Patenting genetic diagnostic methods: NGS, GWAS, SNPs and patents

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This article reviews the problems posed by patent claims to genetic diagnostic methods associated with genome-wide association studies (GWAS) adopting methodologies using next-generation sequencing (NGS) and single nucleotide polymorphisms (SNP). These problems are essentially about experimental reproducibility and the credibility and veracity of reported developments. An analysis of the relevant law demonstrates that the current Australian and United States laws about suitable patentable subject matter differ, and that the current reproducibility (sufficiency, enablement and inutility) standards are unlikely to address these problems. The article concludes that following the United States approach excluding these genetic diagnostic method claims from patenting is one solution. Failing this, improving analysis and quality controls that are now being adopted in the basic research will reduce the nature of the problems, although this will remain problematic for patent examiners and the broader public.

INTRODUCTION

The ability to assess genomes predominantly through next-generation sequencing (NGS) and single nucleotide polymorphism (SNP) genotyping has provided an opportunity to address the genetic basis of disease.¹ This relies on the proposition that there is an interplay between DNA sequences and the environment (and epigenetic factors), with environmental exposures (and epigenetic factors) acting on a genetically susceptible individual to either produce disease or protect from disease.² Thus:

The complete human genome sequence will facilitate the identification of all genes that contribute to disease ... We have determined functional categories for nearly 1,000 documented disease genes, and found striking correlations between the function of the gene product and features of disease, such as age of onset and mode of inheritance. As knowledge of disease genes grows, including those contributing to complex traits, more sophisticated analyses will be possible; their results will yield a deeper understanding of disease and an enhanced integration of medicine with biology.³

The tantalising prospect is that by identifying these genetic factors there will be new and better treatments, including targeted interventions based on genetic risks identified from the genome – the promise of personalised medicine.⁴ This seems plausible as DNA sequences have been definitively and causally linked to diseases, confirming the conditionality of at least some sequences and diseases.⁵ The rapid sequencing of genomes through NGS, combined with powerful computers and statistics, has

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¹ For a listing of currently known genetic conditions and tests, see National Center for Biotechnology Information, "GTR: Genetic Testing Registry", <http://www.ncbi.nlm.nih.gov/gtr>.

² See Manolio T, Brooks L and Collins F, "A HapMap Harvest of Insights into the Genetics of Common Disease" (2008) 118 *Journal of Clinical Investigation* 1590 at 1590. See also Lander E and Schork N, "Genetic Dissection of Complex Traits" (1994) 65(5181) *Science* 2037.

³ Jimenez-Sanchez G, Childs B and Valle D, "Human Disease Genes" (2001) 409 *Nature* 853 at 853.

⁴ See Collins F, "Has the Revolution Arrived?" (2010) 464 *Nature* 674. See also, for example, Manolio, Brooks and Collins, n 2 at 1590; Chakravarti A and Little P, "Nature, Nurture and Human Disease" (2003) 421 *Nature* 412 at 412.

⁵ See, for example, Hemani G et al, "Inference of the Genetic Architecture Underlying BMI and Height With the Use of 20,240 Sibling Pairs" (2013) 93 *American Journal of Human Genetics* 865; Stahl E et al, "Bayesian Inference Analyses of the Polygenic Architecture of Rheumatoid Arthritis" (2012) 44 *Nature Genetics* 483.

now opened the way for these genome-wide association studies (GWAS) to address the presumed complexity of common diseases, relying on the hypothesis of the conditionality already found in some rare diseases.⁶ The output from these GWAS is a huge increase in data and information.

The essential data and information problems posed by this research are twofold:⁷ a problem with inaccurate data;⁸ and a problem with properly recording the steps in analysis (the computational experiments).⁹ Both these problems mean that many experiments are not reproducible so challenging the credibility and veracity of reported information.¹⁰ As a now celebrated example, a GWAS of 801 centenarians and 914 matched controls examining the genetic factors associated with longevity in healthy aging was retracted and later republished in another journal with heavy revision.¹¹ The problems were politely identified as “technical errors” and “an inadequate quality control protocol”.¹² One of the critical errors was the result of combining data from different genotyping platforms that, when combined and used to build a genetic model, revealed inaccurate false positive results – an apparently significant finding when one was not actually present (a Type 1 error).¹³ After being made aware of the apparent problems by the journal,¹⁴ the authors re-examined their experiments and introduced quality control measures, re-analysed the data and then concluded that “the specific details of the new analysis change substantially from those originally published ... to the point of becoming a new report”.¹⁵ One of the headline results changed from, and the language is important, “we built a genetic model that includes 150 [SNPs] and found that it could predict [exceptional longevity] with

⁶ See Attia J et al, “How to Use an Article about Genetic Association: A: Background Concepts” (2009) 301 *Journal of the American Medical Association* 74; Attia J et al, “How to Use an Article about Genetic Association: B: Are the Results of the Study Valid?” (2009) 301 *Journal of the American Medical Association* 191; Attia J et al, “How to Use an Article about Genetic Association: C: What are the Results and Will They Help me in Caring for my Patients?” (2009) 301 *Journal of the American Medical Association* 304.

⁷ Scientific misconduct, peer review, and so on, are also problems, albeit not addressed in this article: see generally “Trouble at the Lab”, *The Economist* (19 October 2013), <http://www.economist.com/news/briefing/21588057-scientists-think-science-self-correcting-alarming-degree-it-not-trouble>; Bohannon J, “Who’s Afraid of Peer Review?” (2013) 342(6154) *Science* 60; Yong E, Ledford H and Van Noorden R, “Research Ethics: 3 Ways to Blow the Whistle” (2013) 503 *Nature* 454; Macilwain C, “The Time is Right to Confront Misconduct” (2012) 488 *Nature* 7; Fang F, Steen G and Casadevall A, “Misconduct Accounts for the Majority of Retracted Scientific Publications” (2012) 109 *Proceedings of the National Academy of Sciences of the United States of America* 17028; Neaves W, “The Roots of Research Misconduct” (2012) 488 *Nature* 121; Corbyn Z, “Misconduct is the Main Cause of Life-Sciences Retractions” (2012) 490 *Nature* 21; Macilwain C, “Scientific Misconduct: More Cops, More Robbers?” (2012) 149 *Cell* 1417; Steen G, “Retractions in the Scientific Literature: Is the Incidence of Research Fraud Increasing?” (2011) 37 *Journal of Medical Ethics* 249.

⁸ See, for example, Editor, “Announcement – Reducing our Irreproducibility” (2013) 496 *Nature* 398 and the articles available in *Nature’s* special collection, “Challenges in Irreproducible Research”, at <http://www.nature.com/nature/focus/reproducibility/index.html>. See also Prinz F, Schlange T and Asadullah K, “Believe it or Not: How Much Can we Rely on Published Data on Potential Drug Targets?” (2011) 10 *Nature Reviews Drug Discovery* 712.

⁹ See, for example, Nekrutenko A and Taylor J, “Next-Generation Sequencing Data Interpretation: Enhancing Reproducibility and Accessibility” (2012) 13(9) *Nature Reviews Genetics* 667.

¹⁰ More broadly, this is a problem among reported science with reports of reproducibility of preclinical findings at less than 25%: see, for example, Prinz, Schlange and Asadullah, n 8; Begley G and Ellis L, “Drug Development: Raise Standards for Preclinical Cancer Research” (2012) 483 *Nature* 531.

¹¹ Sebastiani P et al, “Retraction” (2011) 333(6041) *Science* 404; Sebastiani P et al, “Genetic Signatures of Exceptional Longevity in Humans” (1 July 2010) *Science*, doi: 10.1126/science.1190532; Sebastiani P et al, “Genetic Signatures of Exceptional Longevity in Humans” (18 January 2012) *PLoS One*, doi: 10.1371/journal.pone.0029848.

¹² Alberts B, “Editorial Expression of Concern” (2012) 330(6006) *Science* 912. See also Carmichael M, “The Little Flaw in the Longevity-Gene Study that Could be a Big Problem”, *Newsweek* (6 July 2010), <http://www.newsweek.com/little-flaw-longevity-gene-study-could-be-big-problem-74703>; Sample I, “New Genetic Test can Predict your Chances of Living to 100, Claim Scientists”, *The Guardian* (2 July 2010), <http://www.theguardian.com/science/2010/jul/01/genetic-test-living-to-100>; MacArthur D, “Serious Flaws Revealed in ‘Longevity Genes’ Study”, *Wired* (7 July 2010), <http://www.wired.com/2010/07/Serious-flaws-revealed-in-longevity-genes-study>.

¹³ MacArthur D, “Face Up to False Positives” (2012) 487(7408) *Nature* 427.

¹⁴ Alberts, n 12.

¹⁵ Sebastiani et al, n 11 (2011).

77% accuracy in an independent set of centenarians and controls”¹⁶ to “we built a genetic model that includes 281 [SNPs] and discriminated between cases and controls of the discovery set with 89% sensitivity and specificity, and with 58% specificity and 60% sensitivity in an independent cohort of 341 controls and 253 genetically matched nonagenarians and centenarians (median age 100 years)”.¹⁷ On reconsidering the manuscript for publication, the original journal’s editors stated:

Although the authors remain confident about their findings, *Science* has concluded on the basis of peer-review that a paper built on the corrected data would not meet the journal’s standards for genome-wide association studies. One such standard, for example, is the inclusion of a reliable replication sample that shows comparable results to those in the initial experiments.¹⁸

Hidden in the polite caution from the original journal¹⁹ was the problem that the different genotyping platforms produced errors (the Illumina 370 chip and 610-Quad chip give different results so combining results from across these platforms produced data inaccuracies), and the analysis of the results using statistical methods resulted in false positives (some of the identified SNPs were false positives).²⁰ In retraction, the authors stated “ambiguous SNPs were then removed, and resultant genotype data were validated using an independent platform” and that they “re-analyzed the reduced data set using the same methodology”.²¹ This was not, however, sufficient for the original journal²² and the paper was published elsewhere.²³ Interestingly, and importantly for our purposes, subsequent studies have not been able to confirm the original or updated results,²⁴ leading to the conclusion that the identified SNPs associated with longevity were mere false positives. The same kinds of problems are apparent with NGS sequencing with the added concern of poor statistical evidence.²⁵

This GWAS incident illustrates two problems – first, the problems affecting experimental reproducibility, and secondly, challenging the credibility and veracity of reported developments.²⁶ These are significant because the GWAS results are then used, for example, to support public policy decisions (particularly in health care), to allocate scarce research investments, to recruit researchers to new research trajectories and to support intellectual property claims. The concern in this article is patent claims potentially relying on subject matter that is not (necessarily) reproducible and that might be incorrect. The article first sets out the relevant patent standards for the grant of a patent under the *Patents Act 1990* (Cth). It then sets out some practical examples of GWAS claims – essentially comparing sequences against a reference sequence to identify a correlation that is associated with a GWAS marker. Next, it addresses the threshold patent standard of suitable subject matter by reviewing Australian law and recent developments in the United States. It also addresses the patent thresholds of

¹⁶ Sebastiani et al, n 11 (2010), Abstract.

¹⁷ Sebastiani et al, n 11 (2012), Abstract.

¹⁸ Oransky I, “Sebastiani Group Retracts Genetics of Aging Study from Science”, *Retraction Watch* (21 July 2011), <http://retractionwatch.com/2011/07/21/sebastiani-group-retracts-genetics-of-aging-study-from-science>.

¹⁹ Alberts, n 12. See also Carmichael, n 12; Sample, n 12; MacArthur, n 12.

²⁰ See Carmichael, n 12. See also Welsh J, “Longevity Debate: Chips to Blame?”, *The Scientist* (14 July 2010), <http://www.the-scientist.com/?articles.view/articleNo/29145/title/Longevity-debate--Chips-to-blame->.

²¹ Sebastiani et al, n 11 (2011)

²² See Oransky, n 18.

²³ Sebastiani et al, n 11 (2012).

²⁴ See, for example, Deelen J et al, “Genome-Wide Association Meta-Analysis of Human Longevity Identifies a Novel Locus Conferring Survival Beyond 90 Years of Age” (2014) 23(16) *Human Molecular Genetics* 4420.

²⁵ Pulit S et al, “Association Claims in the Sequencing Era” (2014) 5 *Genes* 196 at 200-204 and the references therein. See also DePristo M et al, “A Framework for Variation Discovery and Genotyping Using Next-Generation DNA Sequencing Data” (2011) 43 *Nature Genetics* 491; McKenna A et al, “The Genome Analysis Toolkit: A MapReduce Framework for Analysing Next-Generation DNA Sequencing Data” (2010) 20 *Genome Research* 1297.

²⁶ See also Lambert C and Black L, “Learning from our GWAS Mistakes: From Experimental Design to Scientific Method” (2012) 13 *Biostatistics* 195.

sufficiency, enablement and inutility; and finally, it sets out a discussion and the conclusion that Australian and United States patent law applying to GWAS diagnostic method claims appear to have diverged.

THE PATENT SCHEME OVERVIEW

The international minimum standards for patents are established by the World Trade Organization's (WTO) *Agreement on Trade-Related Aspects of Intellectual Property Rights* (TRIPS)²⁷ that provides 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".²⁸ The TRIPS requirements have been escalated in some jurisdictions through free trade agreements, such as the *Australia-United States Free Trade Agreement* in Australia, even though these threshold requirements remain the same.²⁹ The TRIPS standards are then implemented in the WTO member states through their domestic laws. In Australia, the *Patents Act 1990* (Cth) provides, in part, that "an invention is a patentable invention ... if the invention, so far as claimed in any claim" is "a manner of manufacture within the meaning of section 6 of the *Statute of Monopolies*", "novel", "involves an inventive step" and is "useful".³⁰ In Australia, a patent must also satisfy the administrative requirements complying with the application procedures,³¹ and the requirement that:

A complete specification must:

- (a) disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the relevant art; and
- (aa) disclose the best method known to the applicant of performing the invention.³²

After a patent application is lodged,³³ it is examined,³⁴ and if the threshold standards are satisfied, will be accepted³⁵ subject to re-examination,³⁶ later challenge (opposition)³⁷ and revocation.³⁸

PRACTICAL EXAMPLES OF GWAS PATENTS

To illustrate GWAS inventions, two patents are examined.³⁹ First is the patent *Genetic loci indicative of propensity for longevity and methods for identifying propensity for age-related disease*.⁴⁰ This patent identified a region on human chromosome 4 linked to the propensity for old age with the

²⁷ Marrakesh Agreement establishing the World Trade Organization, opened for signature 15 April 1994, 1869 UNTS 299 (entered into force 1 January 1995), Annex 1C (*Agreement on Trade-Related Aspects of Intellectual Property Rights*).

²⁸ *Agreement on Trade Related Aspects of Intellectual Property Rights*, Art 27(1).

²⁹ For example, the *Australia-United States Free Trade Agreement* [2005] ATS 1 imposed a number of TRIPS-plus requirements: see Lawson C and Pickering C, "'TRIPS-Plus' Patent Privileges – An Intellectual Property 'cargo cult' in Australia" (2004) 22 *Prometheus* 355.

³⁰ *Patents Act 1990* (Cth), s 18(1). For an overview of Australia's administered patent scheme, see Productivity Commission, *Trade and Assistance Review 2011-12* (2013) pp 65-96.

³¹ *Patents Act 1990* (Cth), ss 29-29B.

³² *Patents Act 1990* (Cth), s 40.

³³ *Patents Act 1990* (Cth), s 29.

³⁴ *Patents Act 1990* (Cth), s 45.

³⁵ *Patents Act 1990* (Cth), s 49.

³⁶ *Patents Act 1990* (Cth), s 97.

³⁷ *Patents Act 1990* (Cth), s 59.

³⁸ *Patents Act 1990* (Cth), s 138.

³⁹ For a broader overview of genetic diagnostic patents, see Huys I et al, "Legal Uncertainty in the Area of Genetic Diagnostic Testing" (2009) 27 *Nature Biotechnology* 903.

⁴⁰ Kunkel L, Puca A and Perls T, *Genetic Loci Indicative of Propensity for Longevity and Methods for Identifying Propensity for Age-Related Disease*, United States Patent No 20040185471-A1 (2004). See also Puca A, Perls T and Kunkel L, *Genetic Loci Indicative of Propensity for Longevity and Methods for Identifying Propensity for Age-Related Disease*, Australian Standard Patent No 2001283267 (2001).

D4S1564 marker.⁴¹ This D4S1564 marker “is indicative of a polymorphic variant associated with increased likelihood for longevity” and so a subject with this marker, or a polymorphism within the locus of this marker, “is indicative of the propensity for extreme old age”.⁴² This D4S1564 marker is a DNA segment of approximately 330 base pairs.⁴³ The example set out in the complete specification details a GWAS of 308 individuals that identifies a region on chromosome 4 suggesting a linkage between the D4S1564 marker region and a propensity for longevity.⁴⁴ The invention as claimed is essentially for an amplified sequence of a marker region and then a comparison against a reference sequence of an old person, Claims 1 (amplifying) and 2 (genotyping) being representative:

- A method for gathering data related to genetic factors that influence longevity, the method comprising:
- [amplifying/genotyping] a segment of DNA from a subject in a region between the genetic markers D4S1564 and D4S1572 on human chromosome 4; and
 - comparing the segment to a reference sequence.⁴⁵

Next is the patent *Single nucleotide polymorphism biomarkers for diagnosing autism*.⁴⁶ This patent sets out a method for the identification, assessment and treatment of autism spectrum disorders.⁴⁷ Essentially the method uses GWAS with thousands of SNPs to link those SNPs with the particular diagnosis of autism, autism risk and specific treatments.⁴⁸ The claims include Claim 1:

A screening method for detecting in a subject a propensity or increased risk for developing an autism spectrum disorder (ASD) comprising detecting the presence of at least one single nucleotide polymorphism (SNP) in at least one target polynucleotide in a subject wherein the SNP comprises rs2277049, rs757099, rs7785107, rs7725785, rs2287581, rs1231339, rs2180055, rs11671930, rs7950390, rs12266938, rs3861787, rs1827924, rs17738966, rs317985, rs730168, rs10519124, rs6482516, or rs2297172, or any combination thereof, and wherein detecting the presence of the SNP in the subject is indicative of a propensity or increased risk of developing an ASD.⁴⁹

Each of these examples illustrates the use of GWAS linking the identification of a particular DNA sequence with some form of decision-making. The next question is whether this is suitable subject matter for a patent and where the boundaries are set?

PATENTING AND SUITABLE SUBJECT MATTER

The threshold requirement in Australia is that “an invention is a patentable invention ... so far as claimed in any claim: (a) is a manner of manufacture within the meaning of section 6 of the *Statute of Monopolies*”;⁵⁰ where the term “invention” is defined 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”.⁵¹ These phrases articulate a requirement for the proper subject matter of patents according to the traditional principles for what can, and cannot, be patented.⁵² In this category, Australian patent law excludes from patentability matter such as discoveries, ideas, scientific

⁴¹ Kunkel, Puca and Perls, n 40 at [009].

⁴² Kunkel, Puca and Perls, n 40 at [009].

⁴³ Kunkel, Puca and Perls, n 40 at [0038].

⁴⁴ Kunkel, Puca and Perls, n 40 at [0040]-[0049].

⁴⁵ Kunkel, Puca and Perls, n 40 at [0056].

⁴⁶ Hu V, *Single Nucleotide Polymorphism Biomarkers for Diagnosing Autism*, United States Patent No 20140045717-A1 (2014).

⁴⁷ Hu, n 46 at [009].

⁴⁸ Hu, n 46 at [0096]-[0097].

⁴⁹ Hu, n 46, p 66.

⁵⁰ *Patents Act 1990* (Cth), s 18(1).

⁵¹ *Patents Act 1990* (Cth), s 3 and Sch 1 (“invention”).

⁵² *NV Philips Gloeilampenfabrieken v Mirabella International Pty Ltd* (1995) 183 CLR 655 at 665 (Brennan, Deane and Toohey JJ), 671-672 (Dawson And McHugh JJ). For an elegant recent statement, see *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [7]-[22] (Emmett J).

theories, schemes and plans, laws of nature, computer programs and mathematical algorithms.⁵³ The decision in *National Research Development Corp v Commissioner of Patents* established that the scope of suitable subject matter needs to be something “that offers some advantage which is material, in the sense that the process belongs to a useful art as distinct from a fine art”⁵⁴ and “that its value to the country is in the field of economic endeavour”.⁵⁵ Based on this very broad ambit, GWAS inventions might appear to be patentable, and Australia has awarded patents to such inventions.⁵⁶ However, such inventions are not patentable in the United States.⁵⁷

In the United States, the equivalent threshold standard is: “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.”⁵⁸ Over time, the language of this threshold standard has been given “wide scope”,⁵⁹ albeit with limits including that a “manufacture” or “composition of matter” described as the “laws of nature, physical phenomena, and abstract ideas”⁶⁰ and “[p]henomenon of nature, though just discovered, mental processes, and abstract intellectual concepts”⁶¹ are not patentable.⁶²

The recent United States Supreme Court decision in *Association for Molecular Pathology v Myriad Genetics Inc* was significant in that it determined that “a naturally occurring DNA segment is a product of nature” and was “not patent eligible merely because it has been isolated”, while a “cDNA is patent eligible because it is not naturally occurring”.⁶³ Perhaps more importantly, however, the Supreme Court did not consider the disputed diagnostic method claims after they were considered by the Federal Circuit and rejected.⁶⁴ The Petition for a Writ of Certiorari before the Supreme Court had posed the question as “Question 2”:

Did the court of appeals err in upholding a method claim by Myriad that is irreconcilable with this Court’s ruling in *Mayo Collaborative Services v Prometheus Laboratories Inc*?⁶⁵

⁵³ See IP Australia, *Australian Patent Office Manual of Practice and Procedure* (last updated 1 April 2015) at [2.9.2], http://www.ipaustralia.gov.au/pdfs/patentsmanual/WebHelp/Patent_Examiners_Manual.htm.

⁵⁴ *National Research Development Corp v Commissioner of Patents* (1959) 102 CLR 252 at 275, citing *Re Virginia-Carolina Chemical Corp’s Application* [1958] RPC 35 at 36.

⁵⁵ *National Research Development Corp v Commissioner of Patents* (1959) 102 CLR 252 at 275.

⁵⁶ See, for example, Shattuck-Eidens D et al, *In Vivo Mutations and Polymorphisms in the 17q-Linked Breast and Ovarian Cancer Susceptibility Gene*, Australian Standard Patent No 686004 (1995) Claims 17-30. The GWAS claim in this patent was not challenged in litigation: see *Cancer Voices Australia v Myriad Genetics Inc* (2013) 99 IPR 567 (Nicholas J).

⁵⁷ For a comparison of United States and European laws on genetic diagnostic method patents, see Huys I, Van Overwalle G and Matthijs G, “Gene and Genetic Diagnostic Method Patent Claims: A Comparison Under Current European and US Patent Law” (2011) 19 *European Journal of Human Genetics* 1104.

⁵⁸ 35 USC § 101.

⁵⁹ *Bilski v Kappos* 130 S Ct 3218 at 3225 (2010); *JEM Ag Supply Inc v Pioneer Hi-Bred International Inc* 534 US 124 at 131 (2001); *Diamond v Chakrabarty* 447 US 303 at 308 (1980).

⁶⁰ *Diamond v Chakrabarty* 447 US 303 at 309 (1980). See also *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 14 (2012); *Bilski v Kappos* 130 S Ct 3218 at 3226 (2010); *Diamond v Diehr* 450 US 175 at 185 (1981).

⁶¹ *Gottschalk v Benson* 409 US 63 at 67 (1972).

⁶² See *Association for Molecular Pathology v United States Patent and Trademark Office* 702 F Supp 2d 181 at 218-219 (2010).

⁶³ *Association for Molecular Pathology v Myriad Genetics Inc* 133 S Ct 2107 at 2111 (2013).

⁶⁴ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1335 (Circuit Judge Lourie), 1337 (Circuit Judge Moore), and 1348 (Circuit Judge Bryson) (2012). For an analysis of the decision, see, for example, Lawson C, “Patenting DNA Sequences after the US Myriad Decision: New Frontiers or Just More of the Same?” (2014) 33 *Biotechnology Law Report* 3.

⁶⁵ *Association for Molecular Pathology v Myriad Genetics Inc*, Petition for a Writ of Certiorari (2012) p i, <http://www.genomicslawreport.com/wp-content/uploads/2012/11/AMP-Myriad-Petition-for-Cert.pdf>. See also *Association for Molecular Pathology v Myriad Genetics Inc* 133 S Ct 694 (2012).

In allowing the appeal, the Supreme Court order *only* provided: “The petition for a writ of certiorari is granted limited to Question 1 [‘Are human genes patentable?’] presented by the petition.”⁶⁶ The effect of this was to confirm the Federal Circuit’s decision about the method claims. This is yet more significant as an earlier petition for certiorari from an earlier appeal in the matter was granted by the Supreme Court and the decision was remanded for further consideration in light of the Supreme Court’s then recent decision in *Mayo Collaborative Services v Prometheus Laboratories Inc.*⁶⁷ The Federal Circuit’s decision confirmed its earlier decision that the disputed diagnostic method claims were patent ineligible.⁶⁸ The significance of the diagnostic method claims was that they were about “comparing” and “analysing” DNA sequences against reference sequences to determine the presence of mutations and predispositions to cancer.⁶⁹ Before the Federal Circuit’s decision, the District Court had also rejected these claims on the basis that they were merely abstract mental processes comparing gene sequences as information.⁷⁰ The Federal Circuit agreed,⁷¹ finding that: “Myriad’s claims do not apply the step of comparing two nucleotide sequences in a process. Rather, the step of comparing two DNA sequences is the entire process that is claimed.”⁷² This was consistent with the Supreme Court’s decision in *Mayo Collaborative Services v Prometheus Laboratories Inc* (and following *Bilski v Kappos*),⁷³ which concluded that a method using scientifically routine procedures to determine metabolite concentrations in blood and then working out the correct dosages was patent ineligible because adding a routine activity to a “law of nature” did not make it patent eligible:

to transform an un-patentable law of nature into a patent-eligible application of such a law, one must do more than simply state the law of nature while adding the words “apply it” ... The case before us ... concerns patent claims covering processes that help doctors who use thiopurine drugs to treat patients with autoimmune diseases determine whether a given dosage level is too low or too high. The claims purport to apply natural laws describing the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects. We must determine whether the claimed processes have transformed these un-patentable natural laws into patent-eligible applications of those laws. We conclude that they have not done so and that therefore the processes are not patentable ... the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field. At the same time, upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries.⁷⁴

⁶⁶ *Association for Molecular Pathology v Myriad Genetics Inc* 133 S Ct 694 (2012).

⁶⁷ See *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1308 (Circuit Judge Lourie) (2012). See also *Association for Molecular Pathology v Myriad Genetics Inc* 132 S Ct 1794 (2012).

⁶⁸ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1333-1335 (Circuit Judge Lourie), 1337 (Circuit Judge Moore), 1348 (Circuit Judge Bryson) (2012).

⁶⁹ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1334-1335 (Circuit Judge Lourie) (2012).

⁷⁰ *Association for Molecular Pathology v United States Patent and Trademark Office* 702 F Supp 2d 181 at 234-237 (2010).

⁷¹ Circuit Judges Moore and Bryson agreed with the decision of Circuit Judge Lourie: *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1337 (Circuit Judge Moore), 1348 (Circuit Judge Bryson) (2012).

⁷² *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1334-1335 (Circuit Judge Lourie) (2012).

⁷³ See *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ (2012); *Bilski v Kappos* 130 S Ct 3218 (2010).

⁷⁴ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 3 (2012). Importantly, the Supreme Court appears not to distinguish between “natural phenomena”, “laws of nature” and “abstract ideas” in applying its suitable subject matter (35 USC § 101) jurisprudence: see, for example, *Association for Molecular Pathology v Myriad Genetics Inc* 133 S Ct 2107 at 2116-2120 (2013) (natural phenomenon); *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 8-19 (2012) (law of nature); *Bilski v Kappos* 561 US _ at 4-13 (2010) (abstract idea).

The relevant representative claims in the *Association for Molecular Pathology v Myriad Genetics Inc* litigation addressed methods of “analysing” or “comparing” a sequence of interest against other sequences to identify the presence of differences linked to a predisposition to a disease.⁷⁵ The representative “analysing” claim was:

A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 12A, 14, 18 or 19 in a human which comprises analysing a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or analysing a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO: 1.⁷⁶

The representative “comparing” claim was:

A method for screening a tumour sample from a human subject for a somatic alteration in a BRCA1 gene in said tumour which comprises: comparing a first sequence selected from the group consisting of a BRCA1 gene from said tumour sample, BRCA1 RNA from said tumour sample and BRCA1 cDNA made from mRNA from said tumour sample with a second sequence selected from the group consisting of BRCA1 gene from a non-tumour sample of said subject, BRCA1 RNA from said non-tumour sample and BRCA1 cDNA made from mRNA from said non-tumour sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumour sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said non-tumour sample indicates a somatic alteration in the BRCA1 gene in said tumour sample.⁷⁷

Myriad (the patent holder) had argued that the transformative steps were extracting the DNA from the tissue sample, sequencing the DNA followed by comparing and analysing the DNA sequence.⁷⁸ The Federal Circuit found these claims invalid because they were nothing more than “the abstract mental steps necessary to compare two different nucleotide sequences”.⁷⁹ In effect, comparing and analysing DNA sequences using a computer was an unpatentable “abstract mental process” because in essence all that was being done was comparing one nucleotide position against another and repeating that process.⁸⁰ And limiting this process to just the claimed genes and sequence was not sufficient to make the subject matter patent eligible.⁸¹ It was probably significant that in this case the claims were *only* to “comparing” and “analysing” sequences and did not include extracting the DNA and sequencing the physical DNA molecules.⁸² Myriad’s attempt to read the claims as involving transformative steps of extracting DNA from a sample, sequencing the DNA molecule and then comparing or analysing the sequences (the machine or transformation test) was rejected because the claims as stated “only recite mental steps, not the structure of physical DNA”.⁸³

⁷⁵ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1309 (Circuit Judge Lourie) (2012).

⁷⁶ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1309 (Circuit Judge Lourie) (2012).

⁷⁷ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1310 (Circuit Judge Lourie) (2012).

⁷⁸ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1334, 1335 (Circuit Judge Lourie) (2012).

⁷⁹ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1334 (Circuit Judge Lourie) (2012).

⁸⁰ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1335 (Circuit Judge Lourie) (2012).

⁸¹ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1334-1335 (Circuit Judge Lourie) (2012), citing *Bilski v Kappos* 130 S Ct 3218 at 3230 (2010), which in turn cited *Diamond v Diehr* 450 US 175 at 191-192 (1981).

⁸² *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1335 (Circuit Judge Lourie) (2012).

⁸³ *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1335 (Circuit Judge Lourie) (2012).

Turning now to the broader standard articulated by the Supreme Court.⁸⁴ The question in *Mayo Collaborative Services v Prometheus Laboratories Inc* was whether the process that assisted doctors determining doses of thiopurine drugs to treat autoimmune diseases was patent eligible. The drugs have harmful side effects so determining the appropriate dose means the drugs are effective while avoiding the harmful side effects.⁸⁵ A typical claim was:

A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

- (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
- (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.⁸⁶

Prometheus Laboratories, the exclusive licensee, sold diagnostic tests that embodied this invention.⁸⁷ Mayo Collaborative Services initially bought and used the tests and then announced that it would use its own diagnostic test.⁸⁸ Prometheus Laboratories claimed infringement, which was rejected by the District Court on the basis that “the correlation between thiopurine metabolite levels and the toxicity and efficacy of thiopurine drug dosages” was “effectively [a] claim [to] natural laws or natural phenomena”.⁸⁹ On appeal to the Federal Circuit, this was reversed because in addition to the correlation there was found to be a “transformation” of the human body or blood by “administering a [thiopurine] drug” and “determining the [resulting metabolite] level”.⁹⁰ This satisfied the then described “machine or transformation test”.⁹¹ The Supreme Court then remanded the matter to be reconsidered in light of the *Bilski v Kappos* decision⁹² that the “machine or transformation test” was “an important and useful clue” rather than a definite standard.⁹³ On reconsideration, the Federal Circuit again considered the patent claims did “not encompass laws of nature or pre-empt natural correlations”.⁹⁴ On appeal to the Supreme Court, the issue was framed as:

whether the claims do significantly more than simply describe these natural relations. To put the matter more precisely, do the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?⁹⁵

The Supreme Court then characterised the claims as “tell[ing] doctors interested in the subject about the correlations that the researchers discovered ... a suggestion that [the doctor] should take

⁸⁴ The United States Supreme Court’s unease with diagnostic method patents can be traced to Breyer J’s dissent, joined by Stevens and Souter JJ, in *Laboratory Corp of America Holdings v Metabolite Laboratories Inc* 548 US 124 (2006).

⁸⁵ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 4 (2012).

⁸⁶ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 5-6 (2012). See also Seidman E and Théorêt Y, *Method of Treating IBD/Crohn’s Disease and Related Conditions Wherein Drug Metabolite Levels in Host Blood Cells Determine Subsequent Dosage*, United States Patent No 6355623 (2002) Claim 1.

⁸⁷ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 6 (2012).

⁸⁸ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 6 (2012).

⁸⁹ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 7 (2012).

⁹⁰ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 7 (2012). See also *Prometheus Laboratories Inc v Mayo Collaborative Services* 581 F 3d 1336 at 1345-1347 (2009).

⁹¹ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 7 (2012).

⁹² *Bilski v Kappos* 561 US _ at 5 (2010).

⁹³ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 7 (2012).

⁹⁴ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 7-8 (2012). See also *Prometheus Laboratories Inc v Mayo Collaborative Services* 628 F 3d 1347 at 1355 (2010).

⁹⁵ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ at 8 (2012).

those laws into account when treating [their] patient”.⁹⁶ As these steps were “well-understood”, “conventional activity previously engaged in” and “routine”: this was not sufficient to “transform” the unpatentable law of nature into a patent eligible application.⁹⁷ Further, the combination of instructions “adds nothing to the laws of nature that is not already present when the steps are considered separately”.⁹⁸ The result of the instructions being that doctors can draw inferences from the correlations in making treatment decisions, with the conclusion being the sum of the separate instructions (rather than something more).⁹⁹

The Supreme Court’s decision restated the common position that under 35 USC § 101¹⁰⁰ “laws of nature, natural phenomena, and abstract ideas” are not patentable¹⁰¹ and concluded that the existing precedents:¹⁰²

insist that a process that focuses upon the use of a natural law also contain other elements or a combination of elements, sometimes referred to as an “inventive concept”, sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself.¹⁰³

The decision left open the question of exactly what steps are sufficient to “transform un-patentable natural correlations into patentable applications”.¹⁰⁴ For “comparing” and “analysing” sequences, however, the *Association for Molecular Pathology v Myriad Genetics Inc* decision is pretty clear – methods of merely “comparing” and “analysing” sequences are unpatentable. Whether this might be ameliorated by other elements – what must be added to a law of nature to make it patent eligible – remains unclear. More broadly, however, it is clear that any exceptions to patentability must be narrowly applied.¹⁰⁵ More recent decisions provide some early insights.

SmartGene Inc v Advanced Biological Laboratories SA concerned a method for selecting a treatment regimen.¹⁰⁶ A representative claim, Claim 1 of the 786 patent, provided:

A method for guiding the selection of a therapeutic treatment regimen for a patient with a known disease or medical condition, said method comprising:

- (a) providing patient information to a computing device comprising:
 - a first knowledge base comprising a plurality of different therapeutic treatment regimens for said disease or medical condition;
 - a second knowledge base comprising a plurality of expert rules for evaluating and selecting a therapeutic treatment regimen for said disease or medical condition;
 - a third knowledge base comprising advisory information useful for the treatment of a patient with different constituents of said different therapeutic treatment regimens; and
- (b) generating in said computing device a ranked listing of available therapeutic treatment regimens for said patient; and

⁹⁶ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US __ at 9 (2012).

⁹⁷ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US __ at 10 (2012).

⁹⁸ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US __ at 10 (2012).

⁹⁹ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US __ at 11 (2012).

¹⁰⁰ Section 101 provides that: “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.”

¹⁰¹ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US __ at 1 (2012), citing *Diamond v Diehr* 450 US 175 at 185 (1981); see also *Bilski v Kappos* 561 US __ at 5 (2010); *Diamond v Chakrabarty* 447 US 303 at 309 (1980).

¹⁰² Citing *Parker v Flook* 437 US 584 at 593 (1978); *Gottschalk v Benson* 409 US 63 at 71-72 (1972); *O’Reilly v Morse* 15 How 62 at 112-120 (1854).

¹⁰³ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US __ at 3 (2012), citing *Parker v Flook* 437 US 584 at 594 (1978); *Bilski v Kappos* 561 US __ at 5 (2010).

¹⁰⁴ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US __ at 11 (2012). This has been the subject of considerable analysis: see, for example, Chao B, “Moderating Mayo” (2012) 107 *Northwestern University Law Review* 82 at 82 and the references therein.

¹⁰⁵ See also *Ultramercial Inc v Hulu LLC* 722 F 3d 1335 at 1342 (2013).

¹⁰⁶ *SmartGene Inc v Advanced Biological Laboratories SA* 2014 WL 259824 at 1 (Fed Cir, 2014).

- (c) generating in said computing device advisory information for one or more therapeutic treatment regimens in said ranked listing based on said patient information and said expert rules.¹⁰⁷

The Federal Circuit characterised the invention as “the mental steps of comparing new and stored information and using rules to identify medical options”.¹⁰⁸ The decision reasoned that the *Mayo Collaborative Services v Prometheus Laboratories Inc* decision (albeit dealing with the “law of nature” rather than an “abstract idea” as in this case) required something “beyond [the] ‘well-understood, routine, conventional activity’”.¹⁰⁹ The Federal Circuit concluded that what was claimed was “familiar mental steps performed by or with a computer” and this was not patentable “without more of significance”.¹¹⁰

Ariosa Diagnostics Inc v Sequenom Inc addressed a method of detecting cell-free foetal DNA (cffDNA) from samples collected from maternal serum or plasma enabling the detection of foetal sex, blood type, pre-eclampsia, and other genotyping.¹¹¹ Claim 1 provided:

A method for detecting a paternally inherited nucleic acid of foetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises:

- amplifying a paternally inherited nucleic acid from the serum or plasma sample; and
- detecting the presence of a paternally inherited nucleic acid of foetal origin in the sample.¹¹²

The District Court first decision was appealed to the Federal Circuit that returned the matter to be considered in light of the Supreme Court decision in *Association for Molecular Pathology v Myriad Genetics Inc*.¹¹³ Back in the District Court, the relevant standard was stated as:

to be patentable, a process that focuses upon the use of a natural law, a natural phenomenon, or an abstract idea must contain other elements or a combination of elements, sometimes referred to as an “inventive concept,” sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law, natural phenomenon, or abstract idea itself.¹¹⁴

The District Court accepted that the claim was to a method that involved applying well-understood, routine and conventional activities in the field at the relevant time to a natural phenomenon and that this was unpatentable.¹¹⁵ The District Court identified the only inventive concept as the newly discovered natural phenomenon of naturally occurring cffDNA, as opposed to other types of DNA, to which conventional techniques of DNA detection had been applied.¹¹⁶

In Australia, the issue has not been as contentious. The equivalent patents litigated in the United States Supreme Court decision in *Association for Molecular Pathology v Myriad Genetics Inc* were litigated in Australia in *Cancer Voices Australia v Myriad Genetics Inc*.¹¹⁷ The disputed claims in Australia only related to claims over isolated naturally occurring DNA and cDNA, and the court decided, contrary to the decision in *Association for Molecular Pathology v Myriad Genetics Inc*, that

¹⁰⁷ *SmartGene Inc v Advanced Biological Laboratories SA* 2014 WL 259824 at 1 (Fed Cir, 2014).

¹⁰⁸ *SmartGene Inc v Advanced Biological Laboratories SA* 2014 WL 259824 at 5 (Fed Cir, 2014).

¹⁰⁹ *SmartGene Inc v Advanced Biological Laboratories SA* 2014 WL 259824 at 5 (Fed Cir, 2014).

¹¹⁰ *SmartGene Inc v Advanced Biological Laboratories SA* 2014 WL 259824 at 5 (Fed Cir, 2014). This was also held to be consistent with the Federal Circuit’s earlier decision in *CyberSource Corp v Retail Decisions Inc* 654 F 3d 1366 at 1373 (2011).

¹¹¹ *Ariosa Diagnostics Inc v Sequenom Inc* 2013 WL 5863022 at 1 (ND Cal, 2013). Other cases also filed about these patents include *Natera Inc v Sequenom Inc*, Case No 12-cv-00132-SI (filed 6 January 2012); *Verinata Health Inc v Sequenom Inc*, Case No 12-cv-865-SI (filed 22 February 2012).

¹¹² *Ariosa Diagnostics Inc v Sequenom Inc* 2013 WL 5863022 at 3 (ND Cal, 2013).

¹¹³ See *Aria Diagnostics Inc v Sequenom Inc* 726 F 3d 1296 (2013).

¹¹⁴ *Ariosa Diagnostics Inc v Sequenom Inc* 2013 WL 5863022 at 8 (ND Cal, 2013), citing *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US _ (2012); *Parker v Flook* 437 US 584 (1978).

¹¹⁵ *Ariosa Diagnostics Inc v Sequenom Inc* 2013 WL 5863022 at 8 (ND Cal, 2013).

¹¹⁶ *Ariosa Diagnostics Inc v Sequenom Inc* 2013 WL 5863022 at 9 (ND Cal, 2013).

¹¹⁷ *Cancer Voices Australia v Myriad Genetics Inc* (2013) 99 IPR 567.

these claims were valid.¹¹⁸ Some of the method claims in the Australian patent were worded slightly differently, even though there was the same effect of comparing/analysing a sequence against a reference sequence and identifying an alteration in the sequence – Claim 17 providing:

A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germline alteration in the sequence of the BRCA 1 gene in a tissue sample of said subject compared to the nucleotide sequence set forth in SEQ.ID No: 1 or a wild-ty[p]e allelic variant thereof, said alteration indicating a predisposition to said cancer being selected from the mutations as set forth in Tables 12, 12A and 14.¹¹⁹

Within the very broad ambit of the Australian patent discourse there is not the nuance, like there is in *Mayo Collaborative Services v Prometheus Laboratories Inc.*,¹²⁰ of a threshold for transforming unpatentable natural correlations into patentable applications. This view is confirmed by the decision in *Grant v Commissioner of Patents*, where the Full Federal Court concluded that “[i]t is necessary that there be some ‘useful product’, some physical phenomenon or effect resulting from the working of a method” for the subject matter to be patentable.¹²¹ There the claim was for a method for structuring a financial transaction so as to protect an individual’s assets from a loss of ownership as a result of a legal liability:

An asset protection method for protecting an asset owned by an owner, the method comprising the steps of:

- (a) establishing a trust having a trustee,
- (b) the owner making a gift of a sum of money to the trust,
- (c) the trustee making a loan of said sum of money from the trust to the owner, and
- (d) the trustee securing the loan by taking a charge for said sum of money over the asset.¹²²

This was not considered to be patentable because there was no “artificial state of affairs, in the sense of a concrete, tangible, physical, or observable effect”.¹²³ The method was effected through a computer and the court clarified that a “product of a method is something in which a new and useful effect may be observed”, and that even though a device was not necessary for a method claim, “[f]or claimed computer programs, the courts looked to the application of the program to produce a practical and useful result, so that more than ‘intellectual information’ was involved”.¹²⁴ As the product of the invention was “at best an abstract, intangible situation, namely that a hypothetical unsecured creditor who recovered judgment against a user of the method could not levy against the user’s assets to the extent they were subject to the charge”, was not a “physical consequence” then the subject matter was unpatentable.¹²⁵ Meanwhile, in *CCOM Pty Ltd v Jieijing Pty Ltd*, a method of graphically representing retrieved desired Chinese characters was a sufficient physical effect and economic endeavour to be patent eligible;¹²⁶ in *International Business Machines Corp v Commissioner of Patents*, a method of using a mathematical formula to produce an improved curved image on a computer screen was patentable;¹²⁷ and in *Welcome Real-Time SA v Catuity Inc*, a method for using a smart card for traders’ loyalty programs that wrote new information to a “behaviour file” and printed a coupon was

¹¹⁸ *Cancer Voices Australia v Myriad Genetics Inc* (2013) 99 IPR 567 at 596.

¹¹⁹ Skolnick M et al, *In Vivo Mutations and Polymorphisms in the 17q-Linked Breast and Ovarian Cancer Susceptibility Gene*, International Patent No WO 96/05306 (1996) p 187 (Claim 17). See Shattuck-Eidens D et al, *In Vivo Mutations and Polymorphisms in the 17q-Linked Breast and Ovarian Cancer Susceptibility Gene*, Australian Standard Patent No 686004 (1995) p 187 (Claim 17).

¹²⁰ *Mayo Collaborative Services v Prometheus Laboratories Inc* 566 US __ at 3 (2012), citing *Parker v Flook* 437 US 584 at 594 (1978); *Bilski v Kappos* 561 US __ at 5 (2010).

¹²¹ *Grant v Commissioner of Patents* (2006) 69 IPR 221 at 231.

¹²² *Grant’s Application* [2004] APO 11 at [2] (D Herald).

¹²³ *Grant v Commissioner of Patents* (2006) 69 IPR 221 at 228.

¹²⁴ *Grant v Commissioner of Patents* (2006) 69 IPR 221 at 228.

¹²⁵ *Grant v Commissioner of Patents* (2006) 69 IPR 221 at 228-229.

¹²⁶ *CCOM Pty Ltd v Jieijing Pty Ltd* (1994) 28 IPR 48.

¹²⁷ *International Business Machines Corp v Commissioner of Patents* (1991) 22 IPR 417.

patentable.¹²⁸ These decisions sit comfortably with the proposition that a GWAS output that identifies DNA sequences correlated with a disease or condition that might be treated is patentable subject matter.

However, there may be a shift starting in Australia. In 2013 in *Research Affiliates LLC v Commissioner of Patents*, a patent claimed:

A computer-implemented method for generating an index, the method including steps of:

- (a) accessing data relating to a plurality of assets;
- (b) processing the data thereby to identify a selection of the assets for inclusion in the index based on an objective measure of scale other than share price, market capitalization and any combination thereof;
- (c) accessing a weighting function configured to weight the selected assets;
- (d) applying the weighting function, thereby to assign to each of the selected assets a respective weighting, wherein the weighting:
 - (i) is based on an objective measure of scale other than share price, market capitalization and any combination thereof; and
 - (ii) is not based on market capitalization weighting, equal weighting, share price weighting and any combination thereof, thereby to generate the index.¹²⁹

The invention related to the making of indexes to direct investing so that based on an index an investor would select particular investment assets (like shares).¹³⁰ The invention applies broadly so an index might encapsulate metrics such as “book value, sales, revenue, earnings, earnings per share, income, income growth rate, dividends, dividends per share, earnings before interest, tax, depreciation and amortisation, etc” or “companies with chief executives having graduated from a particular university”.¹³¹ The investment is made based on a system, method and computer program with the product being a direction about the assets that should be bought for investment.¹³² Based on this direction, an investor would then go and purchase an asset or series of assets.¹³³ IP Australia had rejected the application as not patentable because, while implemented on a computer, the method merely constructed data from an analysis of various other data sets – “the claim as a whole defines the steps to generate the data to support the passive investment scheme”.¹³⁴

Before the Federal Court, the applicant argued that IP Australia’s characterisation of the invention as “a scheme or an investment scheme” was incorrect when in fact it was “a computer-implemented series of steps that, when carried out, generates an index ... a physical, computer-generated file”.¹³⁵ Further, derivation and manipulation of data had a physical effect,¹³⁶ was a process for producing a product,¹³⁷ and the product was “a paradigm case of economic endeavour”.¹³⁸ This was rejected by Emmett J on the basis that:

The method of the claimed invention does not involve a specific effect being generated by the computer. The mere use of a computer necessarily carries with it the writing of information into the computer’s memory. There is a stark contrast between a computer-generated curve [*International Business Machines Corp v Commissioner of Patents*], or a representation of Chinese characters [*CCOM Pty Ltd v Jiejing Pty Ltd*], or the writing of particular information on a smart card [*Welcome Real-Time SA v*

¹²⁸ *Welcome Real-Time SA v Catuity Inc* (2000) 51 IPR 327 at 353.

¹²⁹ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [50].

¹³⁰ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [43].

¹³¹ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [43].

¹³² *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [45]-[46].

¹³³ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [47].

¹³⁴ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [54].

¹³⁵ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [54].

¹³⁶ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [56].

¹³⁷ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [57].

¹³⁸ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [58].

Catuity Inc], on the one hand, and the quite unspecific index, on the other. There is no practical application in the method of the claimed invention for the improved use of computers. The effect of the implementation of the method is not to improve the operation of or effect of the use of the computer. There is nothing in the Specification or claim 1 that discloses how to produce the index.¹³⁹

More generally, Emmett J characterised the application as an invention relying on the proposition that “information of economic significance, once entered into or produced by means of a computer, becomes an economically valuable artificially created state of affairs, and thus patentable”.¹⁴⁰ What appears to be required is something more tangible than just more data. This decision might therefore signal a modification of the Australian law for GWAS diagnostic method claims.

In short, a method correlating a sequence against a reference sequence to identify a predisposition to a disease is undoubtedly patentable in Australia at present and is demonstrated by the clear acceptance of the claim in *Cancer Voices Australia v Myriad Genetics Inc* and its unchallenged state in that litigation. Whether the United States cases will influence future developments is presently unclear, although this seems likely as in applying this broader *Patents Act 1990* (Cth) scheme the *Australia-United States Free Trade Agreement* requires that “[e]ach Party shall endeavour to reduce differences in law and practice between their respective systems”.¹⁴¹ The effect of this provision is to make the United States law relevant in determining the application of the Australian patent scheme and brings Australian law into line with United States laws.

PATENTING AND REPRODUCIBILITY (SUFFICIENCY, ENABLEMENT AND INUTILITY)

A patent must both “disclose [in the complete specification] the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the relevant art”¹⁴² and “[t]he claim or claims must be ... supported by matter disclosed in the specification”.¹⁴³ A patent must also be useful.¹⁴⁴ These provisions require there be an adequate description and definition of the invention (sufficiency), that the invention can be performed by a suitably skilled person (enablement), and that the invention work (utility). For GWAS inventions, this requires an adequate description of the processes of comparing sequences, identifying the relevant sequence motifs that are significant, and correlating the identified sequence motifs with the result identified in the claims.

This sufficiency and enablement needs to be distinguished from inutility (or not useful). Sufficiency and enablement is not satisfied if the information provided in the specification is not sufficient to practice the invention.¹⁴⁵ In contrast, if the information given is followed and the result is not what is claimed then there is inutility.¹⁴⁶ For the purposes of this article, the sufficiency and enablement problem arises where the claim is presumed to be correct and there is not enough (quality and quantity) information set out in the specification to practise the invention. The inutility problem arises where there is presumed sufficient information, which when followed does not produce the claimed result.

The amendment in the *Intellectual Property Laws Amendment (Raising the Bar) Act 2012* (Cth) of the sufficiency and enablement requirement was to confirm that “the specification must make the nature of the invention plain” and “the specification must make it plain how to make or perform the invention”.¹⁴⁷ The intention was that these obligations follow “as close as is practicable”

¹³⁹ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [70].

¹⁴⁰ *Research Affiliates LLC v Commissioner of Patents* (2013) 300 ALR 724 at [71].

¹⁴¹ *Australia-United States Free Trade Agreement* [2005] ATS 1, Art 17.9.14.

¹⁴² *Patents Act 1990* (Cth), s 40(2)(a). See also *Kimberly-Clark Australia Pty Ltd v Arico Trading International Pty Ltd* (2001) 207 CLR 1 at [25].

¹⁴³ *Patents Act 1990* (Cth), s 40(3).

¹⁴⁴ *Patents Act 1990* (Cth), ss 7A, 18(1)(c).

¹⁴⁵ *Tetra Moletric Ltd's Application* (1977) RPC 290 at 297.

¹⁴⁶ *Tetra Moletric Ltd's Application* (1977) RPC 290 at 297.

¹⁴⁷ Explanatory Memorandum, *Intellectual Property Laws Amendment (Raising the Bar) Bill 2011* (Cth) (2011) p 46.

corresponding provisions in the *Patents Act 1977* (UK)¹⁴⁸ and the *Convention on the Grant of European Patents*.¹⁴⁹ An example illustrates this intention. In *EXXON/Fuel Oils*, the invention claimed a distillate fuel with wax crystals “having an average particle size less than 4000 nanometres”.¹⁵⁰ The applicant admitted that the application did not contain a disclosure that would enable a skilled person to obtain fuel oils with average particle size less than 1,000 nanometres.¹⁵¹ The Board of Appeal therefore concluded that an application should contain sufficient information for a suitably skilled person to carry out the invention “within the whole area that is claimed”¹⁵² and “obtain substantially all embodiments falling within the ambit of the claims”.¹⁵³ Where there was a disclosure of only one way of performing the invention then this must enable the skilled person to perform the invention across the whole claimed range, and this was a question of fact.¹⁵⁴

The sufficiency, enablement and inutility problems for GWAS inventions arise because the invention as claimed is not necessarily experimentally reproducible.¹⁵⁵ For IP Australia administering patents, these issues arise at the stages of examination,¹⁵⁶ re-examination,¹⁵⁷ opposition¹⁵⁸ and revocation.¹⁵⁹ The problem, however, is that IP Australia is not well-placed to question the reproducibility of a claim because its assessments are essentially made on the basis of the lodged complete specification and any publicly available data and information (the prior art). The relevant standard applied by a patent examiner is the “balance of probabilities”,¹⁶⁰ which means “highly plausible, more probable than not or prima facie reasonable”.¹⁶¹ In practice, however, if there is a genuine doubt about the correctness of the objection then the applicant is given the benefit of the doubt.¹⁶² The result is that, even though there may be credible doubt about the GWAS claims, the applicant will be given the benefit of that doubt and the sufficiency, enablement and inutility issues overlooked.

DISCUSSION AND CONCLUSIONS

The analysis in this article started out asserting that GWAS claims pose two important problems for patenting – first, the problems affecting experimental reproducibility, and secondly, challenging the credibility and veracity of reported developments. The solution in the United States, demonstrated by the Federal Circuit decision in *Association for Molecular Pathology v United States Patent and Trademark Office* (preceding the Supreme Court decision in *Association for Molecular Pathology v*

¹⁴⁸ See *Patents Act 1977* (UK), s 14(3): “The specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art.”

¹⁴⁹ See *Convention on the Grant of European Patents*, opened for signature 5 October 1973, 1065 UNTS 199 (entered into force 7 October 1977), Art 83: “The European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.”

¹⁵⁰ *EXXON/Fuel Oils* (T 0409/91) [1994] OJEP 653 at 654.

¹⁵¹ *EXXON/Fuel Oils* (T 0409/91) [1994] OJEP 653 at 655, 657.

¹⁵² *EXXON/Fuel Oils* (T 0409/91) [1994] OJEP 653 at 657.

¹⁵³ *EXXON/Fuel Oils* (T 0409/91) [1994] OJEP 653 at 663.

¹⁵⁴ *EXXON/Fuel Oils* (T 0409/91) [1994] OJEP 653 at 657, 662.

¹⁵⁵ A similar problem arises for claims to plants depositing seeds to address the definition and description requirements: see Lawson C, “Depositing Seeds to Comply with the Patents Act 1990 (Cth) – The Adequacy of Definition and Description?” (2004) 23 *University of Tasmania Law Review* 68.

¹⁵⁶ *Patents Act 1990* (Cth), s 45(1)(a); *Patents Regulations 1991* (Cth), reg 3.17B(2).

¹⁵⁷ *Patents Act 1990* (Cth), s 97(2).

¹⁵⁸ *Patents Act 1990* (Cth), s 59(c).

¹⁵⁹ *Patents Act 1990* (Cth), s 101(1).

¹⁶⁰ *Patents Act 1990* (Cth), s 49(1).

¹⁶¹ *Australian Patent Office Manual*, n 53 at [2.13.5.2A].

¹⁶² *Australian Patent Office Manual*, n 53 at [2.13.5.3].

Myriad Genetics Inc), is that mere claims to GWAS diagnostic methods are unpatentable subject matter.¹⁶³ In Australia, the Federal Court's decision in *Cancer Voices Australia v Myriad Genetics Inc*¹⁶⁴ demonstrates that Australia accepts such GWAS diagnostic method patent claims. Australian courts are yet to specifically determine the matter and might be persuaded by the reasoning of the United States cases. This seems likely as, in applying this broader *Patents Act 1990* (Cth) scheme, the *Australia-United States Free Trade Agreement* requires the schemes to converge.¹⁶⁵ This would clearly resolve the problems of GWAS reproducibility, and the credibility and veracity of reported GWAS results, by making these diagnostic method claims unpatentable.

In the meantime, however, there remains the problem that current GWAS patents in Australia are claiming subject matter that cannot necessarily be reproduced and may be incorrect. As the analysis in this article shows, the sufficiency, enablement and inutility requirements are unlikely to be addressed because the patent applicant is given the benefit of any doubt.¹⁶⁶ The question, therefore, is how IP Australia should assess GWAS inventions and what measures should be put in place to increase the certainty that the GWAS invention claims are credible (and real). There is general acceptance that GWAS (and NGS) involve large data sets and computational (and machine) artefacts¹⁶⁷ with considerable attention now being focused on methodologies that improve both the repeatability and credibility and veracity of sequence correlations.¹⁶⁸ Added to this are the imperatives to release sequence data into the public domain through the evolution of the "open science" norms¹⁶⁹ and improved scrutiny before publication.¹⁷⁰ The outcome of these developments is likely to be a greater confidence that claims from GWAS of correlations are correct. In the longer term, however, more complex omics studies that include genomics together with transcriptomics, proteomics, metabolomics, autoantibody profiles and various clinical parameters are likely to raise the same kind of reproducibility and credibility and veracity problems, and perhaps require more careful attention to metadata norms.¹⁷¹ For patenting diagnostic method claims, this is going to remain a problem as IP Australia will never have the ability to independently assess the reproducibility and credibility and veracity of these claims.

However, there remains another intriguing issue. The key challenge in addressing the genetic basis of disease is to resolve the inherited phenotypic variation, or heritability, in a population – how much of the disease among the variation in the population can be attributed to inherited genetic factors and how much is the result of other non-genetic factors (such as the environment). This is necessary because almost all common diseases so far have been associated with some sequences and with an

¹⁶³ See *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 at 1333-1335 (Circuit Judge Lourie), 1337 (Circuit Judge Moore), 1348 (Circuit Judge Bryson) (2012).

¹⁶⁴ *Cancer Voices Australia v Myriad Genetics Inc* (2013) 99 IPR 567 (Nicholas J).

¹⁶⁵ *Australia-United States Free Trade Agreement* [2005] ATS 1, Art 17.9.14.

¹⁶⁶ See *Australian Patent Office Manual*, n 53 at [2.13.5.3].

¹⁶⁷ See, for example, Chrystoja C and Diamandis E, "Whole Genome Sequencing as a Diagnostic Test: Challenges and Opportunities" (2014) 60 *Clinical Chemistry* 724.

¹⁶⁸ See, for example, Duitama J et al, "An Integrated Framework for Discovery and Genotyping of Genomic Variants from High-Throughput Sequencing Experiments" (2014) 42 *Nucleic Acids Research* e44; Pabinger S et al, "A Survey of Tools for Variant Analysis of Next-Generation Genome Sequencing Data" (2014) 15 *Briefings in Bioinformatics* 256; Forster M et al, "From Next-Generation Sequencing Alignments to Accurate Comparison and Validation of Single-Nucleotide Variants: The Pibase Software" (2013) 41 *Nucleic Acids Research* e16; DePristo M et al, "A Framework for Variation Discovery and Genotyping Using Next-Generation DNA Sequencing Data" (2011) 43 *Nature Genetics* 491; Nielsen R et al, "Genotype and SNP Calling From Next-Generation Sequencing Data" (2011) 12 *Nature Reviews Genetics* 443; Davey J et al, "Genome-Wide Genetic Marker Discovery and Genotyping Using Next-Generation Sequencing" (2011) 12 *Nature Reviews Genetics* 499.

¹⁶⁹ See, for example, Kaye J and Hawkins N, "Data Sharing Policy Design for Consortia: Challenges for Sustainability" (2014) 6 *Genome Medicine* 4 and the references therein. See also Contreras J, "Bermuda's Legacy: Policy, Patents, and the Design of the Genome Commons" (2011) 12 *Minnesota Journal of Law, Science and Technology* 61.

¹⁷⁰ See Editor, "Announcement – Reducing our Irreproducibility", n 8.

¹⁷¹ Kolker E et al, "Toward More Transparent and Reproducible Omics Studies Through a Common Metadata Checklist and Data Publications" (2014) 18 *Omics* 10. See also Tenenbaum J, Sansone SA and Haendel M, "A Sea of Standards for Omics Data: Sink or Swim?" (2013) 21(2) *Journal of the American Medical Informatics Association* 200.

assumed contribution from other as yet undiscovered inherited genetic factors. In contrast, there are a minority of well-characterised, highly penetrant and simple trait diseases that are directly correlated with genome sequences.¹⁷² In other words, most common diseases have significant heritability and the quest has been to discover these other contributing genetic factors that together explain these complex traits. This quest has been eagerly pursued through big GWAS projects and with the development of large information databases.¹⁷³ The results so far, however, have been disappointing with identified genetic factors only accounting for a small portion of measured heritability, and a considerable number of different sequences involved with each sequence accounting for only a very small portion of the measured heritability.¹⁷⁴ The iconic example of this problem is the heritability of human height/stature: heritability was measured at 80% (that is, 80% of the variation in height among the individuals was attributed to genetic factors), yet identified genetic factors can only account for about 5% of this variation (that is, 75% of the variation cannot yet be accounted for).¹⁷⁵ In short:

The explosion of [GWAS] has expanded the set of candidate genes and genomic regions for future study ... But progress in chronic disease etiology has been slow, and [GWAS] results have not broken any floodgates of understanding. This is because the studies only nominate candidate villains, and it takes biological insight and studies of mechanism to learn how they erode our health ... the most striking general result that pervades all [GWAS] – the magnitude of genetic effects is uniformly very small. Even for a trait with strong familial clustering, the strongest associations explain little of the genetic variance for the trait.¹⁷⁶

The existing paradigm has been that the “missing heritability”¹⁷⁷ can generally be explained by other genetic factors.¹⁷⁸ The problem remains that the prospect of identifying genetic factors as a basis for new and better treatments, including targeted interventions based on genetic risks identified from the genome – the promise of personalised medicine – now seems “bleak”.¹⁷⁹ The “missing heritability” (sometimes called the “dark matter of the genome”) will need to explain the overwhelming contribution of genetic factors. In short, the current GWAS diagnostic method claims really only account for a very small portion of the “missing heritability”. And this goes back to the United States Supreme Court decision of *Laboratory Corp of America Holdings v Metabolite Laboratories Inc*, in which Breyer J (dissenting from the majority decision) considered that a claim to

¹⁷² Such as cystic fibrosis, sickle cell disease, and so on: see, for example, Jimenez-Sanchez, Childs and Valle, n 3 at 853.

¹⁷³ See, for example, HapMap Project – Manolio, Brooks and Collins, n 2; Gibbs R et al, “The International HapMap Project” (2003) 426 *Nature* 789; 1000 Genomes Project – The 1000 Genomes Project Consortium, “A Map of Human Genome Variation from Population-Scale Sequencing” (2010) 467 *Nature* 1061; ENCYClopedia Of DNA Elements – The ENCODE Project Consortium, “Identification and Analysis of Functional Elements in 1% of the Human Genome by the ENCODE Pilot Project” (2007) 447 *Nature* 799; Roadmap Epigenomics Project – see, for example, Harris A et al, “Comparison of Sequencing-Based Methods to Profile DNA Methylation and Identification of Monoallelic Epigenetic Modifications” (2010) 28 *Nature Biotechnology* 1097.

¹⁷⁴ See, for summaries, Manolio T et al, “Finding the Missing Heritability of Complex Diseases” (2009) 461 *Nature* 747; Dermitzakis E and Clark A, “Life After GWA Studies” (2009) 326 *Science* 239.

¹⁷⁵ See Visscher P, “Sizing Up Human Height Variation” (2008) 40 *Nature Genetics* 489, and the references therein. Another elegant example is the attempts to predict bristle counts in *Drosophila melanogaster* showing that laboratory-based predictions could not be replicated in a more variable environment: Macdonald S, Pastinen T and Long A, “The Effect of Polymorphisms in the Enhancer of Split Gene Complex on Bristle Number Variation in a Large Wild-Caught Cohort of *Drosophila melanogaster*” (2005) 171 *Genetics* 1741.

¹⁷⁶ Dermitzakis and Clark, n 174 at 239.

¹⁷⁷ See Zuk O et al, “The Mystery of Missing Heritability: Genetic Interactions Create Phantom Heritability” (2012) 109 *Proceedings of the National Academy of Sciences* 1193; Manolio et al, n 174.

¹⁷⁸ See, for example, Eichler E et al, “Missing Heritability and Strategies for Finding the Underlying Causes of Complex Disease” (2010) 11 *Nature Genetics* 446; Petronis A, “Epigenetics as a Unifying Principle in the Aetiology of Complex Traits and Diseases” (2010) 465 *Nature* 721 at 722-723; Dermitzakis and Clark, n 174 at 240; Manolio et al, n 174 at 748; Visscher P, “Sizing up Human Height Variation” (2008) 40 *Nature Genetics* 489 at 490; Maher B, “The Case of the Missing Heritability” (2008) 456 *Nature* 18.

¹⁷⁹ Dermitzakis and Clark, n 174 at 239.

a blood assay that correlated with a vitamin deficiency should not be patentable because it was merely a correlation expressed in the language of a process.¹⁸⁰ He then added that there were broader public interest considerations that were relevant as such patent claims:

threaten[] to leave the medical profession subject to the restrictions imposed by this individual patent and others of its kind. Those restrictions may inhibit doctors from using their best medical judgment; they may force doctors to spend unnecessary time and energy to enter into license agreements; they may divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations; they may raise the cost of health care while inhibiting its effective delivery.¹⁸¹

¹⁸⁰ *Laboratory Corp of America Holdings v Metabolite Laboratories Inc* 548 US 124 at 136-138 (2006). The claim was: “A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of: assaying a body fluid for an elevated level of total homocysteine; and correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate” (at 129).

¹⁸¹ *Laboratory Corp of America Holdings v Metabolite Laboratories Inc* 548 US 124 at 138 (2006).