients are set out in Tables 12, 12A and 14, recorded as variations of the coding sequence in SEQ ID No:1. Table 18 identifies "Polymorphisms in BRCA1 Genomic DNA Exons". They are the relevant mutations and polymorphisms mentioned in the claims.

70. The primary judge observed that the disputed claims do not say anything about the length of the polynucleotide chains with which they are concerned. His Honour said :

> "In this regard, there is nothing to suggest either in the claims themselves or in the body of the specification that a complete molecule of DNA as originally found on chromosome 17 that has been isolated, and that includes one or more of the relevant mutations, would be outside the scope of the disputed claims."

In upholding a notice of contention on the appeal, the Full Court interpreted that statement as suggesting that Claim 1 covered the gene comprising the nucleic acid sequence as it exists in nature . Their Honours quoted Lourie J in the United States Court of Appeals for the Federal Circuit in a decision subsequently overturned by the Supreme Court of the United States . Lourie J said :

> "The ability to visualize a DNA molecule through a microscope, or by any other means, when it is bonded to other genetic material [and in a particular regulatory environment] is worlds apart from possessing an isolated DNA molecule that is in hand and usable."

It is not at all clear that in saying what he did, the primary judge was disregarding the setting and functional differences between isolates and the DNA molecule in its cellular

environment. In any event, his Honour went on to say, in a passage relied upon by Myriad, that :

"naturally occurring DNA and RNA as they exist in cells are not within the scope of any of the disputed claims and could never, at least not until they had been isolated, result in the infringement of any such claim."

Nevertheless, the class of isolated nucleic acids covered by the claims is large and diverse.

71. A number of sections of the specification relate to methods for the use of nucleic acids in various ways and the preparation of recombinant or chemically synthesised nucleic acids and vectors. The claims in the patent relating to those matters are not in issue. Nor is there any question about the utility of the applications of isolated nucleic acids reflected in those undisputed claims.

Isolated nucleic acid — composite or extract?

72. There is no claim in the patent for the process of isolation nor could there be as no new process is disclosed. However, in answer to questions from the Court, counsel for Myriad focussed upon an aspect of the evidence about isolation processes in order to deflect a suggestion that an isolated nucleic acid can be viewed as a "piece" of naturally occurring DNA or RNA. He contended that isolation involved alteration of the order of the relevant nucleotides and their reassembly in the order in which they had been placed in the cell. That proposition was supported by reference to the evidence of the expert witness, Dr Suthers. Dr Suthers had agreed that a conventional way of extracting a gene sequence, as distinct from synthesising it, would involve breaking the hydrogen bonds between the bases and breaking some covalent bonds to release the extract. He also agreed that in the mid-1990s a 100,000 base sequence would be broken up into smaller pieces which could then be amplified and stitched together physically or "conceptually".

73. The preceding argument has some similarity to Myriad's submission to the primary judge that Dr Suthers' evidence supported the proposition that there would be at least some breaking of the covalent cells in the sugar phosphate backbone as a result of the isolation process . The primary judge said :

> "It is not apparent to me that every isolated DNA sequence within the scope of the claims must have had at least some covalent bonds broken as a result of the isolation process. Nor would I imply any such requirement into the claims merely because, in Dr Suther's experience, this is what occurs. To interpret the disputed claims in this way would require me to impose an impermissible gloss upon the words of the claim."

Nor, as previously noted, are the claims subject to any process based limitation involving the breaking up and physical stitching together of the sequences comprising the isolated nucleic acids which are the products the subject of the claims. The "conceptual" stitching together, which may be regarded as the ordered compilation of information defining the relevant sequence, falls outside the claims entirely. The claims encompass molecules comprising isolated nucleic acids containing coding nucleotides arranged in the same sequence as appears in the DNA from which they were derived, whether or not introns and other non-coding sections have been removed from the relevant stretch of that DNA.

The primary judge's decision

74. For the primary judge, the issue of patentability turned on :

> "whether an isolated nucleic acid, which may be assumed to have precisely the same chemical composition and structure as that found in the cells of some human beings, constitutes an artificial state of affairs in the sense those words should be understood in the present context."

That approach, as observed earlier, involves application of the verbal formula in NRDC and the apparent assumption, no doubt derived from the way the case was framed before his Honour, that it was a sufficient condition of inherent patentability.

75. His Honour observed that isolated nucleic acids do not exist inside the cell and their isolation required "immense research and intellectual effort." Despite his Honour's reliance upon the "artificial state of affairs" formula, the influence of wider purposive considerations was apparent in his judgment, including the observation that :

> "It would lead to very odd results if a person whose skill and effort culminated in the isolation of a micro-organism (a fortiori, an isolated DNA sequence) could not be independently rewarded by the grant of a patent because the isolated micro-organism, no matter how practically useful or economically significant, was held to be inherently non-patentable."

76. His Honour cited the practice of the Australian Patent Office , and the rejection by Parliament of proposed amendments precluding gene sequences from patentability . Those matters led to no firm conclusion beyond a finding that it was not the intention of Parliament to deal with the issue of gene patenting by way of express exclusion but to leave it to the courts to apply the law as settled in NRDC and other relevant authorities . His Honour referred to patent laws of the European Union as permitting patentability of gene sequences . It is difficult to discern how those matters could have been related to a simple categorical

application of the "artificial state of affairs" criterion. Their relevance can only have been to wider considerations of the kind discussed earlier in these reasons although how they were used was not apparent from his Honour's reasons.

77. In the event, his Honour concluded that each of the disputed claims was to "a manner of manufacture as that expression should now be understood."

The decision of the Full Court

78. The Full Court described the impugned claims as claims "for a product set within a context of invention described in the specification: a context of development, through research and work, of the knowledge of the mutations or polymorphisms in question, and of the finding of the gene in question." Their Honours emphasised the character of the claims as relating to "the nucleic acid as isolated from the cell" and differences between the claimed product and the "naturally occurring product" .

79. Their Honours referred at some length to the decision of the Supreme Court of the United States in Association for Molecular Pathology v Myriad Genetics Inc . That decision was concerned with the application of 35 USC §101 to claims differently expressed from those impugned in this case :

> "1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID No:2.
>
> 2. The isolated DNA of claim 1 wherein said DNA has the nucleotide sequence set forth in SEQ ID No:1 ("the Myriad claims"). The Supreme Court had accepted that the creation of a cDNA sequence from mRNA resulted in an exon-only molecule that was not naturally occurring and was therefore patentable . The Myriad claims, however, fell squarely within a "law of nature" exception. While Myriad had discovered the location of the BRCA1 gene that discovery did not lend to the BRCA1 gene the character of a new composition of matter within 35 USC §101 ."

80. The Full Court preferred the reasoning of the United States Court of Appeals for the Federal Circuit in Association for Molecular Pathology v United States Patent and Trademark Office , which had been overturned by the Supreme Court. Their Honours characterised that reasoning as based on an analysis of the products as products and not of the information that they contained . They held that, consistently with NRDC and Australian law, their analysis should focus on differences in structure and function effected by the intervention of man and not on the similarities .

81. Outside the logical framework which they had defined for their analysis, their Honours adverted to the primary judge's consideration of Australian Patent Office practice, the ALRC Report, and the legislative history. They also referred to the Executive Government's response to the ALRC Report, including its acceptance of the recommendation that the Act not be amended to exclude genetic materials and technologies from patentable subject matter . They said :

> "While these legislative matters do not affect what constitutes patentable subject matter under the rubric of 'manner of manufacture', Parliament has considered, and has specifically declined, to exclude purified and isolated gene sequences from the scope of patentable subject matter."

82. Before the Full Court, Ms D'Arcy submitted that isolated nucleic acid was not materially different to cellular nucleic acid and that naturally occurring DNA and RNA, even in isolated form, are products of nature that could not form the basis of a valid patent. Myriad, on the other hand, contended that its claims were for a product consisting of an artificial state of affairs providing a new and useful effect of economic significance, and that isolated nucleic acid differed from the nucleic acid found in a human cell chemically, structurally and functionally .

83. As previously observed, in its concluding paragraphs, the Full Court eschewed the relevance of policy, moral or social reasons for the exclusion of patents for gene sequences . Like the majority in Chakrabarty, their Honours said of those considerations :

> "It is not a matter for the court, but for Parliament to decide. Parliament has considered the question of the patentability of gene sequences and has chosen not to exclude them but to make amendments to the Act to address, in part, the balance between the benefits of the patent system and the incentive thereby created, and the restriction on, for example, subsequent research."

They characterised the subject matter of the claims as :

•a compound, not information;

• an isolated nucleic acid, which is taken out of the genome and removed from the cell and is unable to be the subject of cellular processes of transcription and translation;

• containing the code for a mutant or polymorphic protein; and

• containing a sequence identified by comparison with tables created following extensive research describing the location of the mutations or polymorphisms in DNA.

84. It was common ground before the Full Court that the isolated nucleic acids had valuable economic uses . In their reasons, their Honours said :

"The isolation of the nucleic acid also leads to an economically useful result — in this case, the treatment of breast and ovarian cancers. This is surely what was contemplated by a manner of new manufacture in the Statute of Monopolies."

The Full Court concluded that the isolated nucleic acids, including cDNA, had resulted in an artificially created state of affairs for economic benefit and that the claimed product was properly the subject of letters patent .

85. The passage quoted in the preceding paragraph, which appears to refer to the process of "isolation", does not disclose a pathway to patentability of the invention as described in Claims 1 to 3. That is so even if they were to be characterised as product claims simpliciter, a characterisation which, as appears below, we do not accept. The economic significance necessary to the patentability of an "artificially created state of affairs" in the sense used in NRDC is not demonstrated by stating that the artificially created state of affairs is a step along the way to a process or method itself claimed as an artificially created state of affairs of economic significance.

Conclusions

86. Myriad submitted, as the Full Court had held, that its claims are for a product. To assess patentability, it said, they must be construed in the same way as any other claim for an invention which is a product. The product was "a chemical compound [which] has no counterpart in nature." That characterisation of the claims superficially accords with their form.

87. The approach taken by the Full Court and urged by Myriad involves an apparently straightforward characterisation based on the formal terms of the patent identifying the isolated nucleic acids as products which, notwithstanding their derivation from naturally occurring DNA, have been brought into existence by human artifice and, in that sense, "made". So characterised, and without further inquiry into the breadth of the claims or their substance, they could be seen to fall comfortably within principles attracting characterisation as a manner of manufacture. None of the purposive or policy factors mentioned earlier in these reasons need be considered on that approach.

88. Identification of the subject matter of the claims as a class of chemical compounds is the premise upon which the Full Court's conclusion is based. It is a premise which, with respect, elevates form over substance to the detriment of the developmental function entrusted to the

Court as explained in NRDC and reflected in the continuing use of the "manner of manufacture" formula in s 18(1)(a) of the Act.

89. The code in the invention as claimed refers to the sequence of nucleotides which, in a cellular environment, can ultimately be translated into the BRCA1 polypeptide. That sequence can properly be described as "information", the ordinary meaning of which includes :

> "Without necessary relation to a recipient: that which inheres in or is represented by a particular arrangement, sequence, or set, that may be stored in, transferred by, and responded to by inanimate things".

Used in that sense, the information stored in the sequence of nucleotides coding for the mutated or polymorphic BRCA1 polypeptide is the same information as that contained in the DNA of the person from which the nucleic acid was isolated. It is the existence of that information which is an essential element of the invention as claimed. The product is the medium in which that information resides. That characteristic also attaches to cDNA, covered by the claims, which is synthesised but replicates a naturally occurring sequence of exons.

90. Ms D'Arcy submitted that none of the chemical, structural or functional differences between isolated nucleic acids and nucleic acids in the cellular environment, relied upon by Myriad, plays any part in the definition of the invention as claimed in each of the claims. She invoked the observation of the plurality opinion of the Supreme Court of the United States in Myriad directed to a common feature of the claims in issue in that case and the claims in issue in this case :

> "Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes."

That characterisation, so far as it emphasises the focus of the claims on genetic information, is applicable to the claims in this case and, contrary to the view of the Full Court, should be accepted.

91. Ms D'Arcy also engaged with the finding by the Full Court that the isolated nucleic acids were patentable as "an artificially created state of affairs". Engaging with that criterion in this case places the question of patentability in too narrow a frame. It invites debates about the application of categories such as "products of nature" versus "artificially created

products" which may be distracting from the central issue, that is whether an essential integer of the claims, the genetic information, takes them outside the category of that which can be "made". But even if the criterion of an "artificially created state of affairs" were to define the area of discourse in this case, the fact of the existence of the requisite mutations or polymorphisms is a matter of chance. It is not something "made". It is not "artificially created".

92. There are perhaps two ways of looking at the role of genetic information in characterising the subject matter of the claims. One way is to say that the chemical formula of any given isolated nucleic acid is defined, in part, by the sequence of nucleotides which it reproduces and, in that sense, is defined by the information embodied in that sequence. Another way is to say that the particular chemical compound embodies and conveys the information. The latter approach gives the priority to the informational aspect which its importance to the utility of the claimed invention warrants.

93. When proper regard is paid to their emphasis on genetic information, the subject matter of the claims lies at the boundaries of the concept of "manner of manufacture". That it does lie at the boundaries is further evidenced by the odd consequence that if the claims are properly the subject of a patent, the patent could be infringed without the infringer being aware of that fact. That consequence coupled with the very large, indeed unquantified size of the relevant class of isolated nucleic acids, all of which bear the requisite information, raises the risk of a chilling effect upon legitimate innovative activity outside the formal boundaries of the monopoly and risks creating a penumbral de facto monopoly impeding the activities of legitimate improvers and inventors .

94. Although it may be said in a formal sense that the invention as claimed, referring to isolated nucleic acids, embodies a product created by human action, that is not sufficient to support its characterisation as a manner of manufacture. The substance of the invention as claimed and the considerations flowing from its substance militate against that characterisation. To include it within the scope of a "manner of manufacture" involves an extension of that concept, which is not appropriate for judicial determination. Further, to include this class of claim within that concept would not contribute to coherence in the law as was the case in Apotex. Nor do Australia's international obligations and the differently framed patent laws of other jurisdictions, which were referred to earlier in these reasons, support the conclusion that this class of claim should fall within the concept.

95. The invention as claimed in Claims 1 to 3 does not meet the requirement of s 18(1)(a) and the appeal should be allowed.

96. The following orders should be made:

1. Appeal allowed.

2. Set aside paragraph 1 of the order of the Full Court of the Federal Court of Australia made on 5 September 2014 and, in its place, order that:

(a) the appeal be allowed; and

(b) paragraph 1 of the order of Nicholas J made on 15 February 2013 be set aside and, in its place, order that claims 1, 2 and 3 of Australian Patent No 686004 be revoked."

Gageler and Nettle JJ.

97. In this matter, the question for the judge at first instance (Nicholas J) and on appeal to the Full Court of the Federal Court of Australia (Allsop CJ, Dowsett, Kenny, Bennett and Middleton JJ) was whether "a valid patent may be granted for a claim that covers naturally occurring nucleic acid ... that has been 'isolated'" . It was held that it may. For the reasons which follow, the appeal to this Court should be allowed and the claims should be held to be invalid.

The patent

98 The claims of the patent that were in suit were as follows :

"1. An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19[ ].

2. An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a mutant BRCA1 polypeptide, said DNA containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations set forth in Tables 12, 12A and 14.

3. An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a polymorphic BRCA1 polypeptide, said DNA containing in comparison to the BRCA1

polypeptide encoding sequence set forth in SEQ.ID No:1 one or more polymorphisms set forth in Tables 18 and 19."

99. It is common ground that the validity of claims 2 and 3 depended on the validity of claim

100. "Nucleic acid" refers to two kinds of chemical compound: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the primary source of genetic information in a human cell. DNA is comprised of "nucleotides". Each nucleotide includes a nitrogenous base, of which there are four kinds (abbreviated as A, G, C and T). Nucleotides are linked end-to-end by covalent bonds to form a polynucleotide chain. The bases protrude from the chain at a perpendicular angle. In the nucleus of a cell, DNA almost always exists as a double helix formed by the intertwining of two polynucleotide chains with the bases lying on the inside of the helix, with each base forming a hydrogen bond with the base on the opposing chain.

101. The sequence of nucleotides in DNA encodes information which is used by the cell to produce, and regulate the production of, proteins. "Polypeptides" are proteins – large, three-dimensional molecules comprised of sequences of amino acids linked by peptide bonds. The mechanism by which proteins are produced is complex, but for present purposes it is sufficient to state that various three-base sequences of nucleotides in DNA correspond with the production of different kinds of amino acids. The sequence of nucleotides dictates the kind and sequence of amino acids produced and thus the composition of the resulting protein. For example, the protein in humans known as "BRCA1" is encoded by a DNA sequence which consists of approximately 6,000 nucleotides in a highly specific sequence.

102. In its natural state, the sequence coding for any particular polypeptide or protein is present as a series of "fragments" along the DNA molecular chain. Each fragment is called an "exon" and each exon is separated from its adjacent exons by sections of non-coding DNA called "introns". Although the introns do not encode a polypeptide or protein, they contain information which helps regulate and execute the cell's response to the information encoded in the exon. The 6,000 nucleotides which encode the BRCA1 polypeptide or protein are present as 24 exons separated by introns.

103. The word "gene" is used in a number of senses. For present purposes, the meaning which is relevant is the unit of DNA that encodes a specific protein. Thus, the BRCA1 gene consists of the 6,000 nucleotides comprised in 24 exons which encode the BRCA1 polypeptide or protein.

104. DNA is "packaged" within the nucleus of human cells as follows. DNA strands are wound around proteins called histones to form nucleosomes, which, in turn, are stacked on

top of each other to form chromatin fibres. Chromatin fibres are organised into chromosomes. Production of proteins in a cell involves complex interactions between DNA and other factors together called the "committee", which includes the histones around which the DNA is wrapped; "regulatory proteins" present in the cell nucleus; other segments of DNA; and the three-dimensional structure of the DNA as packaged in the nucleus. The ultimate composition and structure of the proteins capable of being produced by a particular gene thus depend on several factors in addition to the sequence of nucleotides in the gene.

105. At conception, every human being inherits a half set of his or her mother's genetic information, consisting of 23 chains of DNA with 20,000 genes, and also a half set of his or her father's genetic information, consisting of another 23 chains of DNA with 20,000 genes. During gestation, that information is conveyed into every cell in the human being's body and thus results in two instances of every gene. The failure of one instance of a gene to operate normally can place the human being at a high risk of disease. For example, an abnormality in one instance of a woman's BRCA1 gene places her at high genetic risk of developing breast and ovarian cancer, even though the other instance of the BRCA1 gene may be functioning perfectly normally.

106. Medical genetic testing involves testing genetic material taken from a patient, inter alia, to identify abnormalities known to be indicative of disease. For example, genetic testing of a woman's DNA might identify an abnormal BRCA1 gene and thus reveal that she is at high genetic risk of developing breast and ovarian cancer. Treatment regimens are then structured accordingly.

107. Ordinarily, a test report includes details of any identified mutations of known clinical significance and also details of any variations of thus far unknown clinical significance. The latter are recorded to ensure that when and if the variation is later categorised as a mutation of clinical significance the clinician can inform the patient of its consequences.

108. The tools and techniques of genetic testing are long established and well understood by those who are skilled in the science. DNA is the most common target. A sample of DNA is removed from the patient's body and subjected to a range of processes to determine what if any variations there are between the sequence of nucleotides in the sample and what is known to be the normal sequence of nucleotides for the region of DNA the subject of examination. The variations, described as "mutations" or "polymorphisms", usually occur in exons and result in some abnormality in the protein derived from the gene. But they can also occur in introns. Some variations have been found to be present in a large number of patients and, as a result, have been classified as polymorphisms or mutations. There are also a number of other variations in the DNA sequence which have not yet been categorised as

polymorphisms or mutations but which it may be expected will be so categorised as expert knowledge of a particular gene and familial genetic patterns continues to develop. The assignment of such variations is a major concern for all laboratories providing medical genetic testing services.

109. In order to test a sample of naturally occurring DNA, it is necessary to break open human cells to expose the DNA. The goal is to remove the DNA from its normal cellular environment without corrupting the information contained in the DNA.

110. The DNA thus derived from the extraction process contains all of the DNA molecules from many cells, but the specific region of the DNA which is to be tested may account for only a small fraction of the DNA present in the sample. For example, the entire BRCA1 gene (exons plus introns) represents only 0.003 per cent of the total DNA obtained by such processes and the coding sequence of the BRCA1 gene accounts for an even smaller proportion (0.0002 per cent) of the DNA thereby obtained. Because isolated DNA has been removed from its cellular environment, and in particular from adjacent histones which support it and assist in the execution of its instructions, isolated DNA cannot survive unaided or reproduce. Isolated DNA is incapable of producing proteins as it would within the cell unless certain in vitro processes are performed upon it.

111. The isolation of the specific region of the DNA to be tested requires knowledge of the DNA sequences immediately flanking the target fragment. That information is available in medical databases and medical literature in the public domain. The isolation may be effected by a number of standard techniques but most often by making multiple copies of short fragments of the sequence of interest using a chemical process called PCR. Thus, for example, an exon of the BRCA1 gene may be amplified by the PCR process by ascertaining from the published literature the DNA sequence of a short segment (ordinarily between 50 and 100 nucleotides long) and the ends of the two introns which abut the exon. The amplification process is likely to result in millions of copies of the fragment and little other DNA.

112. The DNA sequence of the amplified fragment is then examined by a variety of methods for variations of established clinical significance as recorded in laboratory-based databases and, increasingly, as recorded in international reference sequences developed under the auspices of professional bodies and governmental agencies in the United States and Europe. As was earlier noticed, the sequence is also checked for variations of unknown significance.

113. Isolating DNA from a patient's cells using this process is useful for a number of purposes, including synthesis of recombinant protein, gene therapy, and as a "probe" to

investigate whether particular genes are being expressed in a patient. None of these processes can be performed on DNA as it exists within a person's cells. But for the purpose of determining whether a patient possesses a mutation or polymorphism in one or both of her BRCA1 genes that could predispose her to a greater risk of breast or ovarian cancer, the utility of isolating the BRCA1 genes from her cells is that the nucleotide sequences in the isolated DNA represent the nucleotide sequences found in the BRCA1 genes in each cell of her body. For this purpose, it is essential that the nucleotide sequence in the isolated nucleic acid is identical to that found in the patient's cells; and the processes described above are designed to ensure that this is so.

The scope of claim 1

114. "Isolated nucleic acid" is defined in the patent as nucleic acid "which is substantially separated from other cellular components which naturally accompany a native human sequence or protein". It is, therefore, the sort of isolated nucleic acid which is routinely produced by pathologists when subjecting DNA to genetic testing as previously described. And, as has already been noticed, it may be created by first stripping the DNA from the cell, ordinarily by means of the application of detergents to release the hydrogen bonds which bind the DNA to the cell, and then isolating and amplifying the fragment of interest using the PCR process or something comparable.

115. The reference in claim 1 of the patent to "coding for a mutant or polymorphic BRCA1 polypeptide" is to an isolated nucleic acid molecule which, when compared to the standard reference sequence set forth in SEQ.ID No:1, exhibits one or more of the 54 mutations or polymorphisms delineated in Tables 12, 12A, 14 and 18.

116. The sequence set forth in SEQ.ID No:1 represents the sequence of A, G, C and T nucleotides that is known to code for the BRCA1 polypeptide. It represents the concatenation of the exons of the BRCA1 gene, and thus is presented as an uninterrupted sequence of nucleotides without introns.

117. The 54 mutations and polymorphisms delineated in Tables 12, 12A, 14 and 18 are claimed to be present in women with familial breast cancer and the claim is supported by evidence referred to in the patent that those mutations have been found to disrupt the function of the BRCA1 gene. As such, the 54 mutations and polymorphisms represent some three per cent of more than 1,600 mutations and polymorphisms of the BRCA1 gene which have now been identified as having clinical significance, and the catalogue continues to grow.

118. The only way of determining whether a patient has a mutation or polymorphism of the BRCA1 gene that is of clinical significance is for a pathologist to take a sample of the

patient's DNA, isolate it from the cell in the manner already described, isolate and amplify the BRCA1 sequence by use of the PCR process, or by means of another comparable process or an analogous synthetic process, and compare the isolated sequence with known comparators recorded in the laboratory and other databases earlier described. It follows that the only means of determining whether a patient is afflicted by any of the mutations or polymorphisms delineated in Tables 12, 12A, 14 and 18 of the patent is for a pathologist to take and analyse a sample of the patient's DNA and compare its sequence to the sequences delineated in Tables 12, 12A, 14 and 18.

119. For convenience throughout the remainder of these reasons, the expression "BRCA1 gene" will be used to refer generally to isolated nucleic acid which codes for a BRCA1 polypeptide and the expression "mutated BRCA1 gene" will be used to refer to an isolated nucleic acid which codes for a BRCA1 polypeptide and which, in comparison to the BRCA1 sequence identified in SEQ.ID No:1, exhibits any of the mutations or polymorphisms identified in Tables 12, 12A, 14 and 18.

What is the product over which a monopoly is claimed?

120. As noted, claim 1 of the patent is a claim for an isolated nucleic acid which, compared to the known sequence of A, G, C and T nucleotides that codes for the BRCA1 gene, contains one or more of the mutations delineated in Tables 12, 12A and 14, or one or more of the polymorphisms set forth in Table 18 ("the specified mutations and polymorphisms"). Thus, as drafted, claim 1 presents as a claim by the first respondent that it has invented and thus is entitled to a monopoly over a manner of manufacture of isolated nucleic acid exhibiting any of the specified mutations and polymorphisms.

121. For reasons which will appear, it is significant that the first respondent does not and could not claim a monopoly over the process or method of manufacture of isolated nucleic acid per se, or for the process or method of manufacture constituted of the separation and amplification of the BRCA1 gene. As was earlier explained, the concepts and methods of manufacturing isolated nucleic acid and isolating and amplifying particular sequences of nucleic acid are long-established standard testing and diagnostic techniques. Presumably, it is for that reason that claim 1 is limited to a claim for a monopoly over the right to "manufacture" what the first respondent calls the "product" which results from isolating the BRCA1 gene when and if the nucleic acid so isolated contains any of the specified mutations and polymorphisms.

Patentable subject matter

122. As at the priority date, a "patentable invention" was defined in s 18(1) of the Patents Act 1990 (Cth) as follows:

> "Subject to subsection (2), a patentable invention is an invention that, so far as claimed in any claim:
>
> (a) is a manner of manufacture within the meaning of section 6 of the Statute of Monopolies; and
>
> (b) when compared with the prior art base as it existed before the priority date of that claim:
>
> (i) is novel; and
>
> (ii) involves an inventive step; and
>
> (c) is useful; and
>
> (d)was not secretly used in the patent area before the priority date of that claim by, or on behalf of, or with the authority of, the patentee or nominated person or the patentee's or nominated person's predecessor in title to the invention."

123. The essential question in this case is whether the subject matter of claim 1 is an invention that so far as claimed is a manner of manufacture within the meaning of s 6 of the Statute of Monopolies as described in s 18(1)(a).

124. As was emphasised in National Research Development Corporation v Commissioner of Patents ("NRDC"), in relation to the Patents Act 1952 (Cth), the conception of a manner of manufacture is not limited to physical production but takes its meaning from the whole category under which all grants of patents which may be made in accordance with the developed principles of patent law are to be subsumed:

"It is of the first importance to remember always that the Patents Act 1952-1955 (Cth), like its predecessor the Patents Act 1903 (Cth) and corresponding statutes of the United Kingdom (see the Patents, Designs and Trade Marks Act 1883, s 46; the Patents Act 1907, s 93; and the Patents Act 1949, s 101), defines the word 'invention', not by direct explication and in the language of its own day, nor yet by carrying forward the usage of the period in which the Statute of Monopolies was passed, but by reference to the established ambit of s 6 of that Statute. The inquiry which the definition demands is an inquiry into the scope of the permissible subject matter of letters patent and grants of privilege protected by the section. It is an inquiry not into the meaning of a word so much as into the breadth of the concept which the law has developed by its consideration of the text and purpose of the Statute of

Monopolies. One may remark that although the Statute spoke of the inventor it nowhere spoke of the invention; all that is nowadays understood by the latter word as used in patent law it comprehended in 'new manufactures'. The word 'manufacture' finds a place in the present Act, not as a word intended to reduce a question of patentability to a question of verbal interpretation, but simply as the general title found in the Statute of Monopolies for the whole category under which all grants of patents which may be made in accordance with the developed principles of patent law are to be subsumed. It is therefore a mistake, and a mistake likely to lead to an incorrect conclusion, to treat the question whether a given process or product is within the definition as if that question could be restated in the form: 'Is this a manner (or kind) of manufacture?' It is a mistake which tends to limit one's thinking by reference to the idea of making tangible goods by hand or by machine, because 'manufacture' as a word of everyday speech generally conveys that idea. The right question is: 'Is this a proper subject of letters patent according to the principles which have been developed for the application of s 6 of the Statute of Monopolies?'"

Threshold quality of inventiveness

125 In NRDC, it was also held that it was enough for a process to constitute a manner of manufacture that it resulted in an artificially created state of affairs of economic significance :

> "Notwithstanding the tendency of these decisions, the view which we think is correct in the present case is that the method the subject of the relevant claims has as its end result an artificial effect falling squarely within the true concept of what must be produced by a process if it is to be held patentable. This view is, we think, required by a sound understanding of the lines along which patent law has developed and necessarily must develop in a modern society. The effect produced by the appellant's method exhibits the two essential qualities upon which 'product' and 'vendible' seem designed to insist. It is a 'product' because it consists in an artificially created state of affairs, discernible by observing over a period the growth of weeds and crops respectively on sown land on which the method has been put into practice. And the significance of the product is economic; for it provides a remarkable advantage, indeed to the lay mind a sensational advantage, for one of the most elemental activities by which man has served his material needs, the cultivation of the soil for the production of its fruits. Recognition that the relevance of the process is to this economic activity old as it is, need not be inhibited by any fear of inconsistency with the claim to novelty which the specification plainly makes. The method cannot be classed as a variant of ancient procedures. It is additional to the cultivation. It achieves a separate result, and the result possesses its own economic utility consisting

> in an important improvement in the conditions in which the crop is to grow, whereby it is afforded a better opportunity to flourish and yield a good harvest."

That holding is, however, to be understood as importing the Court's earlier observations as to the meaning of an "invention" and the idea that all that had come to be understood by that word, as used in patent law, is comprehended in the phrase "new manufactures". It should not be taken to suggest that an "artificial state of affairs" and "economic utility" are the only considerations relevant to whether an invention is "a manner of manufacture" for the purposes of s 18(1)(a) of the Act.

126. For a claimed invention to qualify as a manner of manufacture it must be something more than a mere discovery. The essence of invention inheres in its artificiality or distance from nature; and thus, whether a product amounts to an invention depends on the extent to which the product "individualise[s]" nature . As Professors Sherman and Bently wrote :

> "What then was required in order to move from the realm of discovery to that of invention? The simple answer was that it was necessary to show that abstract principles had been reduced to practice, that Nature had been individualised or activated. ... While philosophical or abstract principles could not on their own be patented, their embodiment in a material or practical form could. In these circumstances it was clear that in law it was the artificial or created nature of the final product, its distance from Nature, which ensured that an object became an invention rather than a mere discovery."

127. The question then is whether the subject matter of the claim is sufficiently artificial, or in other words different from nature, to be regarded as patentable.

128. Relevantly, the artificiality of a product may be perceived in a number of factors, including the labour required to create it and the physical differences between it and the raw natural material from which it is derived. Regardless, however, of the amount of labour involved or the differences between the product and the raw natural material from which it is derived, it is necessary that the inventive concept be seen to make a contribution to the essential difference between the product and nature .

129. Admittedly, it has occasionally been doubted that there is any longer a threshold requirement of inventiveness as opposed to the specific requirements of inventive step and novelty for which s 18(1)(b) provides. It has also been suggested that it would be desirable to collapse the subject matter requirement into the specific inquiries of inventive step and novelty. The Advisory Council on Intellectual Property concluded that it would make sense

for "questions of newness to be dealt with under the specific provisions for novelty and inventive step, rather than under the general umbrella of manner of new manufacture" .

130. But for present purposes, the law on the point appears to be tolerably clear. In Commissioner of Patents v Microcell Ltd, the Full Court held that the subject matter of a claim as disclosed in the specification must possess a quality of inventiveness or, in other words, the use of ingenuity that adds to the sum of human knowledge. In N V Philips Gloeilampenfabrieken v Mirabella International Pty Ltd , the majority recognised that the quality of inventiveness must appear on the face of the specification. In Advanced Building Systems Pty Ltd v Ramset Fasteners (Aust) Pty Ltd ("Ramset"), the majority held that whether claimed subject matter is an invention for the purposes of s 100(1)(d) of the Patents Act 1952 (Cth) is distinct from inquiries as to inventive step, obviousness and novelty under s 100(1)(e) and (g), and that the court below had erred in considering "inventive merit" in light of prior art for the purposes of s 100(1)(d) . The majority distinguished Philips on the basis that it was decided under the Patents Act 1990 (Cth) . But, at a later point in the judgment, the majority also acknowledged that, where the subject matter of a claim as disclosed in the specification is plainly not an invention, the claim should be dismissed .

131. Notwithstanding that Microcell did not establish a discrete "threshold" test , each of those decisions is consistent with the requirement, essential to the concept of a "manner of manufacture", that the subject matter of a claim have about it a quality of inventiveness which distinguishes it from a mere discovery or observation of a law of nature. That requirement is separate and distinct from the other requirements of inventive step and novelty. As Brennan, Deane and Toohey JJ stated in Philips, an alleged invention will :

> "remain unsatisfied if it is apparent on the face of the relevant specification that the subject matter of the claim is, by reason of absence of the necessary quality of inventiveness, not a manner of new manufacture for the purposes of the Statute of Monopolies. That does not mean that the threshold requirement of 'an alleged invention' corresponds with or renders otiose the more specific requirements of novelty and inventive step (when compared with the prior art base) contained in s 18(1)(b). It simply means that, if it is apparent on the face of the specification that the quality of inventiveness necessary for there to be a proper subject of letters patent under the Statute of Monopolies is absent, one need go no further."

Naturally occurring phenomena

132. As counsel for the first respondent stressed repeatedly in the course of argument, the appellant's only basis of objection is lack of patentable subject matter; in particular that,

because the mutated BRCA1 gene was a naturally occurring substance, it was incapable of being a patentable invention. It follows, as the first respondent contended, that other possible grounds of invalidity such as lack of inventive step, lack of novelty and lack of utility are irrelevant.

133. But the fact that the appellant objected on the sole basis of lack of patentable subject matter does not exclude the threshold requirement of inventiveness. For the reasons already given, the threshold requirement of inventiveness is part of the inquiry into whether the subject matter of the claim is a patentable invention.

134. Here, the essence of claim 1 is the correlation between the incidence of cancer and the presence of the specified mutations and polymorphisms in the mutated BRCA1 gene. Such ingenuity as that entails consists in the idea of examining an isolated fragment of a patient's naturally occurring DNA constituted of the BRCA1 gene for the presence or absence of the specified mutations and polymorphisms. The subject matter of the claim does not make any contribution to the inclusion of the specified mutations and polymorphisms in the mutated BRCA1 gene . Their presence or absence in or from it is the result of the isolated BRCA1 gene being part of the naturally occurring DNA from which the sequence is isolated. To adopt and adapt the reasoning in NV Philips' Gloeilampenfabrieken Application, it is "the inevitable result of that which is inherent in the [DNA]" .

135. In this case, the courts below concluded that, despite the presence or absence of the specified mutations and polymorphisms being the result of naturally occurring phenomena, the subject matter of the claim was a patentable invention. The Full Court held so because, as their Honours put it :

> "In Australia, there is no statutory or jurisprudential limitation of patentability to exclude 'products of nature'. To the contrary, the High Court has specifically rejected such an approach. A mere discovery is not patentable and an idea is not patentable, but a 'manner of manufacture', as that term has been developed, isIn our view the products the subject of claim 1 are different to the gene comprising the nucleic acid sequence as it exists in nature."

136. But in fact, there are limits on the patentability of products of nature inasmuch as products of nature do not involve human intervention and therefore are lacking in the necessary quality of inventiveness to qualify as a manner of manufacture . As Professor Sherman observed in his recent article on the subject :

> "The US product of nature doctrine and the Australian test of artificially created state of affairs are the same question asked from different perspectives. In both cases, they

build on an (implicit) image of what it means to invent something; ... nature and artifice are flip sides of the same coin."

137. Of course, as NRDC implies, the application of naturally occurring phenomena to a particular use may be a manner of manufacture if it amounts to a new process or method of bringing about an artificially created state of affairs of economic significance . Even so, the inventor cannot claim to have invented the naturally occurring product as opposed to the process of application. In NRDC, the patentee could not claim to have invented, and therefore there was no suggestion of it laying claim to a monopoly over, the commonplace herbicides which were used in the course of the patentable process. Similarly, in Shell Oil Co v Commissioner of Patents , the patentee could not claim to have invented, and therefore there was no suggestion of laying claim to a monopoly over, the known compounds which were applied as part of the patentable process to a new use of plant growth regulation. So too here, insofar as the invention consists in the application of a naturally occurring phenomenon to a particular use, the inventor cannot claim to have invented the naturally occurring phenomenon as opposed to the method of use and has no claim to a monopoly over the naturally occurring phenomenon as opposed to the method of use. The scope of the invention

138. Certainly, as the Full Court recognised , the substance of the claimed invention consists not only in the discovery of the BRCA1 gene but also in the development of a process or method of detecting the increased likelihood of certain kinds of malignancy by using known techniques to isolate the BRCA1 gene and examining it by the use of known techniques for the presence of the specified mutations and polymorphisms. On that basis, it might fairly be said that a pathologist who isolated a fragment of a patient's DNA comprising the BRCA1 gene and examined it for the presence of the specified mutations and polymorphisms, with the object of identifying the likelihood of malignancy of which the specified mutations and polymorphisms are claimed to be indicia, would make use of the claimed invention. But, equally on that basis, the pathologist would only infringe claims 1 to 3 if the patient's DNA happened to possess one or more of the specified mutations and polymorphisms.

139. Moreover, what if a pathologist had no interest in looking for the specified mutations and polymorphisms – indeed let it be assumed that the pathologist vehemently rejected the conclusion that the specified mutations and polymorphisms were clinically significant – and was concerned with isolating the fragment of a patient's DNA comprising the BRCA1 gene in order only to examine it for different mutations and polymorphisms which the pathologist's independent research had led him or her to conclude were of clinical significance? In those circumstances, the only aspect of the claimed invention of which the pathologist could be said to make any use would be the discovery of the BRCA1 gene; and as has been seen, the

BRCA1 gene is not patentable as such because it is a naturally occurring phenomenon which lacks the quality of inventiveness necessary to qualify as a manner of new manufacture .

140. Of course, that does not mean that an intention to infringe a patent is an essential element of infringement. If an inventor patents a product and another inventor later reinvents it in ignorance of its earlier invention, the subsequent inventor's ignorance is clearly no defence to a claim of infringement . Nor is it to deny that it is permissible in a proper case to define the physical characteristics of an article by reference to the result which the article may achieve or that, in cases where such a method of definition is appropriate, it is no objection to that method of definition that a person skilled in the art may need to experiment to ascertain whether an article made by that person infringes the patent . But, in the former case, there is infringement because the subsequent inventor has employed the manner of manufacture which the earlier inventor invented and, in the latter case, the definition of an article by reference to what it is able to achieve is permissible because the article is patentable in itself.

141. By contrast, a pathologist who employs established technology to isolate a fragment of naturally occurring DNA comprising the BRCA1 gene does not employ any method invented by the first respondent and, as has been seen, because the BRCA1 gene is a naturally occurring phenomenon, it is not patentable in itself. Nor does it assist the first respondent to point to the inventiveness involved in the combination of its discovery of the BRCA1 gene with the first respondent's system for isolating and examining the gene for the presence of the specified mutations and polymorphisms; for as Sir Wilfrid Greene MR said in Mullard Radio Valve Co Ltd v British Belmont Radio Ltd :

> "an article which is not in itself patentable cannot be made the subject of a good ... claim merely by pointing out that, if it is used in a particular way or in a particular collocation, it will produce novel and useful results."

The substance and effect of claim 1

142. That invites the question of whether the wording of claim 1 properly reflects the substance of the claimed invention.

143. The judge at first instance held it was enough to uphold claim 1 on the basis that isolated nucleic acid containing the specified mutations and polymorphisms "constitutes an artificial state of affairs in the sense those words should be understood in the present context" . The Full Court emphasised that claim 1 is drafted as a claim for a compound – an isolated nucleic

acid – as opposed to a claim to information, and that the product the subject of claim 1 is different from the gene comprising the nucleic acid sequence as it exists in nature :

> "Claim 1 is not to the genetic code. What is claimed is an isolated nucleic acid, a chemical molecule characterised in a certain way, which is chemically, structurally and functionally different to what occurs in nature. There is a distinction between a claim to an isolated nucleic acid comprised in part of a sequence of nucleotide bases and a claim to a written sequence of nucleotides which may be identical to the corresponding sequence in the natural cell. The claim is to be construed according to the normal principles of claim construction. To identify the invention as lying in the concept of information said to be embodied in a sequence of nucleotides ignores the language of the claim."

144. The way in which a claim is drafted cannot, however, transcend the reality of what is in suit . As Lord Loreburn LC observed in British Vacuum Cleaner Company Ltd v London and South Western Railway Company, albeit in dissent in the result, "[i]t is an abuse, which cannot be too sedulously watched and prevented by Courts of law, when a patentee, even if he is really an inventor, so shapes his claim that it may cover what he has not invented at all" . Monopolies are granted for inventions, not for the inventiveness of the drafting with which applicants choose to describe them. Hence, as was observed in Eli Lilly & Co's Application , where an alleged invention is based on the discovery of the particular properties of known compounds, care must always be taken to examine the form of claim actually made. Whatever words have been used, the matter must be looked at as one of substance and effect must be given to the true nature of the claim.

145. No doubt the motive consideration in Eli Lilly was that methods of treatment of illness or disease of human beings were at that time not regarded as patentable. That is no longer the case in this country . But the point remains that care must be taken to examine the form of claim actually made to see if it is in fact an attempt to establish a monopoly for the manufacture of a substance for a purpose for which a monopoly cannot be claimed. More generally, an "invention is to be understood as a matter of substance and not merely as a matter of form" . If a claim drafted as a product claim is in truth a "'disguised' process claim" , it will be treated as such.

146. As already noticed, the first respondent did not invent and cannot claim to have invented the process of isolating nucleic acid or the process of amplifying for genetic testing the fragment comprising the BRCA1 gene. The technologies for each are longstanding and well

known to those who are skilled in the science. Nor did the first respondent invent a method for infusing any such fragment of isolated DNA with the specified mutations and polymorphisms . Nor would there have been the slightest utility in doing so. The only relevant clinical significance of the presence of the specified mutations and polymorphisms in an isolated fragment is that the fragment has been extracted from the naturally occurring DNA in the cell and thus that the specified mutations and polymorphisms were present in the cell before being so extracted.

147. It was not disputed that the first respondent might justly lay claim to the discovery that, if an isolated fragment comprising the BRCA1 gene is found upon examination to exhibit the specified mutations and polymorphisms, their presence is or may be indicative of particular kinds of malignancy in the cell. Nor was it disputed that a process or method of using known technology to isolate a sequence of nucleic acid comprising the BRCA1 gene and examining it for the presence of the specified mutations and polymorphisms for the purpose of detecting or predicting malignancy might be patentable. But, as has been observed, the discovery of a natural correlation is not patentable as such and its discovery does not entitle the first respondent to patent the BRCA1 gene as a product, whether or not afflicted by the specified mutations and polymorphisms .

148. The fair basis cases provide an analogy which assists in illuminating the point. As they show, a claim for a new use of an old product does not confer a monopoly over the old product (just the new use). Parity of reasoning dictates that application of a method of detecting the increased likelihood of certain kinds of cancer by isolating the BRCA1 gene and comparing it to the reference sequence does not confer a monopoly over the mutated BRCA1 gene.

149. In Mullard Radio Valve Co Ltd v Philco Radio and Television Corporation of Great Britain Ltd, the claim in suit was for a "discharge tube having at least three auxiliary electrodes between the cathode and the anode, characterised in that the auxiliary electrode nearest to the anode is directly connected to the cathode so as to be maintained continuously at the cathode potential" . It was, however, established by the evidence that the discharge tube was a triode of known construction in which the anode was connected to the cathode and could only achieve its avowed object of maintaining the anode at the cathode potential if the three electrodes were connected in a particular sequence. The patentee's inventive idea thus consisted only in the discovery that in that particular juxtaposition the tube achieved that object. Accordingly, the claim was not fairly based on the invention because it went beyond the ambit of the patentee's inventive step. As Lord Macmillan said :

"If an inventor claims an article as his invention but the article will only achieve his avowed object in a particular juxtaposition and his inventive idea consists in the discovery that in that particular juxtaposition it will give new and useful results, I do not think that he is entitled to claim the article at large apart from the juxtaposition which is essential to the achievement of those results."

150. Similarly, in Adhesive Dry Mounting Company Ltd v Trapp & Co, Parker J held that :

"The first question which arises on this Claim is, whether it claims the pellicle therein described, or merely the use of this pellicle in the process claimed in the first Claiming Clause. If the former, the Letters Patent would entitle the Patentees to prevent the use of such a pellicle by others, whatever might be the purpose for which it was used. If the latter, the Letters Patent would only entitle the Patentees to restrain the use of such a pellicle in any process substantially the same as the process referred to in the first Claiming Clause. ... The idea of using an old material for an entirely new purpose, not being analogous to purposes for which it has theretofore been used, may be good subject-matter, but such idea, however ingenious, can hardly justify a claim for the material itself."

151. So too, in Wellcome Foundation Ltd v Commissioner of Patents, where the claim in suit was for a known chemical substance together with a set of instructions for its use for a previously unknown purpose of treating anaplasmosis in cattle, the Court said that :

"What the applicant seeks is a monopoly in an old substance limited to its use in the process which is the subject of claims 17 to 28. It is one thing to say that the inventor of a process is entitled to a monopoly, albeit limited, in the product of that process. It is quite another and different thing to say that the inventor of a process is entitled to a monopoly in a substance which is used merely as an ingredient in that process. In the latter case the invention claimed makes no contribution to the manufacture of the substance. At best, it takes advantage of properties in the substance hitherto unknown or unsuspected.

A further answer to the appellant's submission is that there is no distinction between the claim to the process and the claim to the substance when the substance claim is limited to its use in the process. So much appears from the judgment of Parker J in Adhesive Dry Mounting Company Ltd v Trapp & Co".

152. In the same way here, it is one thing to say that the first respondent has invented a process which consists in isolating and examining the fragment comprising the BRCA1 gene for the presence of the specified mutations and polymorphisms as an indicium of malignancy.

It is quite another and different thing to say that the first respondent, as inventor of that process, is entitled to a monopoly over the mutated BRCA1 gene, which is used merely as an ingredient in that process. The invention claimed makes no contribution to the manufacture of the substance. At best, it takes advantage of properties in the substance hitherto unknown or unsuspected. Just as there was no difference between the process and the product in Wellcome Foundation, there is no distinction between a claim to the process of isolating the BRCA1 gene for the purpose of examining it for the presence of the specified mutations and polymorphisms and the claim to the BRCA1 gene itself. Claim not defined by chemical composition

153. Counsel for the first respondent stressed more than once in argument that claim 1 was for a discrete chemical molecule achieved by the breaking of chemical covalent bonds in the course of the extraction and amplification processes employed in deriving isolated nucleic acid from the source DNA. According to the first respondent, that significantly distinguished claim 1 from the first respondent's claim for patent protection in respect of the BRCA1 gene simpliciter which the Supreme Court of the United States rejected in Association for Molecular Pathology v Myriad Genetics Inc . As the plurality of the Supreme Court of the United States observed in that case :

> "[The first respondent's] claims [are not] saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule. [The first respondent's] claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA."

154. As counsel for the first respondent ultimately conceded, however, because of the variable length once isolated of the fragments which may comprise the BRCA1 gene, in truth the claim made in relation to the BRCA1 gene relates to a very large if not infinite number of isolated nucleic acids with different molecular structures according to, inter alia, the number of exons isolated, the degrees of purification achieved in the extraction and amplification processes, and the presence of mutations and polymorphisms in the consequent extraction. Nor is there any conceivable way in which the processes could be adjusted by reference to any disclosed chemical formula to avoid the presence of the specified mutations and polymorphisms and thereby infringement of the patent . It follows that, in reality, the claim in suit is no more expressed in terms of a chemical formula than was the claim in respect of the BRCA1 gene simpliciter which was rejected in the United States.

The reasoning of the courts below

155. The judge at first instance considered that it followed from what was said in NRDC about a process being patentable when it results in an artificially created state of affairs of economic significance that the artificially created state of affairs of economic significance which results from isolating and amplifying the BRCA1 gene and discovering that it is afflicted by one or more of the specified mutations and polymorphisms is a patentable product. His Honour added that three considerations fortified him in that view. The first was that NRDC was "deliberate in its use of very expansive language" and emphasised "the 'broad sweep' of the concept involved" . The second was that "[e]xtraction of nucleic acid requires human intervention that necessarily results in the rupture of the cell membrane and the physical destruction of the cell itself" . And the third was that :

> "It would lead to very odd results if a person whose skill and effort culminated in the isolation of a [DNA sequence] could not be independently rewarded by the grant of a patent because the isolated [DNA sequence], no matter how practically useful or economically significant, was held to be inherently non-patentable."

156. The Full Court adopted a generally similar approach but with greater emphasis on the artificiality of isolated nucleic acid. Their Honours said that :

> "What is being claimed is not the nucleic acid as it exists in the human body, but the nucleic acid as isolated from the cell. The claimed product is not the same as the naturally occurring product. There are structural differences but, more importantly, there are functional differences because of isolation. As Lourie J explains, 'the ability to visualise a DNA molecule through a microscope, or by any other means, when it is bonded to other genetic material ... is worlds apart from processing an isolated DNA molecule that is in hand and usable'. The isolation of the nucleic acid also leads to an economically useful result – in this case, the treatment of breast and ovarian cancers. This is surely what was contemplated by a manner of new manufacture in the Statute of Monopolies."

157. With respect, there are problems with the reasoning at both levels. First and foremost, claim 1 is not a claim for a monopoly over nucleic acid isolated from the cell. Nor could it be. The process of isolating nucleic acid from the cell for the purposes of genetic testing is a matter of longstanding practice and diagnostic technique. Pathologists have long routinely isolated fragments of nucleic acid by the PCR process of amplification, and the DNA sequences of the BRCA1 exons by which pathologists are guided in that process are well described in medical literature . Other things being equal, they are free (without fear of contravention of any patent to which the first respondent might lay claim) to "manufacture"

isolated nucleic acid in order both to check it against known reference comparators and to check it for variations of unknown clinical significance.

158. Secondly, and for the same reason, the fact that isolated nucleic acid is a product which is "chemically, structurally and functionally different" from the naturally occurring DNA from which it is isolated – essentially because the isolation process consists of chemically stripping away the histones which control and execute the function of the exons in the cell and separating the fragment intended for examination – is for all intents and purposes beside the point. It would be to the point if the first respondent had invented and was claiming a new method for isolating nucleic acid; but claim 1 does not disclose any such method.

159. Thirdly, although claim 1 is restricted to isolated nucleic acid comprising the mutated BRCA1 gene, claim 1 does not disclose any method of infusing the isolated BRCA1 gene with the specified mutations and polymorphisms or otherwise facilitating their presence. As was earlier noticed, a pathologist has no way of knowing whether a patient's DNA, and therefore isolated nucleotides coding for the BRCA1 polypeptide, are afflicted by the specified mutations and polymorphisms until and unless the pathologist first isolates the patient's DNA, amplifies the fragment of it and examines it for the presence of the specified mutations and polymorphisms.

160. Consequently, so far from being a claim for a manner of manufacture of isolated nucleic acid constituted of the mutated BRCA1 gene, claim 1 is in truth a claim for a monopoly over the right to apply long-established methods for the isolation and amplification of specific nucleotide fragments to the isolation and amplification of a patient's naturally occurring BRCA1 gene, where and if it is found upon subsequent examination that the patient's BRCA1 gene happened to be afflicted by any of the specified mutations and polymorphisms.

161. That is not a valid claim of a manner of manufacture of a product. By definition, a manner of manufacture is an artificial thing or state of affairs which involves an element of inventiveness. Although the isolation of nucleic acid comprising the BRCA1 gene is a man-made process, it does not involve any element of inventiveness. It is no more than the application of a recognised diagnostic technique to a known purpose of examining fragments of human DNA.

162. The selection of the fragment which comprises the BRCA1 gene is novel, in the sense that it reflects the first respondent's discovery of the significance of the SEQ.ID No:1 sequence. But the first respondent does not and cannot claim to be entitled to a monopoly over the right to isolate the fragment which codes to the SEQ.ID No:1 sequence, or indeed to isolate any other fragment of the DNA polymer. The presence of the specified mutations and

polymorphisms in the isolated nucleic acid is also of critical importance inasmuch as it reflects the first respondent's discovery of the correlation between their presence and the heightened probability of cancer. But nothing that is done in the course of isolating the BRCA1 gene has any effect on whether the specified mutations and polymorphisms will be present. Their presence or absence in or from the isolated nucleic acid is entirely dependent upon whether they were present in or absent from the DNA of the patient from whom the isolated nucleic acid was extracted, and in effect that is the antithesis of a man-made artificial state of affairs.

163. Fourthly, whether or not the processing of an isolated molecule is "worlds apart" from the ability to visualise a DNA molecule through a microscope or by other means is also beside the point. Claim 1 is not a claim for a monopoly over the right to isolate and amplify the fragment of the BRCA1 gene.

164. Fifthly, it is not the isolation of nucleic acid, or even the isolation and amplification of the fragment comprising the BRCA1 gene, which leads to the "economically useful result" of treating breast and ovarian cancers. It is rather the first respondent's discovery of a naturally occurring correlation between the presence of the specified mutations and polymorphisms in such a fragment (and thus in the DNA in the cell from which the fragment is derived) and an increased probability of actual or potential malignancy.

165. Sixthly, the discovery of a naturally occurring correlation between the presence of the specified mutations and polymorphisms in an isolated fragment comprising the BRCA1 gene and an increased likelihood of actual or potential malignancy in the cell from which the fragment is derived is not what was contemplated by a "manner of new manufactures" in the Statute of Monopolies. As was observed in Ramset , although discovery of a naturally occurring phenomenon or a correlation between naturally occurring phenomena adds to the sum of human knowledge, s 6 of the Statute of Monopolies was concerned with a manner of new manufacture; and neither naturally occurring phenomena, nor the correlation between naturally occurring phenomena, is a manner of new manufacture. A manner of new manufacture necessitates invention and, as Buckley J said in Reynolds v Herbert Smith & Co Ltd :

> "Invention ... adds to human knowledge, but not merely by disclosing something [not previously known]. Invention necessarily involves also the suggestion of an act to be done, and it must be an act which results in a new product, or a new result, or a new process, or a new combination for producing an old product or an old result."

166. Finally, much of the judgment at first instance and of the judgment of the Full Court appears to attribute misplaced significance to the conclusion reached in NRDC earlier set out that it was sufficient to render patentable the process or method of production there in suit that it had as its end result an artificially created state of affairs of economic significance. The judge at first instance concluded, and the Full Court appears to have taken a similar view, that: "It is apparent from this passage that a product that consists of an artificially created state of affairs which has economic significance will constitute a 'manner of manufacture'."

167. With respect, that is not apparent and it is not the case. The passage of the judgment in NRDC in question was explicitly directed to whether a process or method of applying a known product to a new application qualified as a manner of manufacture within the meaning of s 6 of the Statute of Monopolies. It was sufficient, to conclude that it did, that the process resulted in "some product whereby the validity of [the process] can be tested" . It was held that, by reason of the direction of development in patent law since the 17th century and the direction which it must take in modern society, the notion of a manner of manufacture comprised of the result of a method or process is not confined to a tangible product but extends to an artificially created state of affairs of economic significance . But it does not follow that it is enough to found a claim for a monopoly in relation to a product, as opposed to a process by which the product is created, to demonstrate that an artificially created state of affairs of economic significance results from the application of a process to the product for which product no claim for a monopoly has been or could be made.

168. It is not disputed that a process or method of detecting the increased likelihood of certain kinds of malignancy by isolating the BRCA1 gene and examining it for the presence of any of the specified mutations and polymorphisms may be patentable subject matter as a process (subject to considerations of novelty and inventive step when compared to the prior art base). But, to repeat, claim 1 is not a claim for any such process. It is a claim for a monopoly over such isolated fragments of naturally occurring DNA as comprise the BRCA1 gene as are found upon examination to contain the (naturally occurring) specified mutations and polymorphisms.

169. In the result, the claim extends too far. The difficulty for the first respondent is that, having discovered a presumably good and perhaps ground-breaking process for detecting the probability of certain kinds of malignancy by reference to the presence of particular mutations and polymorphisms in the BRCA1 gene, the first respondent has attempted to patent those sequences of the gene themselves notwithstanding that, even when isolated, they are naturally occurring and therefore not new .

Contemporary contextual considerations

170. Both parties to the appeal sought to support their positions by reference to contemporary practice in the European Union. The course of argument highlighted a controversy between them as to whether claim 1 would meet the requirements for patentability prescribed by the applicable Directive . That is not a controversy which needs to be resolved. The structure and prescriptive detail of European patent legislation in its application to biotechnology and genetic engineering are such that the resolution of the controversy could provide little assistance in determining whether the claim is a proper subject for letters patent according to the principles which have been developed for the application of s 6 of the Statute of Monopolies.

171. The first respondent also sought to support its position by reference to the practice of the Australian Patent Office since 1995 of accepting the patentability of isolated nucleic acid sequences as well as to the history of executive consideration and legislative amendment of the Patents Act since 2002, both of which were explained in sufficient detail by the trial judge . The legislative history does not go so far as to demonstrate a legislative endorsement of the Patent Office practice. Nor has the Patents Act been amended in a way which necessarily assumes the patentability of isolated nucleic acid sequences . The most that can legitimately be drawn from the legislative history is a repeated legislative acceptance that, unlike the position in the European Union, issues of patentability in biotechnology and genetic engineering in Australia will continue to be resolved, consistently with NRDC, according to the principles which have developed for the application of s 6 of the Statute of Monopolies, except as otherwise specifically provided in s 18(2) and (3) of the Patents Act. That is to highlight the critical question, not to answer it.

Conclusion and orders

172. The appeal should be allowed. We agree with the orders proposed in the judgment of French CJ, Kiefel, Bell and Keane JJ.

Gordon J.

Introduction

173. Specific mutations or polymorphisms in the BRCA1 gene are indicative of a predisposition to breast cancer and ovarian cancer. That was a fact before the first respondent, "Myriad", worked it out.

174. Myriad worked it out; it gained knowledge of it. How did it do this? Using conventional isolation techniques, Myriad located the BRCA1 gene and observed that specific mutations or polymorphisms in the BRCA1 gene occurred in patients with breast cancer or ovarian cancer. Myriad concluded that those specific mutations or polymorphisms in the BRCA1 gene are indicative of a predisposition to breast cancer and ovarian cancer.

175. Myriad filed a patent which contains 30 claims ("the Patent"). Claims 4 30 are for applications arising from the fact that specific mutations or polymorphisms in the BRCA1 gene are indicative of a predisposition to breast cancer and ovarian cancer. Those claims are not the subject of challenge.

176. Claims 1-3 are not claims to applications arising from the fact that specific mutations or polymorphisms in the BRCA1 gene are indicative of a predisposition to breast cancer and ovarian cancer. But neither are claims 1-3 claims to the fact itself. Claims 1-3 do not claim the fact that specific mutations or polymorphisms in the BRCA1 gene are indicative of a predisposition to breast cancer and ovarian cancer.

177. Claims 1-3 are claims to a product: an isolated nucleic acid which has one or more specific mutations or polymorphisms in the BRCA1 gene. The methods of isolating nucleic acid were not new and were not claimed. The methods of identifying the mutations and polymorphisms in the BRCA1 gene were not new and were not claimed.

178. Claims 1-3 are to any and every isolated example of the BRCA1 gene, or a portion of the BRCA1 gene, which discloses the existence of one or more specific mutations or polymorphisms. Therefore, the question in this appeal is whether an isolated nucleic acid which has one or more specific mutations or polymorphisms in the BRCA1 gene is a proper subject for the grant of a patent under s 18(1)(a) of the Patents Act 1990 (Cth) ("the Act"). The answer is no.

Structure

179. These reasons will consider the legislation and the facts and then turn to consider the proper construction of the disputed claims and the patentability of those claims.

Legislation

180. As at the priority date, s 18 of the Act, entitled "[p]atentable inventions", relevantly provided:

> "(1) Subject to subsection (2), a patentable invention is an invention that, so far as claimed in any claim:

(a) is a manner of manufacture within the meaning of section 6 of the Statute of Monopolies; and

(b) when compared with the prior art base as it existed before the priority date of that claim:

(i) is novel; and

(ii) involves an inventive step; and

(c) is useful; and

(d) was not secretly used in the patent area before the priority date of that claim by, or on behalf of, or with the authority of, the patentee or nominated person or the patentee's or nominated person's predecessor in title to the invention.

(2) Human beings, and the biological processes for their generation, are not patentable inventions." (emphasis added)

181. "[I]nvention" was defined in Sched 1 to the Act to mean "any manner of new manufacture the subject of letters patent and grant of privilege within section 6 of the Statute of Monopolies, and includes an alleged invention".

182. Section 6 of the Statute of Monopolies is not in the Act. It relevantly provides :

"That any Declaration before mentioned shall not extend to any Letters Patents and Grants of Privilege for the term of fourteen years or under, hereafter to be made of the sole working or making of any manner of new Manufactures within this Realm, to the true and first Inventor and Inventors of such Manufactures, which others at the time of making such Letters Patents and Grants shall not use, so as also they be not contrary to the Law nor mischievous to the State, by raising prices of Commodities at home, or hurt of Trade, or generally inconvenient". (emphasis added)

183. Finally, to understand what is specified and claimed in the Patent, reference should be made to s 40 of the Act, entitled "[s]pecifications", which relevantly provided:

"(1) A provisional specification must describe the invention.

(2) A complete specification must:

(a) describe the invention fully, including the best method known to the applicant of performing the invention; and

(b) where it relates to an application for a standard patent – end with a claim or claims defining the invention; and

…

(3) The claim or claims must be clear and succinct and fairly based on the matter described in the specification.

(4) The claim or claims must relate to one invention only."

184. It is in that statutory context that the disputed claims are to be considered.

Facts

The Patent

185. The title of the "invention" is "[i]n vivo mutations and polymorphisms in the 17q-linked breast and ovarian cancer susceptibility gene". It has a priority date of 12 August 1994.

186. The invention is described as follows :

"The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer, in particular, breast and ovarian cancer. More specifically, the invention relates to germline [heritable] mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The present invention further relates to somatic [non-heritable] mutations in the BRCA1 gene in human breast and ovarian cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic [non-heritable] mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer."

187. The invention is said to be "an isolated polynucleotide comprising all, or a portion of the BRCA1 locus or of a mutated BRCA1 locus, preferably at least eight bases and not more than about 100 kb in length". The locus of a gene refers to its location.

188. The "[d]etailed description of the invention" further states:

> "It is a discovery of the present invention that the BRCA1 locus which predisposes individuals to breast cancer and ovarian cancer, is a gene encoding a BRCA1 protein, which has been found to have no significant homology with known protein or DNA sequences. This gene is termed BRCA1 herein. It is a discovery of the present invention that mutations in the BRCA1 locus in the germline [heritable] are indicative of a predisposition to breast cancer and ovarian cancer. Finally, it is a discovery of the present invention that somatic [non-heritable] mutations in the BRCA1 locus are also associated with breast cancer, ovarian cancer and other cancers, which represents an indicator of these cancers or of the prognosis of these cancers. The mutational events of the BRCA1 locus can involve deletions, insertions and point mutations within the coding sequence and the non-coding sequence. We have discovered that there are mutations in the coding sequence of the BRCA1 locus in kindreds which are responsible for the 17q-linked cancer susceptibility known as BRCA1. This gene was not known to be in this region." (emphasis added)

189. The Patent contains 30 claims. Claims 1-3 are disputed. Each of those claims is to a product, not a process. Those claims are:

> "1. An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19[ ].
>
> 2. An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a mutant BRCA1 polypeptide, said DNA containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations set forth in Tables 12, 12A and 14.
>
> 3. An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a polymorphic BRCA1 polypeptide, said DNA containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more polymorphisms set forth in Tables 18 and 19."

190. The terms "mutation" and "polymorphism" are not defined in the Patent.

191. Claims 4-30 of the Patent are not in dispute. In general terms, those claims are to various applications arising from the fact that Myriad located the BRCA1 gene and

concluded that specific mutations or polymorphisms in the BRCA1 gene are indicative of a predisposition to breast cancer and ovarian cancer. They are claims to a probe (claim 4), vectors (claims 5-7), methods of producing mutant or polymorphic BRCA1 polypeptides (claims 8-9), preparations and uses of polypeptides (claims 10-16) and various methods of diagnosis (claims 17-30).

192. Questions of novelty and inventive step (s 18(1)(b)) and usefulness (s 18(1)(c)) were not in issue. In particular, it was accepted that the identification of the BRCA1 gene, its nucleic acid sequence and the characteristics and sites of the mutations involved an inventive step resulting from data collated from over 13,000 patients. That inventive step is not the subject of any claim. This is not surprising. The inventive step could not have been patentable; it was no more than facts.

193. The question in this appeal is whether what is claimed in claims 1-3 is the proper subject of letters patent. To answer that question, it is necessary to understand the relevant science and consider what in fact Myriad did.

Cells

194. Cells can be divided into three main parts – the cell membrane, the nucleus and the cytoplasm. The cell membrane defines the outer boundary of the cell and separates its contents from the cell's environment. The nucleus appears as a cell within a cell. It is demarcated within the cell by the nuclear membrane. The nucleus remains in constant communication with other sub-structures in the cytoplasm. The cytoplasm comprises everything between the cell membrane and the nuclear membrane.

Nucleic acids – DNA and RNA

195. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are found in the nucleus. DNA contains the genetic information that directs the growth, development, maintenance and reproduction of the human body. DNA is made up of repeating monomer units, connected by chemical bonds to form one larger molecule. DNA consists of a long chain of many copies of small molecules called nucleotides (referred to as a polynucleotide chain). The entirety of the DNA sequence in a human (the human genome) comprises approximately 3.2 billion individual nucleotides.

196. The genetic information in DNA is copied by the cell into RNA, a chemically related form. DNA and RNA are collectively referred to as nucleic acids.

197. It is possible to create synthetic DNA. For example, complementary DNA (cDNA) is an artificial form of DNA which is made using a form of RNA (mRNA) as a template to create

DNA that is complementary, but not identical, to naturally occurring DNA. cDNA is used in research.

Nucleotides, codons, proteins

198. A nucleotide – the building block of DNA – is comprised of three separate chemical groups: a nitrogenous base, a phosphate group and a five-carbon sugar group. There are four types of nitrogenous bases found in DNA. These nitrogenous bases (usually referred to by their initial letter) are adenine (A), guanine (G), cytosine (C) and thymine (T). RNA has uracil (U) instead of thymine.

199. The genetic code consists of groups of three nucleotides. These nucleotide groups are called triplets or codons. The grouping of four possible nucleotides in DNA (A, G, C, T) and RNA (A, G, C, U) into different codons permits 64 possible combinations of nucleotides. Most of these 64 codons code for or represent an amino acid. There are 20 different amino acids known in nature. The sequences of the codons, representing specific amino acid sequences, are used by the cell to produce or regulate the production of a particular protein. A number of codons code for the same amino acid. Indeed, most amino acids have multiple codons. This means that a number of DNA or RNA sequences can code for the same protein.

200. A protein is a polypeptide (or in some cases, a number of polypeptides) comprised of a sequence of amino acids linked together. Each type of protein has its own unique amino acid sequence. Proteins come in an immense variety of different shapes and sizes, and perform many different and complex functions. Some proteins regulate cell division.

Exons and introns

201. In its natural state, the DNA sequence that encodes a specific protein is not present as a single continuous sequence. The sequence coding for a particular protein is present as a series of fragments along the DNA molecule, called exons. Each exon is separated from adjacent exons by a stretch of non-coding DNA, called introns. Introns do not encode a protein but they contain information that helps regulate the utilisation by the cell of the encoded information in the exons.

202. So where are we? A DNA sequence comprises nucleotides grouped into threes, referred to as codons. The codons code for certain amino acids, which in turn are linked together to make a protein. It is now necessary to examine what happens when the sequence of codons that encodes a protein is mutated or damaged. When this occurs, abnormal or uncontrolled cell division may result. This abnormal or uncontrolled cell division is referred to as cancer.

DNA variations, mutations and polymorphisms

203. The sequence of DNA is highly variable between people. If the complete DNA sequences of any two unrelated people are compared, there will be millions of points in the sequences at which the two people's sequences differ. These differences account, in part, for differences in physical and mental attributes in people drawn from the general population, and for the different risks of disease identified in different families.

204. For medical purposes, the variations in DNA sequence between people can be divided into three categories.

205. First, a variation in a person's DNA sequence can interfere with gene function and place that person at high risk of developing disease. These variations (referred to as mutations) usually occur in an exon and result in some abnormality in the protein derived from that gene. The variations can also occur in an intron and interfere with the regulation of the production of a protein from that gene. In either case, the variations are of clinical consequence and are relevant to medical decision-making. Mutations may cause disease, or be benign. Mutations are private to an individual or that individual's immediate family.

206. Where a variation is an insertion or deletion of one nucleotide in the coding sequence of the gene, the variation changes the information content of the gene and almost always causes the gene to malfunction. Such variations are deemed to cause disease unless there is clear evidence to the contrary. The coding sequence of a gene typically consists of a thousand or more nucleotides. The deletion or duplication of any one of these nucleotides is likely to cause the gene to malfunction. In other words, a gene could potentially have more than a thousand mutations.

207. Second, other variations in a person's DNA sequence are referred to as polymorphisms. These may occur in an exon and result in a difference in the protein derived from that gene. The variations may alternatively reside in an intron and have no impact on the formation of the protein from that gene. A polymorphism is a genetic variant which has arisen in a distant common ancestor and is therefore not unique to an individual or that individual's immediate family. Forty per cent of women in the general female population have one or more polymorphisms in the BRCA1 gene that are not found in the remaining 60 per cent of the population.

208. Third, there are many variations in a person's DNA sequence that have been identified but have not yet been categorised as mutations or polymorphisms. These variations may result in some difference in the protein derived from that gene, but are of unknown clinical

consequence. These variations are irrelevant to medical decision-making unless new knowledge allows them to be categorised as mutations or polymorphisms in the future.

209. Approximately one woman in 800 in the general female population has a mutation in the BRCA1 gene sequence that places her at high genetic risk of developing breast cancer and ovarian cancer. In any one year, a variation of unknown clinical significance is identified in approximately 15 per cent of women having tests for unknown variations in the BRCA1 gene.

Extracting, isolating and sequencing DNA

210. Myriad extracted, isolated and sequenced the DNA of the BRCA1 gene in what the appellant accepts was a "fine piece of science". However, in doing so, Myriad used well-established processes of DNA extraction, isolation and sequence comparison. DNA is typically obtained from cells removed from a sample of tissue or blood extracted from an individual. A sample will need to be processed before it is tested. It is necessary to break open the cells and expose the DNA. The goal of processing the sample is to remove the DNA from its normal cellular environment without corrupting the information content of the DNA. The DNA sequence of the processed DNA must accurately reflect the sequence of the DNA in the patient's cells for the pathology test to have any medical validity and be relevant for decision-making. These extraction processes are not new.

211. The DNA derived by an extraction process will contain all of the DNA molecules from many cells. The specific region of DNA that is the target of the test may account for only a tiny fraction of the DNA present in the sample. The entire BRCA1 gene (exons plus introns) represents only 0.003 per cent of the total DNA obtained by extraction processes. The coding sequence of the BRCA1 gene accounts for an even smaller proportion (0.0002 per cent) of the DNA obtained by extraction processes.

212. The DNA sample is then amplified by removing or diluting DNA that is not of interest. This is usually done by making multiple copies of short fragments of the sequence that is of interest by a chemical process called polymerase chain reaction (PCR). In an hour, a technician can make millions of copies of a fragment so that the concentration of the fragment is dramatically increased while the remaining DNA stays at its initial concentration.

213. The DNA sequence of the amplified fragment can then be determined by a variety of methods, either as a test for unknown variations or a test for known variations. The DNA sequence identified in the sample is compared to a normal reference sequence. A reference sequence may be defined by the laboratory doing the test or by reference to international

reference sequences developed under the auspices of professional bodies and government agencies in the United States of America and Europe.

214. During cross-examination, Dr Suthers, who was called by the appellant to give expert evidence, explained amplification and sequencing in these terms:

> "The conventional way of doing it was that you would break it up into small pieces, you would amplify them and you would stitch them together. Talking colloquially? – You may stitch the information together. You may, in some situations, physically stitch the amplified DNA together, but usually it was a matter of taking discrete bits of information from each of the fragments and knitting those together conceptually into information such as sequence ID number 1. …

When you talk about information, what you're doing is you're seeking to identify the nitrogenous bases? – Yes. So that what you're doing, is you take the gene, you break it up and amplify the bits so that you can identify the nitrogenous bases that are there found … and from that either physically or intellectually, you can put the sequence of bases – the bases that you believe are relevant for coding the polypeptide? – Correct."

215. Differences between the sequence from the patient's sample and the reference sequence are then reported. The methods for identifying the differences are not new.

216. In claims 1-3, the reference sequence is SEQ.ID No:1. SEQ.ID No:1 is a DNA sequence for the BRCA1 gene. It consists of 5,914 base pairs and represents the coding sequence of a nucleic acid (cDNA) which encodes the BRCA1 polypeptide. It is an artificial, constructed combination of sequences from cDNA clones, hybrid selection sequences and amplified PCR products. It is set out in the Patent.

Approach to proper construction of a patent

217. A patent grants a monopoly. A patent gives the patentee "the exclusive rights, during the term of the patent, to exploit the invention and to authorise another person to exploit the invention" .

218. What then is a patentable invention?

219. The primary or threshold requirement of a "patentable invention" is that it be an "invention" . The first step is to ask whether what is identified in the claim is an invention. Of course, establishing that there is an invention does not lead to the conclusion that a patent should be granted. Other requirements in the Act must be satisfied . An invention is a necessary, but not sufficient, element of entitlement to a patent.

220. There is no exhaustive or positive definition of "invention". Relevantly, s 18(1)(a) of the Act provided that a patentable invention is an invention that is "a manner of manufacture within the meaning of section 6 of the Statute of Monopolies". "[I]nvention" was defined in Sched 1 to the Act to mean "any manner of new manufacture the subject of letters patent and grant of privilege within section 6 of the Statute of Monopolies".

221. The question is therefore whether what is identified in the claim is "a proper subject of letters patent according to the principles which have been developed for the application of s 6 of the Statute of Monopolies" . To determine whether what is claimed falls within this definition, it is necessary to look at the subject matter of each claim separately and independently from other claims in the patent . And the enquiry is necessarily fact-specific . It is approached on a case-by-case basis .

Discovery, invention, work of nature, laws of nature

222. Whether there is an invention falls to be determined by reference to the specific terms of the claim and not by first seeking to characterise the claim (or elements of it) as a "discovery", rather than an "invention", or as "naturally occurring" or "a principle of nature" or by seeking to apply some other general label.

223. There may be discovery without invention . But the distinction between discovery and invention is not precise enough to be other than misleading . Terms such as "the work of nature" and "the laws of nature" are also vague, ambiguous and malleable .

224. As was said in National Research Development Corporation v Commissioner of Patents, "[e]verything that happens may be deemed 'the work of nature', and any patentable composite exemplifies in its properties 'the laws of nature'. Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost any patent" .

225. It follows that the appellant's contentions that naturally occurring things, or products or phenomena or principles of nature , are excluded as a proper subject matter of a patent, and that a distinction can and should be drawn between the "discovery of one of nature's laws" and of its "application to some new and useful purpose" , should not be accepted as providing a basis for allowing the appeal.

226. The question to ask is whether what is identified in the claim is a proper subject of letters patent according to the principles which have been developed for the application of s 6 of the Statute of Monopolies. In this appeal, the answer to that question depends on the identification of the subject matter of the disputed claims.

Subject matter of the claims

227. What then is the subject matter of the claims? For present purposes it is sufficient to focus on claim 1, as claims 2 and 3 are derivative, or a subset, of claim 1. Claim 1 is:

> "An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19."

228. The subject matter of the claim is not all isolated nucleic acids or isolated nucleic acid generally. It is not a claim to a process. The Patent does not describe how the nucleic acid is isolated. That is not surprising. There is no dispute that the methods involved in isolating and sequencing nucleic acid were well known. Indeed, nucleic acids have been isolated since at least the early 1990s and, in any case, prior to Myriad's isolation of the nucleic acids the subject of the claim.

229. Claim 1 is a product claim. The claim is to a product comprised of isolated nucleic acid having a particular characteristic. The characteristic is the isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, where the sequence of the isolated nucleic acid contains one or more of the mutations or polymorphisms set forth in particular tables. It is the combination of isolated nucleic acid and the existence of one or more of the mutations or polymorphisms that provides the subject matter of the claim. The isolation permits identification of the presence of the characteristic. And without the characteristic, the claimed product does not exist.

230. It is this interrelationship between the isolation of the nucleic acid and the identification of the characteristic which demonstrates why claim 1 is not a claim to a patentable product. The balance of this section of the judgment explains why this is so. It is structured as follows:

> "(1) The claim is to multiple products, not a single product: [231]-[239];
>
> (2) Although Myriad claims a class of chemical compounds as a product, it cannot delineate the bounds of its claim by reference to chemical composition: [240]-[243];
>
> (3) Myriad did not create, make or alter the characteristic, the code: [244]-[249];
>
> (4) There is no idea, concept or principle embodied in a manner of new manufacture: [250]-[258]; and

(5) The claim is too broad: [259]-[264].

Claim to multiple products, not a single product"

231 First, the claim is not a claim to a single product. Each time a person's nucleic acid with the characteristic is isolated, the result is different. The sources of the variations are numerous. It is necessary to explain why that is so.

Length of sequence varies

232. The Patent specification states that the DNA sequences used in the claimed invention will usually comprise "at least about five codons (15 nucleotides), more usually at least about 7-15 codons, and most preferably, at least about 35 codons" . That is, one can take a variable number of nucleotides for a sample. There is no uniformity in the size of the sample. The length of the sequence will likely vary for each sample. To fall within the claim, those sequences, whatever their length, are required to have a particular characteristic – the isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, where the sequence of the isolated nucleic acid contains one or more of the mutations or polymorphisms set forth in particular tables.

Composition of each sample varies

233. There are two aspects to this variation – substance and method.

234.First, as a matter of substance, the sequence of DNA is highly variable between people. As has been explained , if the complete DNA sequences of any two unrelated people are compared, there will be millions of points at which the two people's sequences will differ. Many variations in a person's DNA sequence are of no clinical significance. But just because a genetic variation is of no clinical significance does not mean that it does not exist.

235. The 54 mutations identified in the Patent account for about three per cent of the mutations in the BRCA1 gene that have been documented so far. The number, and extent, of mutations will differ between patients. So, for example, in South Australia, about 10 per cent of women tested have a mutation of some sort in the BRCA1 gene. As noted earlier, approximately one woman in 800 in the general female population has a mutation in the BRCA1 gene that places her at high genetic risk of developing breast cancer and ovarian cancer.

236. Some evidence of the extent of these variations can be seen in the Patent specification and, in particular, in Tables 12, 12A and 14 (recording the mutations) and Table 18 (recording the polymorphisms), which together provide the characteristic for claim 1. More

than 50 separate codons are identified as affected by an identified mutation or polymorphism. The location of the codons is not uniform. The codons are randomly located throughout the sequence.

237. For example, in Tables 12, 12A and 18, for each identified codon, a specific nucleotide change and a specific amino acid change (or frameshift) is identified. For one particular codon, two different nucleotide changes giving rise to the same amino acid change are identified. One particular nucleotide change and resulting amino acid change (which acted as a stop) is identified as affecting two different codons. For two particular codons, two different mutations are identified.

238. Second, there are at least two methods by which the composition of the patient's sample (in this case, the sequence of nucleotides in the BRCA1 gene) is identified. As has been explained , the amplified DNA may be physically stitched together or information from fragments can be conceptually stitched together. A product where the amplified DNA has been physically stitched together appears differently from one where the DNA is conceptually, but not physically, stitched together. The products would appear differently, yet each could fall within claim 1.

239. The claim is to multiple products, not a single product.

Myriad cannot delineate bounds of claimed class of chemical compounds

240. Myriad describes the claim as being to a class of chemical compounds.

241. Isolated nucleic acid with one or more of the identified mutations or polymorphisms is a chemical compound. However, as a result of one or more of the variations identified above, it is not possible for Myriad to record all of the various chemical compounds (or products) that might be produced by isolating an individual's nucleic acid. For example, as Myriad accepted during argument, the claim is to an "extremely wide number" of chemical compounds where the compound formulae would vary according to the number of sequences extracted but the compound would nevertheless contain one or more of the specific mutations or polymorphisms.

242. As has been seen, changes in chemical composition are not limited to variation in the number of nucleotides . So, although the claimed product is a chemical compound, Myriad did not and cannot delineate the bounds of the class of compounds by reference to the chemical composition of the class of the claimed product. Instead, Myriad sought to delineate the boundaries of the claim by reference to what it described as the "characteristics

identified within the claim" – the specific mutations and polymorphisms, represented by the code.

243. It is then necessary to consider the identified code.

Myriad did not create, make or alter the characteristic, the code

244. Claim 1 is to "[a]n isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19" (emphasis added).

245. "Coding" is not defined in the Patent. "Encode" is defined in the Patent in the following terms:

> "A polynucleotide is said to 'encode' a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for and/or the polypeptide or a fragment thereof. The anti-sense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom."

246. The Full Court identified a distinction between the terms "code for" and "encode" . The distinction drawn was that "code for" was passive and was to be understood as "carrying the code" or "having the potential to produce the polypeptide", whereas "encode" was active and meant "actually to produce the polypeptide" (original emphasis).

247,. Before this Court, it was common ground that on the proper construction of claim 1 in the Patent, "coding for" refers to the possession of a relevant code. The relevant code is identified as one or more of the specific mutations or polymorphisms listed in specified tables in the Patent.

248. Myriad identified the location of the BRCA1 gene. Myriad identified its nucleic acid sequence and the characteristics and sites of specific mutations and polymorphisms from data collated from over 13,000 patients. Myriad did not create, make or alter any of the nucleic acid sequence in the BRCA1 gene. Myriad did not create, make or alter any one of the mutations and polymorphisms listed in the tables specified in the claim. Each mutation and polymorphism identified in the tables has the same sequence in its native state in the cell and when isolated. Indeed, as addressed above , each sample needs to contain the same sequence in the cell and when isolated if it is to be usefully assessed.

249. Specific tables identify and list specific mutations and polymorphisms represented by the code. That the specific mutations and polymorphisms are indicative of a predisposition to breast cancer and ovarian cancer is a fact. That fact existed before Myriad worked it out. It is unsurprising that Myriad does not seek to patent that fact. A fact is not a manner of new manufacture within the meaning of s 6 of the Statute of Monopolies. More is required.

No idea, concept or principle embodied in a manner of new manufacture

250. Another way of testing claim 1 is to identify what was Myriad's idea, concept or principle and what it did with that idea, concept or principle.

251. In Lockwood Security Products Pty Ltd v Doric Products Pty Ltd [No 2], this Court stated :

> "Distinctions between the idea or concept or principle informing an invention and the means of carrying it out or embodying it in a manner of new manufacture have long been made despite certain expressions of caution from time to time. In Hickton's Patent Syndicate v Patents and Machine Improvements Co Ltd, Fletcher Moulton LJ stated that 'invention may lie in the idea, and it may lie in the way in which it is carried out, and it may lie in the combination of the two'.
>
> In a sense, an idea simpliciter cannot be patented, as no patent will be granted except to a manner of manufacture within s 6 of the Statute of Monopolies. An idea which is part, even the main part, of an inventive step 'has got to end in a new method of manufacture'." (original emphasis; footnotes omitted)

252. In this passage, the reference to Fletcher Moulton LJ's statement in Hickton's Patent Syndicate v Patents and Machine Improvements Co Ltd was incomplete. The statement by Fletcher Moulton LJ read:

> "In my opinion, invention may lie in the idea, and it may lie in the way in which it is carried out, and it may lie in the combination of the two; but if there is invention in the idea plus the way of carrying it out, then it is good subject-matter for Letters Patent." (emphasis added)

253. What was Myriad's idea, concept or principle, and what did Myriad do with that idea, concept or principle that can be recognised as carrying out that idea or embodying that idea in a manner of new manufacture?

254. Here, having located the BRCA1 gene and identified its nucleic acid sequence, Myriad's idea, concept or principle is that specific mutations or polymorphisms in that sequence suggest a predisposition to breast cancer and ovarian cancer.

255. How then is that idea carried out in claim 1? It is not. It is not and could not be carried out – as claim 1 suggests – by creating a product comprising isolated nucleic acid from a patient which contains the identified characteristic in any one of its many forms. As has been seen, Myriad does not claim the methods by which it isolates the nucleic acid or the methods by which it identifies the sequence of the patient's nucleic acid. Myriad does not claim the characteristic. Claim 1 is not a claim to the idea, concept or principle.

25. What then did Myriad do? It took the idea, concept or principle that specific mutations or polymorphisms in that sequence suggest a predisposition to breast cancer and ovarian cancer and moved to carry out that idea, concept or principle, or embody it in a manner of new manufacture, in claims 4-30. The validity of those claims is not in issue.

257. Claim 4 may be taken as an example. In simple terms, it comprises a nucleic acid probe in which the nucleotide sequence is a portion of an isolated nucleic acid with the characteristic identified in claim 1. In general terms, a probe is a fragment of isolated nucleic acid of variable length which is used to detect the presence of complementary nucleotide sequences and to investigate tissue samples to see whether particular genes are being expressed. A probe for BRCA1 alleles may be derived from sequences of the BRCA1 region or its cDNA. Probes are usually constructed artificially and have a radioactive label attached.

258. The invention in claim 4 carried into effect the idea that specifically identified mutations or polymorphisms in a sequence of the BRCA1 gene suggest a predisposition to breast cancer and ovarian cancer by testing for the presence of one or more of the specifically identified mutations or polymorphisms. That is an invention.

Breadth of claim in the Patent

259. Myriad acknowledges that a sample taken from a patient will infringe claim 1 if one or more of the specific mutations and polymorphisms identified in the claim are present, even if the testing is not directed at the BRCA1 gene or the identified mutations and polymorphisms. That is a problem.

260. It is a problem because it will not be evident whether the isolated nucleic acid contains one or more of the specific mutations and polymorphisms identified in the claim until the isolated nucleic acid has been tested. The consequence is that, if claim 1 is valid, when a

researcher or medical practitioner isolates the BRCA1 gene in a woman who does not have one or more of the specific mutations or polymorphisms, there is no infringement of the Patent. But if the woman does have one or more of the specific mutations or polymorphisms, there is infringement of the Patent. In both cases, the conduct of the researcher or medical practitioner is the same. Put differently, if claim 1 is valid, it will in practice prevent isolation and testing of the BRCA1 gene even if a researcher or medical practitioner is diagnostically testing for a purpose unrelated to detection of predisposition to one of the identified cancers. Not only that, Myriad would have an exclusive right to isolate the nucleic acid without having claimed the process of isolation.

261. Those consequences demonstrate that if claim 1 is valid it would extend the concept of what is patentable subject matter within s 6 of the Statute of Monopolies and therefore s 18(1)(a) of the Act, and the limits of the monopoly that would be granted, too far.

262. As French CJ said in Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd , there is a public interest in using the grant of a monopoly to encourage technical innovation. But French CJ also acknowledged a competing public interest "in ensuring unconstrained access by medical practitioners and their patients to new medical methods and processes" .

263. Here, a grant of a monopoly for claim 1 has the potential to inhibit other researchers and medical practitioners from diagnostically testing the BRCA1 gene for an entirely different purpose. Here, unlike in Apotex, the interests of inventors, investors and the public will not conflict if the patentability of claim 1 is rejected. Those interests will not conflict because other researchers and medical practitioners will be able to continue to isolate and test the BRCA1 gene, regardless of the purpose for which they are testing, and Myriad will have the benefit of the patentability of the applications specified in claims 4-30.

264. In other words, Myriad cannot monopolise the many iterations of the claimed product but it can exploit the applications that have been constructed to take advantage of the knowledge it has about the location and identity of some of the mutations and polymorphisms in the BRCA1 gene that indicate a predisposition to breast cancer and ovarian cancer. Proper subject matter of a patent?

265. The subject matter of each of claims 1-3 is not patentable according to the principles which have been developed for the application of s 6 of the Statute of Monopolies.

266. No single product is identified. Although each iteration of the claimed product is a chemical compound, Myriad did not and cannot delineate the bounds of the class of chemical compounds by reference to the chemical composition of every possible product.

267. Instead, Myriad sought to delineate the boundaries of each claim by reference to what it described as isolated nucleic acid having the "characteristics identified within the claim" – the specific mutations and polymorphisms, represented by the code. Myriad did not create, make or alter those specific mutations and polymorphisms. Myriad identified that specific mutations and polymorphisms in the BRCA1 gene indicated a predisposition to breast cancer and ovarian cancer. That fact existed before Myriad worked it out.

268. Claims 1-3 are not claims to the fact that specific mutations and polymorphisms in the BRCA1 gene are indicative of a predisposition to breast cancer and ovarian cancer. Nor are claims 1-3 claims to applications of that fact.

269. Instead, claims 1-3 are claims to a product: an isolated nucleic acid which has one or more specific mutations or polymorphisms in the BRCA1 gene. The methods of isolating the nucleic acid were not new and were not claimed. The methods of identifying the mutations and polymorphisms in the BRCA1 gene were not new and were not claimed. Claims 1-3 are to any isolated example of the BRCA1 gene which discloses the characteristic – one or more specific mutations and polymorphisms in the BRCA1 gene that are indicative of a predisposition to breast cancer and ovarian cancer.

270. For those reasons, there is a lack of invention in claims 1-3.

271. At this point, something more should be said about NRDC and about the reasons given in the Full Court below.

NRDC and the Full Court below

272. In NRDC, the Court concluded that, in order to be the proper subject of letters patent, a method must have "as its end result an artificial effect falling squarely within the true concept of what must be produced by a process if it is to be held patentable" . The Court continued:

> "The effect produced by the appellant's method exhibits the two essential qualities upon which 'product' and 'vendible' seem designed to insist. It is a 'product' because it consists in an artificially created state of affairs, discernible by observing over a period the growth of weeds and crops respectively on sown land on which the method has been put into practice. And the significance of the product is economic; for it provides a remarkable advantage, indeed to the lay mind a sensational advantage … Recognition that the relevance of the process is to this economic activity old as it is, need not be inhibited by any fear of inconsistency with the claim to novelty which the specification plainly makes. … [The process] achieves a separate result, and the result possesses its own economic utility". (emphasis added)

273. In CCOM Pty Ltd v Jiejing Pty Ltd , the passage in NRDC was said to require "a mode or manner of achieving an end result which is an artificially created state of affairs of utility in the field of economic endeavour".

274. The question which arises here is whether the passage extracted at [272] above should be applied to a product claim. Or to put the same question differently – is the existence of "an artificially created state of affairs of utility in [a] field of economic endeavour" sufficient to make a product a proper subject for the grant of a patent?

275. A number of points should be made. First, these passages are not a statute. Like any statements in reasons for judgment they must be read and understood in their context.

276. Second, the issue this Court was addressing in NRDC was a different issue – whether a claimed new process resulted in a product sufficient to attract patentability. As was observed in Grain Pool of Western Australia v The Commonwealth , NRDC held that "the requirement of a 'vendible product' for a valid process claim meant no more than that the end produced be of utility in practical affairs" (emphasis added). It was not the "effect produced" by the application of the process that was considered patentable. It was the inventive process that was the subject of the patent, which was held valid on the basis that applying it resulted in a product consisting in an artificial state of affairs of economic significance. The passage in NRDC is appropriate when considering the patentability of a process.

277. Third, it is necessary to approach the question of the patentability of a product claim separately and independently. Each claim is a product claim, not a process claim. Each claim is to isolated nucleic acid with a characteristic – the coding for a mutant or polymorphic BRCA1 polypeptide, being one or more of the mutations or polymorphisms selected from the mutations and polymorphisms set forth in particular tables.

278. Fourth, in the present appeal, the application of the passage from NRDC to claims 1-3 is inapposite. It is inapposite because applying or asking what the Full Court below saw as the questions posed in NRDC led to an incorrect approach to the construction of claims 1-3. The approach was incorrect because those questions necessarily required identification of an artificial state of affairs of some economic significance, rather than directing attention to the more fundamental questions "what is the subject matter of the claim", "what is the invention" and "what are the facts and matters which are relied upon to justify a conclusion that the claim contains an invention?"

279. The Full Court's finding that claim 1 was to "an isolated nucleic acid, a chemical molecule characterised in a certain way, which is chemically, structurally and functionally different to what occurs in nature" does not take account of the words of the claim. As a matter of substance, each of claims 1-3 focuses on the existence of one or more elements of an identified code: a code which is found in the nucleic acid isolated from a patient and which necessarily must be identical to the coding sequence in that patient. None of the asserted chemical, structural and functional differences identified by the Full Court play any part in the definition of the invention "so far as claimed" in each of claims 1-3 or in the description of the invention in the specification.

280. To put it in terms of chemical composition, the Full Court's statement that chemical changes in the isolated nucleic acid are of "critical importance" is misplaced. The Full Court correctly identified that isolated nucleic acid, removed from the cellular environment, does not act chemically as a template for "dynamic processes that result in the production of the polypeptide" . But that is not the claimed product. Myriad claims a chemical compound. And Myriad did not and cannot delineate the bounds of the class of compounds by reference to the chemical composition of every possible product. Instead, Myriad sought to delineate the boundaries of each claim by reference to what it described as the "characteristics identified within the claim" – the specific mutations and polymorphisms, represented by the code. The claimed product is isolated nucleic acid which might provide "a state of knowledge for the person upon which to contemplate, or assess, treatment" . What enables that is the code.

281. To put it in functional terms, the fact that the isolated DNA has one or more of the characteristics of the code is the function. The fact that isolated nucleic acids cannot produce the natural polypeptide is irrelevant. Production of natural polypeptide is not a characteristic of claims 1-3.

282. To put it in structural terms, the relevant structural attribute is that the product (the isolated DNA from a patient) contains an identical coding sequence to the coding sequence in the patient. The fact that, as a consequence of isolation of the nucleic acid from the cell, other parts of the cell and the DNA are removed in that process is irrelevant.

Consequences of invalidity

283. A claim must be valid across its whole scope . It was common ground that if claims 1-3 did not contain patentable subject matter, then those claims would not be saved where they extend to forms of nucleic acid that have been synthesised in the laboratory (cDNA).

284. Myriad submitted that such a result would put Australia out of step with some of its trading partners including the European Union and the United States of America . That issue, if it is to be addressed, is a matter for the legislature. It is no basis to extend s 18(1) of the Act to claims 1-3.

Conclusion and orders

285. The appeal should be allowed. I agree with the orders proposed in the judgment of French CJ, Kiefel, Bell and Keane JJ.